Annals of Oncology

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Abstract Book of the
43rd ESMO Congress (ESMO 2018)

Munich, Germany
19–23 October 2018

Guest Editors: ESMO 2018 Congress Scientific Committee

Annals of Oncology

Official Journal of the European Society for Medical Oncology and the Japanese Society of Medical Oncology

Executive editor: Lewis Rowett
Editorial office: Paola Minotti Bernasconi, Giovannella Porcu, Annals of Oncology, Via Ginevra 4, 6900 Lugano, Switzerland

Annals of Oncology is covered in C.A.B. International, Current Clinical Cancer, Current Contents/Clinical Medicine®, Current Contents/Life Sciences, Elsevier BIOBASE/Current Awareness in Biological Sciences, EMBASE/Excerpta Medica, IBIDS, Index Medicus/MEDLINE, The International Monitor in Oncology, Medical Documentation Service, Science Citation Index® and Science Citation Index Expanded.

Subscriptions

A subscription to *Annals of Oncology* comprises 12 issues plus supplements in each volume. Prices include postage, and for subscribers outside the UK delivery is by Standard Air.

Annual Subscription Rate (Volume 29, 12 issues, 2018)

Institutional - Academic / Non profit only
Print and Online £1754.00/$3508.00/€2631.00
Online Only £1202.00/$2404.00/ €1803.00
Print Only £1617.00/$3233.00/€2425.00

Institutional - Corporate
Print and Online £2193.00/$4385.00/€3289.00
Online Only £1503.00/$3005.00/€2254.00
Print Only £2021.00/$4041.00/€3031.00

Personal
Print and Online £1262.00/$2526.00/€1893.00
Please note: US$ rate applies to US & Canada, Euros applies to Europe, UK£ applies to UK and Rest of World.

There may be other subscription rates available, for a complete listing please visit https://academic.oup.com/annonc/subscribe

Full prepayment, in the correct currency, is required for all orders. Orders are regarded as firm and payments are not refundable. Subscriptions are accepted and entered on a complete volume basis. Claims cannot be considered more than FOUR months after publication or date of order, whichever is later. All subscriptions in Canada are subject to GST. Subscriptions in the EU may be subject to European VAT. If registered, please supply details to avoid unnecessary charges. For subscriptions that include online versions, a proportion of the subscription price may be subject to UK VAT. Personal rate subscriptions are only available if payment is made by personal cheque or credit card and delivery is to a private address.

The current year and two previous years' issues are available from Oxford Journals. Previous volumes can be obtained from the Periodicals Service Company at http://www.periodicals.com/oxford.html or Periodicals Service Company, 11 Main Street, Germantown, NY 12526, USA. Email: psc@periodicals.com. Tel: (518) 537-4700. Fax: (518) 537-5899

For further information, please contact: Journals Customer Service Department, Oxford University Press, Great Clarendon Street, Oxford OX2 6DP, UK. Email: jnls.cust.serv@oup.com. Tel (and answerphone outside normal working hours): +44 (0)1865 353907. Fax: +44 (0)1865 353485. **In the US, please contact:** Journals Customer Service Department, Oxford University Press, 2001 Evans Road, Cary, NC 27513, USA. Email: jnlorders@oup.com. Tel (and answerphone outside normal working hours): 800 852 7323 (toll-free in USA/Canada). Fax: 919 677 1714. **In Japan, please contact:** Journals Customer Service, Oxford University Press, 4-5-10-8F Shiba, Minato-ku, Tokyo 108-8386, Japan. Tel. +81 3 5444 5858. Fax. +81 3 3454 2929. E-mail: custserv. jp@oup.com

DOI: For information about DOIs and to resolve them, please visit http://www.doi.org

Methods of payment. (i) Cheque (payable to Oxford University Press, to Oxford University Press, Cashiers Office, Great Clarendon Street, Oxford OX2 6DP, UK) in GB£ Sterling (drawn on a UK bank), US$ Dollars (drawn on a US bank), or EU€ Euros. (ii) Bank transfer to Barclays Bank Plc, Oxford Group Office, Oxford (bank sort code 20-65-18) (UK), overseas only Swift code BARC GB 22 (GB£ Sterling to account no. 70299332, IBAN GB89BARC20651870299332; US$ Dollars to account no. 66014600, IBAN GB27BARC20651866014600; EU€ Euros to account no. 78923655, IBAN GB16BARC20651878923655). (iii) Credit card (Mastercard, Visa, Switch or American Express).

Annals of Oncology (ISSN 0923-7534) is published monthly by Oxford University Press, Oxford, UK and distributed in the USA by UKP Worldwide, 3390 Rand Road, South Plainfield, NJ 07080. Periodicals postage paid at Rahway, NJ. POSTMASTER: Send address changes to *Annals of Oncology*, Oxford University Press, C/O 3390 Rand Road, South Plainfield, NJ 07080.

Subscription records are maintained at Oxford University Press, Oxford, UK.

Supplements, reprints and corporate sales

For requests from industry and companies regarding supplements, bulk article reprints, sponsored subscriptions, translation opportunities for previously published material, and corporate online opportunities, please email: special. sales@oup.com, fax: +44 (0) 1865 353774 or visit http://www.oupmediainfo.com/#!/reprints-eprints.

Permissions

For information on how to request permissions to reproduce articles/information from this journal, please visit https://academic.oup.com/journals/pages/access_purchase/rights_and_permissions.

Advertising

Advertising, inserts and artwork enquiries should be addressed to Advertising and Special Sales, Oxford Journals, Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP, UK. Tel: +44 (0)1865 354767; Fax +44 (0)1865 353774; E-mail: jnlsadvertising@oup.com

Environmental and ethical policies

Oxford Journals, a division of Oxford University Press, is committed to working with the global community to bring the highest quality research to the widest possible audience. Oxford Journals will protect the environment by implementing environmentally friendly policies and practices wherever possible. Please see https://academic.oup.com/journals/pages/about_us/ethical_policies for further information on environmental and ethical policies.

Drug disclaimer

All reasonable precautions have been taken by the authors, editors and publisher to verify drug names and doses, the results of experimental work and the clinical findings published in this journal. The opinions expressed are those of the authors, and not necessarily those of the editors or publisher. The ultimate responsibility for the use and dosage of drugs mentioned in *Annals of Oncology* and in the interpretation of published material lies with the medical practitioner. The editors and publisher can accept no liability whatsoever in respect of any claim for damages arising therefrom. Please inform the editors of any errors.

Notice:

The content of the abstracts contained in this Abstract Book is subject to an embargo.

Abstracts accepted for presentation at ESMO 2018 as Poster will be published online via the ESMO website at 00:05 CEST on **Tuesday, 9 October 2018.**

Abstracts accepted for presentation at ESMO 2018 as Proffered Paper (oral presentation) or Poster Discussion will be published online via the ESMO website at 12:00 CEST on **Friday, 19 October 2018.**

All Late-breaking abstracts (Proffered Paper and Poster Discussion) will be made public at the start of the official Congress session during which they are presented.

The Publication schedule of Abstracts and Late-breaking abstracts selected for inclusion in the **ESMO Press Programme,** will be available 10 days before the Congress.

Disclaimer:

No responsibility is assumed by the organizers for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of the rapid advances in medical sciences, we recommend that independent verification of diagnoses and drug dosages should be made.

Every effort has been made to faithfully reproduce the abstracts as submitted. However, no responsibility is assumed by the organizers for any omissions or misprints.

Typeset by Cenveo Publisher Services, Bangalore, India.
Printed by Bell and Bain Ltd., Glasgow, UK.

Annals of Oncology

Official Journal of the European Society for Medical Oncology

Volume 29, 2018 Supplement 8

Abstract Book of the
43rd ESMO Congress (ESMO 2018)
Munich, Germany

19–23 October 2018

Guest Editors:
ESMO 2018 Congress Scientific Committee

OXFORD
UNIVERSITY PRESS

Annals of Oncology

Official Journal of the European Society for Medical Oncology

GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Volume 29, 2018 Supplement 8

Abstract Book of the 43rd ESMO Congress (ESMO 2018)
19–23 October 2018, Munich, Germany

Note: Abstract suffixes
"O" indicates a submitted abstract accepted for Proffered Paper (oral) presentation
"PD" indicates a submitted abstract accepted for Poster Discussion presentation
"P" indicates a submitted abstract accepted for Poster presentation
"TiP" indicates a submitted abstract accepted for Poster presentation (Trial in Progress)
"__PR" indicates a submitted abstract selected for inclusion in the ESMO Press Programme

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

The European Society for Medical Oncology (ESMO)

ESMO is the leading professional organisation for medical oncology. With 18,000 members representing oncology professionals from over 150 countries worldwide, ESMO is the society of reference for oncology education and information. ESMO is committed to offer the best care to people with cancer, through fostering integrated cancer care, supporting oncologists in their professional development, and advocating for sustainable cancer care worldwide.

Founded in 1975, ESMO has European roots with a global reach. Home for all oncology stakeholders, ESMO connects professionals with diverse expertise and experience. Its education and information resources support an integrated multi-professional approach to cancer care, from a medical oncology perspective. ESMO seeks to erase boundaries in cancer care, whether between countries or specialities, and pursue its mission across oncology, worldwide.

Drawing on 40 years of experience and around 500 expert committee members, ESMO serves its members and the oncology community through:

- Post-graduate oncology education and training
- Career development and leadership training for the next generations of oncologists
- International congresses and workshops to share expertise and best practice, learn about the most up-to-date scientific advances, and connect with colleagues in related disciplines
- Continuously reviewed, evidence-based standards for cancer care in Europe
- Advocacy and consultation to foster a favourable environment for scientific research

Cancer care is rapidly becoming more integrated and more specialised; whether their field is research, diagnosis, treatment, care, or advocacy, oncology professionals need to both build their specialist knowledge and connect with the best practitioners in other disciplines worldwide. ESMO membership makes this possible.

www.esmo.org.

ESMO Executive Board

The European Oncology Nursing Society (EONS)

The **European Oncology Nursing Society (EONS)** is an independent charity dedicated to the professional support and development of cancer nurses across Europe and beyond. EONS consists of individual members and national societies, providing leadership in all areas of cancer nursing with a core focus on communications, advocacy, research and education.

Our **mission** is to ensure that all people affected by cancer benefit from the care of highly educated, well-informed and competent cancer nurses.

Our **vision** is that cancer nursing will be recognised by the cancer community, national and European-level policy makers, as a profession with specialised training and qualifications available across the continent. Working conditions for cancer nurses will be optimal, providing a commensurate financial income as well as protecting and promoting individual well-being. We anticipate that this will produce a relatable improvement in the health and clinical outcomes for people affected by cancer.

EONS' strategic goals

By the end of 2020, EONS will have achieved the following:

1. Cancer nursing is recognised across Europe for its positive impact on the lives of people affected by cancer through C.A.R.E. - Communication, Advocacy, Research and Education.
2. All cancer nurses have access to specialised education that is aligned with the EONS Cancer Nursing Education Framework.
3. All cancer nurses gain official recognition, reward and respect as a result of the RECaN and advocacy campaigns.
4. All cancer nurses are connected in order to exchange and share information and support for their work.
5. EONS facilitates, leads and promotes collaborative cancer nursing research across Europe.
6. EONS leads EU-wide advocacy initiatives at EU policy level.
7. EONS provides evidence-based advice to people and organisations affected by cancer on healthy lifestyles and cancer prevention.

Finally, we envisage that all our members will become confident and empowered cancer nurses operating as leaders in research, practice and education within multi-professional teams.

EONS Executive Board

ESMO 2018 Congress Officers

2018 ESMO and Congress President
Josep Tabernero, Barcelona, Spain

Scientific Chair
Solange Peters, Lausanne, Switzerland

Educational Chair
Andrés Cervantes, Valencia, Spain

Congress Press Officer
Pilar Garrido, Madrid, Spain

Local Officer
Volker Heinemann, Munich, Germany

Scientific Committee

Basic science
Chair: Richard Marais, Manchester, UK
David Adams, Cambridge, UK
Alberto Bardelli, Turin, Italy
Anton Berns, Amsterdam, The Netherlands
Leonor David, Porto, Portugal
Thomas Helleday, Sheffield, UK
Yardena Samuels, Rehovot, Israel
Sheila Singh, Hamilton, ON, Canada
Therese Sørlie, Oslo, Norway
Charles Swanton, London, UK
Emmy Verschuren, Helsinki, Finland
Christof von Kalle, Heidelberg, Germany

Breast cancer, early stage
Chair: Carlos Caldas, Cambridge, UK
Hervé Bonnefoi, Bordeaux, France
Jean-Marc Classe, Nantes-Saint-Herblain, France
Charlotte Coles, Cambridge, UK
Javier Cortés, Madrid, Spain
Suzette Delaloge, Villejuif, France
Carsten Denkert, Berlin, Germany
Angelo Di Leo, Prato, Italy
Véronique Diéras, Paris, France
Helena Earl, Cambridge, UK
Claire Isacke, London, UK
Jos Jonkers, Amsterdam, The Netherlands
Sabine Linn, Amsterdam, The Netherlands

Breast cancer, metastatic
Chair: Fatima Cardoso, Lisbon, Portugal
Joan Albanell, Barcelona, Spain
Lisa Carey, Chapel Hill, NC, USA
Giuseppe Curigliano, Milan, Italy
Nagi S. El Saghir, Beirut, Lebanon
Prudence Francis, Melbourne, Australia
Nadia Harbeck, Munich, Germany
Sibylle Loibl, Neu-Isenburg, Germany
Olivia Pagani, Bellinzona, Switzerland
Frederique Penault-Llorca, Clermont-Ferrand, France
Roman Rouzier, Paris, France
Britta Weigelt, New York, NY, USA

CNS tumours
Chair: Matthias Preusser, Vienna, Austria
Carmen Balaña, Badalona, Spain
Anna S. Berghoff, Vienna, Austria
Priscilla Brastianos, Boston, MA, USA
Roger Henriksson, Stockholm, Sweden
Emilie Le Rhun, Lille, France
Stefan Pfister, Heidelberg, Germany
Michele Reni, Milan, Italy
Joan Seoane, Barcelona, Spain
Joerg Tonn, Munich, Germany
Martin van der Bent, Rotterdam, The Netherlands
Michael Weller, Zurich, Switzerland
Frank Winkler, Heidelberg, Germany

Developmental therapeutics
Chair: Alex A. Adjei, Rochester, MN, USA
Udai Banerji, London, UK
Christian Blank, Amsterdam, The Netherlands
Maria Grazia Daidone, Milan, Italy
Christian Dittrich, Vienna, Austria
Boon Cher Goh, Singapore
Allan Jordan, Manchester, UK
Matthew Krebs, Manchester, UK
Christophe Le Tourneau, Paris, France
Paul Morten Mau-Sorensen, Copenhagen, Denmark
Christian Rolfo, Baltimore, MD, USA
Teresa Troiani, Naples, Italy

Gastrointestinal tumours, colorectal
Chair: Dirk Arnold, Hamburg, Germany
Alfredo Falcone, Pisa, Italy
Matthias Guckenberger, Zurich, Switzerland
Miriam Koopman, Utrecht, The Netherlands
Roberto Labianca, Bergamo, Italy
Tim Maughan, Oxford, UK
Peter Naredi, Gothenburg, Sweden
Gerald Prager, Vienna, Austria
Jens Ricke, Munich, Germany
Ramon Salazar, Barcelona, Spain
Owen Sansom, Glasgow, UK
Karen-Lise Spindler, Aarhus, Denmark
Alexander Stein, Hamburg, Germany
Julien Taieb, Paris, France
Vincenzo Valentini, Rome, Italy

Gastrointestinal tumours, non-colorectal
Chair: Yoon-Koo Kang, Seoul, Republic of Korea
Stefano Cascinu, Modena, Italy
Ann-Lii Cheng, Taipei, Taiwan
Michel Ducreux, Villejuif, France
Manuel Hidalgo, Madrid, Spain
Florian Lordick, Leipzig, Germany
Eileen Mary O'Reilly, New York, NY, USA
Cornelis van de Velde, Leiden, The Netherlands
Marcel Verhei, Nijmegen, The Netherlands
Ian Chau, Sutton, UK
Claus-Henning Koehne, Oldenburg, Germany
Andrew Biankin, Glasgow, UK
Claus Jorgensen, Manchester, UK

Genitourinary tumours, prostate
Chair: Silke Gillessen, Manchester, UK and St. Gallen, Switzerland
Himisha Beltran, New York, NY, USA
Johann de Bono, Sutton, UK
Ignacio Durán, Seville, Spain
Chris Parker, London, UK
Eleni Efstathiou, Houston, TX, USA
Nicholas James, Birmingham, UK
Bertrand Tombal, Brussels, Belgium
Scott Tomlins, Ann Arbor, MI, USA
Aristotelis Bamias, Athens, Greece
Ronald de Wit, Rotterdam, The Netherlands
David Waugh, Belfast, UK
Robert Bristow, Manchester, UK

Genitourinary tumours, non-prostate
Chair: Karim Fizazi, Villejuif, France
Axel Bex, Amsterdam, The Netherlands
Petri Bono, Helsinki, Finland
Gedske Daugaard, Copenhagen, Denmark
Jourik Gietema, Groningen, The Netherlands
Marco Gizzi, Charleroi, Belgium
Andrea Necchi, Milan, Italy
Thomas Powles, London, UK
Anna Patrikidou, Sutton, Surrey, UK
Maria De Santis, Coventry, UK
Cora Sternberg, Rome, Italy
Laurence Albiges, Villejuif, France
Fernando Calais da Silva, Lisbon, Portugal

Gynaecological cancers
Chair: Susana Banerjee, London, UK
Antonio González-Martin, Madrid, Spain
Philipp Harter, Essen, Germany
David Huntsman, Vancouver, BC, Canada
Domenica Lorusso, Milan, Italy
Christian Marth, Innsbruck, Austria
Ana Oaknin, Barcelona, Spain
Sandro Pignata, Naples, Italy
Isabelle Ray-Coquard, Lyon, France
Cristiana Sessa, Bellinzona, Switzerland
Karina Dahl Steffensen, Vejle, Denmark
Jonathan Ledermann, London, UK

Haematological malignancies
Chair: Marco Ladetto, Alessandria, Italy
Christian Buske, Ulm, Germany
Elias Campo, Barcelona, Spain
Martin Dreyling, Munich, Germany
Andrea Filippi, Turin, Italy
Martin Jädersten, Stockholm, Sweden
Steven Le Gouill, Nantes, France
Andrés José María Ferreri, Milan, Italy
Bruno Paiva, Pamplona, Spain
Michele Ghielmini, Bellinzona, Switzerland
John Radford, Manchester, UK

Immunotherapy of cancer
Chair: George Coukos, Lausanne, Switzerland
Helen Gogas, Athens, Greece
Periklis Foukas, Lausanne, Switzerland
John Haanen, Amsterdam, The Netherlands
Fernanda Herrera, Lausanne, Switzerland
Aurélien Marabelle, Villejuif, France
Inge-Marie Svane, Herlev, Denmark
Fiona Thistlethwaite, Manchester, UK
Ulrich Keilholz, Berlin, Germany
Athanasios Kotsakis, Heraklion, Greece
Eli Pikarsky, Jerusalem, Israel
Johanna Joyce, Lausanne, Switzerland

NETs and endocrine tumours
Chair: Marianne Pavel, Erlangen, Germany
Eric Baudin, Villejuif, France
Detlef K. Bartsch, Marburg, Germany
Martin Fassnacht, Würzburg, Germany
Rocio Garcia Carbonero, Madrid, Spain
Andreas Kjaer, Copenhagen, Denmark
Matthew Kulke, Boston, MA, USA
George Pentheroudakis, Ioannina, Greece
Guido Rindi, Rome, Italy
Alfredo Berruti, Brescia, Italy
Nicola Fazio, Milan, Italy
Jérôme Bertherat, Paris, France

Head and neck cancer
Chair: Amanda Psyrri, Athens, Greece
Ana Castro, Porto, Portugal
Ezra Cohen, San Diego, CA, USA
Sandrine Faivre, Paris, France
Alessandro Franchi, Florence, Italy
Jean-Pascal Machiels, Brussels, Belgium
Hisham Mehanna, Birmingham, UK
Marco Merlano, Cuneo, Italy
Esat Mahmut Ozsahin, Lausanne, Switzerland
Irene Braña, Barcelona, Spain
Lisa Licitra, Milan, Italy
Paul Brennan, Lyon, France
Kevin Harrington, London, UK

Melanoma and other skin tumours
Chair: Caroline Robert, Villejuif, France
Paolo Ascierto, Naples, Italy
Reinhard Dummer, Zurich, Switzerland
Paul Lorigan, Manchester, UK
Georgina Long, Sydney, Australia
Celeste Lebbé, Paris, France
Antoni Ribas, Los Angeles, CA, USA
Piotr Rutkowski, Warsaw, Poland
Susana Puig Sarda, Barcelona, Spain
James Larkin, London, UK
Ignacio Melero, Pamplona, Spain
Daniel Peeper, Amsterdam, The Netherlands
Marisol Soengas, Madrid, Spain

Non-metastatic NSCLC and other thoracic malignancies
Chair: Enriqueta Felip, Barcelona, Spain
Lukas Bubendorf, Basel, Switzerland
Wilfried Eberhardt, Essen, Germany
Cécile Le Pechoux, Villejuif, France
Silvia Novello, Orbassano, Italy
Suresh Ramalingam, Atlanta, GA, USA
Paul Van Schil, Edegem, Belgium
Johan Vansteenkiste, Leuven, Belgium
Heather Wakelee, Stanford, CA, USA
Corinne Faivre-Finn, Manchester, UK
Pieter Postmus, Leiden, The Netherlands
Mariano Barbacid, Madrid, Spain
John Brognard, Bethesda, MD, USA

NSCLC, metastatic
Chair: Martin Reck, Grosshansdorf, Germany
Benjamin Besse, Villejuif, France
Dirk De Ruysscher, Maastricht, The Netherlands
Simon Ekman, Stockholm, Sweden
Keith Kerr, Aberdeen, UK
Tony SK Mok, Hong Kong, China
Sanjay Popat, London, UK
Noemi Reguart, Barcelona, Spain
James Spicer, London, UK
Raffaele Califano, Manchester, UK
Federico Cappuzzo, Ravenna, Italy
Charles Rudin, New York, NY, USA

Public health and health economics
Chair: Carin Uyl-de Groot, Rotterdam, The Netherlands
Peter Boyle, Ecully, France
Elisabeth de Vries, Groningen, The Netherlands
Ferry A.L.M. Eskens, Rotterdam, The Netherlands
Jan de Maeseneer, Ghent, Belgium
Maarten IJzerman, Enschede, The Netherlands
Michel Coleman, London, UK
Beth Woods, New York, NY, USA
Alex Eniu, Cluj-Napoca, Romania
Francesco Perrone, Naples, Italy

Sarcoma
Chair: George Demetri, Boston, MA, USA
Sebastian Bauer, Essen, Germany
Sylvie Bonvalot, Paris, France
Rick Haas, Amsterdam, The Netherlands
Robin Jones, London, UK
Daniela Katz, Jerusalem, Israel
Maud Toulmonde, Bordeaux, France
Eva Wardelmann, Muenster, Germany
Paolo G. Casali, Milan, Italy
Axel Le Cesne, Villejuif, France
Jonathan Fletcher, Boston, MA, USA

Supportive and palliative care
Chair: Karin Jordan, Heidelberg, Germany
Matti Aapro, Genolier, Switzerland
Guido Cavaletti, Milan, Italy
Annie Young, Coventry, UK
Joern Herrstedt, Odense, Denmark
Stein Kaasa, Trondheim, Norway
Dorothy Keefe, Adelaide, Australia
Christina Ruhlmann, Odense, Denmark
Anton Snegovoy, Moscow, Russia
Florian Scotté, Paris, France
Florian Strasser, St. Gallen, Switzerland

Translational research
Chair: Fabrice André, Villejuif, France
Caroline Dive, Manchester, UK
Gert Attard, Sutton, UK
René Bernards, Amsterdam, The Netherlands
Emiliano Calvo, Madrid, Spain
Rodrigo Dienstmann, Barcelona, Spain
Dennis Lo, Hong Kong, China
Peter Kuhn, Los Angeles, CA, USA
Sergio Quezada, London, UK
Pierre Saintigny, Lyon, France
Bakhos A. Tannous, Boston, MA, USA
Nicola Normanno, Naples, Italy
Giampaolo Tortora, Verona, Italy

The European Society for Medical Oncology wishes to express its appreciation and gratitude to all of the above experts for their major effort in reviewing and selecting the content of this Abstract Book.

EONS11 at ESMO 2018

Scientific Committee
Co-Chair: Lena Sharp, Stockholm, Sweden
Valentina Biagioli, Rome, Italy
Eileen Furlong, Dublin, Ireland
Patrick Jahn, Halle, Germany
Gabi Knotgen, Munich, Germany
Co-Chair: Daniel Kelly, Cardiff, UK
Harald Titzer, Vienna, Austria
Emma Woodford, Brussels, Belgium
Christian Wylegalla, Freiburg, Germany

The European Oncology Nursing Society wishes to express its appreciation and gratitude to all of the above experts for their major effort in reviewing and selecting the Cancer Nurses content of this Abstract Book

ACKNOWLEDGEMENT

ESMO gratefully acknowledges the valuable contribution of the following organisations in the ESMO 2018 Congress through their presence in the exhibition hall, organisation of satellite symposia sessions, or via sponsorship activities (as of August 2018).

10x Genomics
AbbVie, Inc.
Accell Clinical Research
Accord Healthcare
Advanced Accelerator Applications
Almac Diagnostics
Amgen (Europe) GmbH
Amoy Diagnostics Co., Ltd.
Aptitude Health
Aptus Health
ArcherDX
AROG Pharmaceuticals
Astellas Pharma Europe Ltd.
AstraZeneca
Bavarian Nordic
Baxter Healthcare SA
Bayer
Beacon Medicare Limited
BeiGene, Ltd.
Biocartis NV
Bioclinica
Biocytogen LLC
Biomapas
Biopticon
Bio-Rad Laboratories GmbH
Biotype
BMJ
BMS Pfizer Alliance
Boehringer Ingelheim
Bristol-Myers Squibb
Calithera Biosciences
Cancers MDPI
Caris Life Sciences
Catalysis S.L.
Celgene
Celldex Therapeutics
Celltrion Healthcare Co., Ltd.
Cepheid
Clinical Research Malaysia (CRM)
Clovis Oncology
Cmed
Colloboration for Oncology Data in Europe (CODE)
Covance/Chiltern
Covaris
Daiichi-Sankyo
DAVA Oncology
Definiens
Delcath Systems
DocCheck Medical Services GmbH
Dr. Reddys Laboratories
ECS-Screening
Eisai Europe Ltd.
Elsevier B.V.
EMJ - European Medical Journal
Erytech Pharma
Eurofins Clincial Diagnostics
Europital
EUSA Pharma (UK) Ltd.
Exelixis
F.Hoffmann-La Roche
Fresenius Kabi
Gedeon Richter
Genmab
Genomic Health International Sarl
geneXplain GmbH
Gilead Sciences Inc.
GSK
HalioDx
Halozyme
Helsinn Healthcare SA
HTG Molecular Diagnostics
IBM Watson Health
Ice Cold Mouthpiece
Immunomedics
Incyte Biosciences International Sarl
Institut Curie
Invivoscribe
Iovance Biotherapeutics
Ipsen
IQVIA
ITM Isotopen Technologien Muenchen AG
JAMA Network
Janssen
Karger Publishers
LeCancer.fr
Lilly
Loxo Oncology, Inc.
M3 Global Research
MacroGenics, Inc.
medac GmbH
Median Technologies
Medifood Hungary Innovation Kft
Medscape Oncology
Merck
MGZ - Medical Genetics Center
Molecular Health GmbH
MSD
Mylan
Myriad Genetics
NanoString Technologies
NEJM Group
NeoGenomics
Noona Healthcare Oy
Novartis Oncology
Novella Clinical, a Quintiles company
Novosanis NV
Nutricia Advanced Medical Nutrition
Omnicare Pharma GmbH
Oncare GmbH
OncLive
OncoDNA S.A.
Oncology Central
Oncology Learning Network
oncomark Ltd.
ONCOMPASS Medicine
Oxford University Press
Paxman
Paxxo AB
PER Global, LLC
Personal Genome Diagnostics
Pfizer Oncology
PharmaMar
Pharmadab d.o.o.
Phillips Molecular
Pierre Fabre Oncology
Pivotal
Precision for Medicine, Oncology and Rare Disease
prIME Oncology
Puma Biotechnology
Rakuten Aspyrian
Samsung Bioepis Co., Ltd.
Sandoz
Sanofi Genzyme
Seattle Genetics
SeraCare Life Sciences
Servier
Sivan Innovation Ltd.
Sophia Genetics
Sotio a.s.
Springer Healthcare
STADAPHARM GmbH
Stemline Therapeutics
Stilla Technologies
Sysmex Inostics GmbH/Sysmex Europe GmbH
Takeda Oncology
Tesaro
TEVARIS GmbH
The Video Journal of Oncology
Thermo Fisher Scientific
Varian Medical Systems
Wisepress Ltd.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii1–viii13, 2018
doi:10.1093/annonc/mdy268

BASIC SCIENCE

1O KRAS mutant and RAS/BRAF wild type colorectal cancer cells exhibit differences in the rewiring of signal transduction that can impact on future therapeutic strategies

A. Georgiou[1], A. Stewart[2], P. Thavasu[2], E.A. Coker[2], S. Poelsterl[2], B. Al-Lazikani[2], D. Cunningham[3], S. Whittaker[2], U. Banerji[4]

[1]Cancer Therapeutics, Institute of Cancer Research/ Royal Marsden NHS Foundation Trust, Sutton, UK, [2]Cancer Therapeutics, Institute of Cancer Research, Sutton, UK, [3]Medicine, Royal Marsden NHS Foundation Trust, Sutton, UK, [4]Drug Development Unit, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, UK

2O Receptor tyrosine kinase dependent PI3K activation is an escape mechanism to vertical suppression of the EGFR/RAS/MAPK pathway in KRAS-mutated colorectal cancer cell lines

P.P. Vitiello[1], C. Cardone[1], D. Ciardiello[1], G. Barra[1], N. Matrone[1], V. Belli[1], G. Martini[2], L. Poliero[1], C. Borrelli[1], M. Terminiello[1], T. Troiani[1], F. Morgillo[1], F. Ciardiello[1], E. Martinelli[1]

[1]Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [2]Centro Cellex, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

3PD Human melanoma cells from different disease stages prime amino acid signature of conditional media indicating signalling in the tumor microenvironment

M. Hohenegger[1], C. Wasinger[1], A. Hofer[2], O. Spadiut[2]

[1]Pharmacology, Medical University Vienna, Vienna, Austria, [2]Institute for Chemical, Enviromental and Biological Engineering, Technical University Vienna, Vienna, Austria

4PD Immunomodulatory effect of hepatocyte growth factor on monocytes in human gastric cancer

L. Hirsch[1], J. Palle[1], A. Lapeyre-Prost[1], S. Pernot[1], T. Voron[1], E. Tartour[1], J. Taieb[2], M. Terme[1]

[1]INSERM U970, Paris Cardiovascular Research Center, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [2]Department of Gastroenterology and Digestive Oncology, Hôpital Européen Georges-Pompidou, Paris, France

5PD Patritumab (anti-HER3 antibody) augments anti-tumor immune response of adoptive transfer of autologous activated T cells for patient-derived xenograft models of breast cancer

E. Suzuki, T. Kotake, T. Nishimura, A. Yamaguchi, F. Pu, M. Toi

Breast Surgery, Kyoto University-Graduate School of Medicine, Kyoto, Japan

6P Molecular characterization and search for founding effects in Canarian families with hereditary breast and ovarian cancer syndrome

E. Llabres Valenti[1], A.M. Sanchez de Abajo[2], J. Brenes Castro[1], A. Ramchandani Vaswani[1], A. Gómez de Liaño[1], A. Hernández[1], M. Cejuela[1], J.A. Rodriguez Garcia[1], E. González[1], E. Vicente[1]

[1]Medical Oncology, Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain, [2]Biochemistry, Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain

Background: The Hereditary Breast and Ovarian Cancer Syndrome (HBOC) is an autosomal dominant disease caused by germline mutations in BRCA1 (17q21) and BRCA2 (13q12) genes. The identification of BRCA1/2 genes has represented a great advance in the management of families with HBOC allowing carriers to follow up personalized and early detection of tumors at a very early stage.

Methods: Descriptive study of the Canarian families with mutation in BRCA1/2, analyzing clinical, anatomopathological and resulting parameters of the genetic analysis. The screening of point mutations was performed in all exons encoders and adjacent intron sequences by HRM (High Resolution Melting) and subsequent characterization of the patterns altered by sequencing direct. The study of large genomic rearrangements was carried out by MLPA (Multiplex Ligation-dependent Probe Amplification).

Results: Of the 611 families evaluated in the hereditary cancer clinic, 385 have genetic test completed. 55 families have been identified with a pathogenic mutation (14.2%); 36 different mutations (19 in BRCA1 (32 families) and 17 in BRCA2 (23 families). The spectrum of pathogenic mutations identified in the BRCA1 gene suggested strong founder effects on the island of Gran Canaria, where we have detected a recurrent mutation [c.3582-3589del8] (p.His1195PhefsTer21)] that explains more than 70% of families with mutation in BRCA1.

Conclusions: The percentage of pathogenic mutations in Canary HBOC families was 14.2%, similar to that detected in other populations. However, our data showed the presence of a founding mutation which explains more than 70% of our families in Gran Canaria with mutation in BRCA1, which could help us to optimize the algorithms for the study of mutations in these genes.

Legal entity responsible for the study: Elisenda Llabrés Valentí.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

7P Effect of the polymorphism rs2066844 of the NOD2 gene on colon cancer incidence in a high cardiovascular risk population: Modulation by gender

J.B. Ramirez Sabio[1], J.V. Sorlí[2], I. González-Monje[2], C. Ortega-Azorín[2], Ó. Coltell[3], D. Corella[2]

[1]Medical Oncology, Hospital de Sagunt, Sagunt, Spain, [2]Preventive Medicine Department and CIBER Fisiopatología de la Obesidad y Nutrición, Universitat de València, Valencia, Spain, [3]Computer Languages and Systems, Universitat Jaume I, Castellón, Spain

Background: The nucleotide-binding oligomerization domain containing 2 (NOD2) gene is located on chromosome 16q21. It is expressed in monocytes, macrophages, epithelium of the digestive tract, breast, lung and in the kidney and is associated with the chronic inflammatory process and regulating apoptosis. A crucial role has been described in the maintenance of immune homeostasis and in the relationship with the microbiota. This gene has been linked to diseases such as Crohn's disease but also to gastric cancer, colon, endometrium, breast, ovary, bladder, lung or larynx. Our aim has been to estimate the association between polymorphism rs2066844 of the NOD2 gene on colon cancer by gender in a Mediterranean population.

Methods: We have carried out an observational study at baseline and longitudinally in the PREDIMED-Valencia study including 1094 participants (696 women) at high cardiovascular risk aged 67±6 years. We prospectively analyzed cancer incidence as a secondary outcome in this study. Lifestyle, clinical and biochemical variables were assessed by standardized methods. DNA was isolated from blood and the selected polymorphisms were determined.

Results: We detected 21 new cases of colon cancer from 2003 to 2014, representing 1.9% of all cancers and 10% of all cancer cases in men and 11% in women respectively. In our study it was observed that the variant rs2066844 was related to the new cases of colon cancer in women but not in men. The allelic frequency of the T allele was 0.054, for which the carriers of the T allele were grouped in front of the CC carriers. When assessing the risk of having suffered colon cancer according to the genotype of this variant, it was observed that the individuals carrying the T allele presented a higher risk OR = 8.7: CI 95% (2.2-23.4); P = 0.002 after adjustment for sex, age, intervention group, tobacco smoking, alcohol drinking and intake of omega-3 fatty acids.

Conclusions: rs2066844 of the NOD2 gene could be associated with colon cancer in women in a high cardiovascular risk population.

Clinical trial identification: ISRCTN35739639.

Legal entity responsible for the study: University of Valencia.

Funding: Instituto de Salud Carlos III.

Disclosure: All authors have declared no conflicts of interest.

8P Effect of the polymorphisms rs1476413, rs1801131, rs4846052 and rs6541003 of the MTHFR gene on prostate cancer in a high cardiovascular risk population

J.B. Ramirez Sabio[1], J.V. Sorlí[2], C. Ortega-Azorín[2], J.A. Pérez-Fidalgo[3], E.M. Asensio[2], D. Corella[2]

[1]Hospital de Sagunt, Sagunt, Valencia, Spain, [2]Preventive Medicine and CIBER Fisiopatología de la Obesidad y Nutrición, Universitat de València, Valencia, Spain, [3]Medical Oncology, Hospital Clínico Universitario de València, Valencia, Spain

Background: Some genetic variants of the Methylenetetrahydrofolate Reductase (MTHFR) gene can lead to high levels of homocysteine and hinder the ability to process folate. Some genetic variants of this gene are related to susceptibility of many diseases such as cancer. Our aim has been to estimate the association between polymorphisms rs1476413, rs1801131, rs4846052 and rs6541003 of the MTHFR gene on prostate cancer in a Mediterranean population.

Methods: We have carried out an observational study at baseline and longitudinally in the PREDIMED-Valencia study including 398 men at high cardiovascular risk. We prospectively analyzed cancer incidence as a secondary outcome in this study. Lifestyle, clinical and biochemical variables were assessed by standardized methods. DNA was isolated from blood and the selected polymorphisms were determined.

Results: We detected 21 new cases of prostate cancer from 2003 to 2014, representing 1.9% of all cancers and 5.3% of all cancer cases in men. The analysis of the risk of prostate cancer in the variants described was carried out grouping the carriers of the allele less frequent. The allelic frequency of the rs1476413 was 0.219 for not affected participants while it was 0.074 in the cases. The crude OR = 0.24 (95%CI 0.08-0.74) p = 0.013 and OR = 0.23 (95%CI 0.08-0.71) p = 0.010 after adjustment (by age, intervention group and smoking habit). For the rs1801131, the allelic frequency was 0.271 for not affected participants while it was 0,148 in the cases. The crude OR = 0.33 (95%CI 0.13-0.83) p = 0.019 and OR = 0.33 (95%CI 0.13-0.84) p = 0.020 after adjustment. For the rs4846052, the allelic frequency was 0.390 for not affected participants while it was 0.278 in the cases. The crude OR = 0.43 (95%CI 0.19-0.95) p = 0.038 and OR = 0.43 (95%CI 0.19-0.97) p = 0.043 after adjustment. For the rs6541003 was the allelic frequency was 0.380 for not affected participants while it was 0.259 in the cases. The crude OR = 0.39 (95%CI 0.17-0.87) p = 0.021 and OR 0.39 (95%CI 0.17-0.88) p = 0.023 after adjustment.

Conclusions: The rs1476413, rs1801131, rs4846052 and rs6541003 of the MTHFR gene were protective against the development of prostate cancer in a high cardiovascular risk population.

Clinical trial identification: ISRCTN35739639.

Legal entity responsible for the study: University of Valencia.

Funding: Instituto de Salud Carlos III.

Disclosure: All authors have declared no conflicts of interest.

9P Association of a genetic variant in cyclin-dependent kinase inhibitor 2A gene with the increased risk of breast cancer

S. Shahid Sales[1], M. Mehramiz[2], S.A. Aledavood[3], M. Joudi Mashhad[4], S. Ahmadi Simab[3], A. Avan[2]

[1]Clinical Oncology, Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [2]Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, [3]Cancer Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Background: Breast cancer is second leading cause of cancer-related-deaths in women, supporting the need for the detection of novel prognostic biomarkers for risk stratification. There is growing body of evidence showing the association of common genetic variants on chromosome 9p21 with an increased risk of developing different tumors and metabolic disorders. Here we investigated the association of a genetic variant in CDKN2A/B, rs1333049, for the first time in 303 subjects with and without breast cancer.

Methods: Method: Genotyping was carried out using TaqMan real time PCR method in case and control groups. The associations of this genetic variant were evaluated with breast cancer risk and pathological information of patients.

Results: We observed that the minor allele homozygote situation of this genetic variant in total population was 10%, while this condition in heterozygote was 38%. the logistic regression under recessive genetic model revealed that breast cancer patients with GG genotype had higher risk of breast cancer, compared to CC/CG genotypes (e.g., OR = 2.8, 95% CI:1.4-5.4, p = 0.001), after adjusted for age, and BMI.

Conclusions: We demonstrated that patients carrying the GG genotype for CDKN2A/B rs1333049 polymorphism had an increased risk of breast cancer susceptibility, indicating further studies in a larger and prospective setting to show the value of emerging marker as a risk stratification biomarker in breast cancer.

Legal entity responsible for the study: Mashhad University of Medical Sciences, Mashhad, Iran.

Funding: Mashhad University of Medical Sciences, Mashhad, Iran.

Disclosure: All authors have declared no conflicts of interest.

10P Investigating the role of HAT protein TIP60 in regulating functional dynamics of nuclear receptor PXR

K. Bakshi

Lifescience, Shiv Nadar University, Greater Noida, India

Background: PXR (Pregnane Xenobiotic Receptor) belongs to the class II family of nuclear receptor (NR). PXR is considered as a master regulator of xenobiotic metabolism. PXR gets activated in a ligand-dependent manner and then heterodimerizes with RXR. PXR can also get activated via post-translational modifications and leads to cross-talk between signaling pathways. PXR is shown to be acetylated in vivo and this acetylation regulates its selective functions independent of ligands. However, the molecular players behind this acetylation and the impact of this acetylation in intracellular dynamics of PXR is not known. TIP60 is a lysine acetyltransferase which acetylates histones as well as non-histone proteins like ATM/ATR kinases and p53, and plays a role in DNA damage and repair pathway and in apoptosis. TIP60 is shown to interact with class I of NR. Thus, it might be interesting to reveal the role of TIP60 in acetylation of class II NR PXR.

Methods: We performed in vitro and in vivo co-immunoprecipitation assay and live cell imaging to show interaction as well as domain mapping. We found the site of acetylation in PXR by in silico and in vitro assay. To examine whether TIP60-PXR complex has any influence on these cellular processes, we performed cell migration, cell adhesion, cell proliferation and cell invasion assays.

Results: In this study, we are trying to dissect the mechanism of PXR activation and functional dynamics by TIP60 dependent acetylation. We found the sites of interaction as LBD of PXR with NR box of TIP60 and thus TIP60 mediated subcellular dynamics of PXR. Also, we have found TIP60 mediated the acetylation site of PXR at lysine 170. This novel complex is independent of ligand and does not form a complex with RXR. Also, this complex does not activate ligand dependent PXR target genes. Interestingly, PXR augments TIP60 acetylation on histones. We further discovered TIP60-PXR complex promotes cell migration and adhesion, which might lead to their involvement in physiological or pathophysiological conditions.

Conclusions: This is the first report demonstrating the exclusive interaction of TIP60 with unliganded PXR and uncovers a potential role for the TIP60-PXR complex in cell migration and cell adhesion.

Legal entity responsible for the study: ICMR and Shiv Nadar University.

Funding: ICMR.

Disclosure: The author has declared no conflicts of interest.

11P The role of downregulated SIRT3 expression in patients with hepatocellular carcinoma

H. Jo, S. Hwang, M. Lee

Division of Life Sciences, College of Life Science and Bioengineering, Incheon University, Incheon, Republic of Korea

Background: Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer-related deaths worldwide. The only drug currently approved for clinical use in the treatment of advanced HCC is sorafenib, a tyrosine kinase inhibitor. However, many patients with HCC are resistant to sorafenib and sensitivity to sorafenib differs according to the progression of liver cancer. SIRT3, a member of the mammalian sirtuin family, is localized to the mitochondria and regulates metabolic activity. To date, a few studies have investigated the effects of SIRT3 on prognosis and drug resistance in patients with HCC.

Methods: A correlation study between SIRT3 and other genes was conducted through the TCGA online data portal site (http://cancergenome.nih.gov). To determine the protein expression of SIRT3, immunohistochemistry (IHC) was performed with liver cancer tissue using various antibodies. To investigate whether the expression of SIRT3 in HCC is related to the resistance to sorafenib, we treated sorafenib after the modulation of SIRT3 levels in HCC cell lines (overexpression in Huh7, knockdown in HepG2 and Hep3B cells) and conducted functional assays.

Results: We identified that SIRT3 expression is downregulated in patients with HCC and high GLUT1 (glucose metabolism index) and Ki67 (proliferation index) expression. In addition, analysis of Cancer Imaging Archive data (TCGA) revealed a negative correlation between GLUT1 and SIRT3 mRNA expression and also HIF1a and SIRT3 mRNA expression. There was also a negative correlation between Ki67 and SIRT3 mRNA expression. After sorafenib treatment, SIRT3 protein expression was highly downregulated in various HCC cell lines (HepG2/Hep3B/SK-Hep1/Huh7). These cells altered their therapeutic resistance to sorafenib via SIRT3 modulation through a 2 dimensional (D)/3D cell culture system.

Conclusions: Taken together, our results show that SIRT3 acts as a tumor suppressor and plays an important role in therapy resistance for HCC.

Legal entity responsible for the study: Misu Lee.

Funding: The National Research Foundation of Korea (Seoul, Korea; Grant Nos. NRF-2015R1D1A1A01057737, NRF-2018R1C1B6003894).

Disclosure: All authors have declared no conflicts of interest.

12P Prediction of and intervention in colorectal cancer risk with artificial intelligent system

Y. Ge[1], C.W. Ma[2], L. Tao[1], M.F. Han[1], L. Ma[3], G. Li[4], L.M. Ma[3], Q. Lu[2], Z. Wu[3], P.F. Yu[3], Y.F. Yang[3], Y.Y. Ma[2], B.B. Song[3], W. Gao[3]

[1]Research Center, Fuyang City No.2 Hospital, Fuyang, China, [2]Scientific Research, American Intelligent Health, Bellevue, WA, USA, [3]Scientific Research, Beijing Yiwang Data Technology, Beijing, China, [4]Research Support, Fu Wai Hospital, Beijing, China

Background: Colorectal cancer is the third most common cancer worldwide, with nearly 1.4 million new cases diagnosed in 2012. It is also one of the most common cancers in China, with nearly 200,000 people dying annually as a result of colorectal cancer. Prediction and intervention of colorectal cancer risk would save millions of lives worldwide. The purpose of this study is to provide a simple, effective and economic method to help people predict and intervene in colorectal cancer risk.

Methods: A total of 720182 subjects including 18406 colorectal cancer patients and 701776 normal people (see the table for details) were involved in the study. The data were used in the study including demographic, CBC, CMP, lipids and urinalysis data. Analysis of covariance, logistic analysis and discriminant analysis were used to identify the significant factors and to build the colorectal cancer risk prediction model and the significant level was set at $p < 0.05$. SAS was used as the primary statistical analysis tool.

Table: 12P Subject by gender

Subject	2012-2015				2016			
	Male	Female	Total	% of Males	Male	Female	Total	% of Males
Colorectal cancer patients	8,002	5,224	13,226	60.5%	3,115	2,065	5,180	60.1%
Healthy individuals	335,021	205,678	540,669	62.0%	99,349	61,728	161,077	61.7%
Total	343,023	210,902	553,925	61.9%	102,464	63,793	166,257	61.6%

Results: The analysis showed that CBC, CMP, lipids and urinalysis data can significantly distinguish healthy individuals from colorectal cancer patients and those data can be used to build colorectal cancer risk prediction models. The predicting accuracy was 96.1% and the clinical verification rate was 95.7%. Top parameters were selected through the discriminant analysis and logistic analysis. Some parameters, such as red cell distribution width, red cell count, leukocyte percentage and age are positively correlated with colorectal cancer risk, and others, such as albumin, platelet count, hematocrit and platelet distribution width are negatively correlated with colorectal cancer risk.

Conclusions: This research shows that the routine blood and urine test results can be used to predict colorectal cancer risks and the accuracy of the prediction is over 95%. The research would provide an effective, convenient and economical method to help people predict and intervene in colorectal cancer risk.

Legal entity responsible for the study: Fuyang No2. Hospital and Beijing Yiwang Data Technology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

13P Measuring the efficiency of cancer care in Europe

R. Althin[1], R. Färe[2], S. Grosskopf[2], B. Jönsson[3], N. Wilking[4]

[1]Research, The Swedish Institute for Health Economics, Lund, Sweden, [2]Economics, Oregon State, Corvallis, OR, USA, [3]Economics, Stockholm School of Economics, Stockholm, Sweden, [4]Oncology, Skane University Hospital, Lund, Sweden

Background: The rationale of this study is to develop the use of Data Envelopment Analysis (DEA) to measure and compare the efficiency of breast and lung cancer care in Europe in order to inform related policy discussions. In the wake of the increasing prevalence of cancer and pressures on constrained healthcare budgets, understanding how to make the most of available resources is essential to sustainable cancer care. DEA is a well-established instrument capable of identifying best practice in a complex production process such as cancer care with rapid change in technologies. DEA could be used to compare different production units such as e.g., countries, regions, or hospitals. In this study, we use real life data to evaluate the country specific performance of cancer care in Europe.

Methods: DEA is capable of handling many inputs and many outputs simultaneously to estimate the best practice of cancer care. The method is independent of unit of measurement allowing for the use of input and output quantities measured in different units. No data on prices are needed. For this application publicly available, aggregate, retrospective, and comparable data on breast cancer (BC) and lung cancer (LC) from Eurostat, WHO, and OECD was used in the analysis. In the model input variables such as number of radiation units, number of oncologists, and oncology drugs was used to produce survival and quality of life.

Results: The data displayed large differences in both inputs and outputs between countries and over time (2001-2015) and this was reflected in the performance measures. The efficiency base case in 2015 in BC identified 6 efficient countries out of the 23 included with a mean inefficiency of 80% and a minimum of 0.49%, i.e. the same outcome could have been produced with 49% of the inputs used. In the 2015 LC base case there were 8 efficient countries with a mean inefficiency of 82% (minimum 0.51%).

Conclusions: DEA is a policy relevant approach to measure and improve cancer care efficiency in Europe in order to provide information for decisions aimed at reducing waste and ensure better outcomes for patients. The research highlights key inefficiencies and opportunities to improve resource allocation in European cancer care.

Legal entity responsible for the study: The Swedish Institute for Health Economics.

Funding: Bristol-Myers Squibb.

Disclosure: All authors have declared no conflicts of interest.

14P Circulating cell-free DNA isolated from plasma of mesenteric veins predicts prognosis in stage II colorectal cancer patients

C-Y. Yang[1], C-H. Lin[2], J-K. Jiang[3]

[1]Department of Education and Research, Taipei City Hospital, Taipei, Taiwan, [2]Institute of Microbiology and Immunology, National Yang-Ming University, Taipei, Taiwan, [3]Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan

Background: It is difficult to predict relapse in patients with stage II colorectal cancer (CRC). In recent years, circulating cell-free DNA (cfDNA) from peripheral blood represents a promising biomarker for detection, monitoring and survival prediction of metastatic colorectal cancer (CRC). However, its prognostic significance in patients with stage II CRC remains uncertain.

Methods: In this study, the blood samples were drawn from mesenteric vein (MV) and peripheral vein (PV). MV and PV cfDNA level was quantified by real-time quantitative PCR of ALU repeats. The cfDNA from MV and PV was quantified and the correlation among the cfDNA concentration, clinicopathological features and multivariate survival was analyzed in CRC patients.

Results: Our results showed the MV cfDNA concentrations were lower in early stage than late stage CRC. We also found that MV cfDNA level was positively correlated with tumor size. Stage II CRC patients with higher cfDNA concentrations have better prognosis than those with lower cfDNA concentrations.

Conclusions: These results indicated that MV cfDNA concentration has prognostic value in stage II CRC patients and may act as an additional biomarker in stage II CRC patients for receiving chemotherapy criteria.

Legal entity responsible for the study: Chih-Yung Yang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

15P Clonality of uterine carcinosarcoma as a factor of clinical prognosis

N. Levitskaya[1], O. Vostriukhina[2], I. Poddubnaia[1]

[1]Oncology, Russian Medical Academy of Continuous Vocational Training, Moscow, Russian Federation, [2]Molecular and Radiation Biophysics, Petersburg Nuclear Physics Institute Named by B.P. Konstantinov, Leningradskaya Oblast, Gatchina, Russian Federation

Background: Uterine carcinosarcoma is a malignant mixed Mullerian tumour, composed of epithelial and stromal components. Most uterine carcinosarcomas are monoclonal tumours, but a small proportion of them is a collision of carcinoma and sarcoma.

Methods: This research is based on the investigation of formalin-fixed, paraffin-embedded tissue blocks from 13 women undergoing primary surgical treatment between 1961–2010, that were retrieved from the archival collections of the pathoanatomical department of the Institute of Oncology named after N.N. Petrov. Mutations of TP53, PTEN and K-RAS genes were analyzed to determine clonality of uterine carcinosarcoma. DNAs were extracted by proteinase K digestion («Fisher» US) by the method of Herrington, C.S. & McGee, J.O. Mutations of TP53, PTEN and K-RAS were defined by single-strand conformation polymorphism with the next sequence. The found mutations in the TP53 (exons 5-9), PTEN (exons 5, 8), K-RAS (exon 1) genes were compared in epithelial and stromal components of 13 uterine carcinosarcomas. The tumours were classified as monoclonal in the presence of identical mutations in epithelial and stromal components, in the presence of different mutations - as biclonal. Of 13 cases 7 (53.8%) were monoclonal, 6 (46.2%) – biclonal.

Results: We evaluated clinical and histopathologic features of monoclonal and biclonal uterine carcinosarcomas. Monoclonal tumours showed worse prospects than the biclonal ones: 1-yr overall survival - 20% vs 37% ($p = 0.0078$). In all cases (100%) of monoclonal tumors the average length of full remission was three times shorter than in cases of biclonal tumours.

Table: 15P Comparison of monoclonal and biclonal carcinosarcomas

Clinical and morphological features of uterine carcinosarcoma	Monoclonal tumours	Biclonal tumours	p ≦
Tumours invades the serosa of the corpus uteri, %	100 %	50 %	$p < 0.0001$
Lymphovascular invasion	80%	0	$p < 0.0001$
Average size of the tumour (cm^3)	1305.8	131.5	$p < 0.05$
Length of full remission	7.75	24.6	$p < 0.05$

Conclusions: Clonality of the uterine carcinosarcomas may be a clinical marker as it determines the prospects of the disease, influencing the overall survival rate. Biclonal carcinosarcomas have a lesser potential for malignant development and are characterized by stronger survival capacity compared with the monoclonal tumours.

Legal entity responsible for the study: Department of Oncology of the Russian Medical Academy of Continuous Vocational Training.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

16P ODM-207: A novel BET bromodomain inhibitor with antitumor activity in nonclinical models of ER+ breast cancer

A. Moilanen[1], J. Lindqvist[1], M. Björkman[1], R. Riikonen[1], D. Nicorici[1], E. Mattila[1], C. Abbineni[2], M. Jaleel[2], J. Eriksson[3], P. Kallio[1]

[1]Orion Corporation, Orion Pharma, Espoo, Finland, [2]Aurigene Discovery Technologies Limited, Bangalore, India, [3]Åbo Akademi University, University of Turku, Turku, Finland

Background: The bromodomain and extraterminal (BET) family of proteins are chromatin readers that promote the transcription of several important cell identity genes. BET inhibitors have shown promising antitumor activity in a variety of pre-clinical cancer models, as BET inhibition abrogates the transcription of several key oncogenes in a cell type-specific manner. Hence, the purpose of this study was to determine the anticancer activity of the novel BET inhibitor ODM-207 in ER+ breast cancer models and to look for cancer-associated signaling pathways suppressed by BET inhibitors.

Methods: ER+ breast cancer cell lines were studied for sensitivity to ODM-207 and the in vivo efficacy was assessed using the ER+ Ma3366 patient-derived xenograft model. For gene expression analyses, breast cancer cells were treated with ODM-207 or reference BET inhibitor JQ1 and differentially expressed genes were analysed by RNA-sequencing. The ability of ODM-207 to regulate anticancer signaling pathways was validated by western blotting. Synergistic drug interactions were profiled using five-concentration dose response matrices.

Results: ODM-207 is a novel BET inhibitor structurally distinct from JQ1 and its benzodiazepine-related derivatives. In this study, we show that ODM-207 effectively inhibits the proliferation of ER+ breast cancer cell lines as well as suppresses the growth of patient-derived xenograft tumors. Furthermore, ODM-207 and the JQ1 targeted several pathways important for cancer progression such as the DNA damage and repair pathways.

Conclusions: Our results indicate that ODM-207, which is currently in Phase I clinical trials for treating solid tumors, causes significant growth inhibition in pre-clinical models of ER+ breast cancer, and regulates signaling pathways involved in breast cancer cell survival.

Legal entity responsible for the study: Orion Corporation, Orion Pharma.

Funding: Orion Corporation, Orion Pharma.

Disclosure: A. Moilanen, M. Björkman, R. Riikonen, D. Nicorici, E. Mattila, P. Kallio: Employee: Orion Corporation, Orion Pharma. J. Lindqvist: Employee: Orion Corporation, Orion Pharma, Åbo Akademi University. C. Abbineni, M. Jaleel: Employee: Aurigene Discovery Technologies Limited. J. Eriksson: Employee: Åbo Akademi.

17P HER2-positive breast cancer resistance to trastuzumab is associated with metabolic switch

R. Dubianski[1], E. Sarnowska[2], M. Leszczynski[2], S. Kubala[3], W. Olszewski[4], N. Rusetska[2], A.I. Jagiello-Gruszfeld[1], R. Konopinski[2], T.J. Sarnowski[3], J.A. Siedlecki[2], Z.I. Nowecki[1]

[1]Department of Breast Cancer and Reconstructive Surgery, The Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology (MCMCC), Warsaw, Poland, [2]Department of Molecular and Translational Oncology, The Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland, [3]Department of Protein Biosynthesis, Institute of Biochemistry and Biophysics PAS, Warsaw, Poland, [4]Department of Pathology and Laboratory Medicine, The Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland

Background: Overexpression of the HER2 (ErbB2 or HER2/neu) receptor occurs in 20-25% of breast cancer patients population and is related to more aggressive disease. Implementation of trastuzumab to the treatment of HER2-positive breast cancer improved the results of the treatment in this subgroup of patients. However, the resistance to trastuzumab occurs in some patients. The presence of the nuclear localization of HER2 was also noticed. The aim of this work was to verify the molecular basis of resistance to transtuzumab and correlation between the resistance and the nuclear localization of HER2 protein.

Methods: Among more than 650 patients treated with trastuzumab in MSCMCC 50 patients with resistance to trastuzumab, and 50 well responding to the treatment were chosen. The percentage of the cells with HER2 localized in the nucleus were counted. Additionally, the transcriptomic analysis of HER2 positive breast cancer cell line resistant to trastuzumab was performed. The HER2 ChIP seq and Co-IP from SK-BR3 cell nuclei followed by mass spectrometry analysis were obtained.

Results: In breast cancer with HER2 overexpression nuclear staining was present in immunochemistry. The comparative transcriptomic reanalysis of GEO datasets performed on trastuzumab resistant cell lines and sensitive cell lines revealed that in trastuzumab resistant cell lines the reprogramming of cell metabolism takes place. The most common disturbances were detected in the expression of genes involved in the lipids metabolism, glycolysis and vitamin A metabolism. Moreover, among 308 genes upregulated in trastuzumab resistant breast cancer cells the 216 genes were directly bound/regulated by BRG1 ATPase-the core subunit of SWI/SNF chromatin remodeling complex which is known regulator of metabolism related genes. Among 151 downregulated genes 67 were directly targeted by BRG1. Similarly, the another SWI/SNF ATPase (BRM) – directly targeted 151 of 308 upregulated and 32 of 151 downregulated genes. These results strongly suggested the direct regulation or interdependence of HER2 and SWI/SNF complex.

Conclusions: In HER2 cancer cells resistant to transtuzumab treatment the strong metabolic switch is observed. Moreover, the SWI/SNF complex and nuclear HER2 can be involved in this process.

Legal entity responsible for the study: Maria Sklodowska - Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland.

Funding: Maria Sklodowska - Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland.

Disclosure: All authors have declared no conflicts of interest.

18P Combination treatment with the PARP inhibitor niraparib and chemotherapeutics in a preclinical model of KRAS/BRAF mutated colorectal cancer cell lines across the four consensus molecular subtypes

P.P. Vitiello, C. Cardone, D. Ciardiello, V. Belli, N. Matrone, C. Borrelli, L. Poliero, V. De Falco, E.F. Giunta, P. Vitale, N. Zanaletti, G. Tirino, T. Troiani, F. Ciardiello, E. Martinelli

Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: DNA damage response (DDR) is crucial in a variety of tumours. Colorectal cancer (CRC) shows some features of dependency upon DDR such as frequent activation of RAS-MAPK pathway, that is strongly associated with mitotic stress. Moreover, several approved chemotherapeutics in CRC are typical DNA damaging agents that require active DDR systems in cancer cells to be tolerated (e.g. irinotecan and oxaliplatin). It has been recently shown that PARP inhibitors are able to potentiate the anti-proliferative effect of irinotecan and oxaliplatin, particularly in MSI tumours. However, there is still no correlation between niraparib response and Consensus Molecular Subtypes (CMS).

Methods: We analysed the sensitivity using MTT proliferation assay to the PARP-inhibitor niraparib used alone or in combination with either 5-fluorouracil (5FU), irinotecan (active metabolite SN38) or oxaliplatin in a panel of 8 KRAS (HCT15, LOVO, LS1034, SW1116, SW948, HCT116, SW480) or BRAF (WiDr) mutated CRCs, from the four CMS clusters. Combination index analysis was performed in order to evaluate the synergism between niraparib and the chemotherapeutics. Further characterization of sensitive cell lines was performed using western blot, cell cycle and apoptosis analyses.

Results: Niraparib showed synergistic activity when used in combination with chemotherapeutics in most cell lines used. In particular, the combination with SN38 exhibited the strongest synergism, while synergism with 5FU was only evident in a minority of the analysed cell lines. Synergistic effect between niraparib and chemotherapy was evidenced across all the four CMS. Cell cycle and apoptosis assays revealed differences in sensitive cell lines in terms of increased induction of apoptosis.

Conclusions: Combination of niraparib and chemotherapy in RAS/BRAF mutated CRC is synergistic irrespectively of CMS. SN38 is the best candidate for combination. Further analyses are needed in order to find other markers predictive of good response to PARP inhibitors and chemotherapy in this model.

Legal entity responsible for the study: Department of Precision Medicine, Università della Campania Luigi Vanvitelli.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

19P Exosomal microRNA-32-5p induces multidrug resistance in hepatocellular carcinoma via the PI3K/AKT pathway

X. Fu[1], M. Liu[1], S. Qu[1], J. Ma[1], Y. Zhang[1], T. Shi[1], H. Wen[1], Y. Yang[2], S. Wang[1], J. Wang[1], K. Nan[1], Y. Yao[1], T. Tian[1]

[1]Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University (School of Medicine), Xi'an, China, [2]The Third Department of Cardiology, Shaanxi Provincial People's Hospital, Xi'an, China

Background: Multidrug resistance is the main obstacle for hepatocellular carcinoma (HCC) treatment. Through bioinformatics prediction, literature review, and real-time PCR, we found that elevated miR-32-5p was associated with tumorigenesis in different cancer types, including HCC. miR-32-5p also contributes to castration resistance, radioresistance and chemoresistance in prostate cancer, but its function in multidrug resistance is still unclear. Exosomes are the most abundant type of extracellular vehicles (EVs), containing RNAs (especially miRs), proteins and other bioactive molecules. Recently, exosomes generated from chemoresistant cells have been proven to deliver miRs and transfer malignant phenotype to sensitive cells. Here we aim to find out the function of miR-32-5p in inducing multidrug resistance and the possible underlying mechanisms.

Methods: We detected the expression of miR-32-5p and PTEN in the cells and exosomes from both the multidrug-resistant and the sensitive cell lines, HCC and para-carcinoma liver tissues through real-time PCR. Dual-luciferase reporter assay verified PTEN is the target of miR-32-5p. Exosomes were obtained and confirmed through ultracentrifuge and Nano Analyzer. Gain- and loss-of-function experiments, rescue experiments, an exosome biogenesis inhibitor, and nude mice xenograft models were used to determine the underlying mechanisms of miR-32-5p and PTEN, as well as exosomal miR-32-5p in inducing multidrug resistance in vitro and in vivo.

Results: miR-32-5p was significantly elevated in multidrug-resistant HCC cell line, Bel/5-FU as well as the exosomes derived from Bel/5-FU. An inverse correlation between miR-32-5p and PTEN was confirmed in HCC cell lines and patients; moreover, high expression of miR-32-5p and low expression of PTEN were positively associated with poor prognosis. Both in vitro and in vivo expriments reveal that exosomal miR-32-5p leads to multidrug resistance by targeting PTEN and activating the PI3K/Akt pathway through promoting EMT and angiogenesis.

Conclusions: Our study demonstrated that the multidrug-resistant cell, Bel/5-FU delivers miR-32-5p to sensitive cell, Bel7402 by exosome and activates the PI3K/Akt pathway to further induce multidrug resistance by modulating angiogenesis and EMT.

Legal entity responsible for the study: The First Affiliated Hospital of Xi'an Jiaotong University.

Funding: National Natural Science Foundation of China (No. 81301909 and 81672810). International cooperation project in science and technology of Shaanxi province (No. 2016KW-017). Natural Science Foundation of Shaanxi Province (No.2017JM8019).

Disclosure: All authors have declared no conflicts of interest.

20P Effect of the polymorphism rs2470893 of the CYP1A1 gene on ovarian and endometrial cancer in Mediterranean women

J.B. Ramirez Sabio[1], J.V. Sorlí[2], R. Barragán[2], F-C. Rebeca[2], E.M. Asensio[2], D. Corella[2]

[1]Medical Oncology, Hospital de Sagunt, Sagunt, Spain, [2]Preventive Medicine Department and CIBER Fisiopatología de la Obesidad y Nutrición, Universitat de València, Valencia, Spain

Background: The CYP1A1 gene is located on chromosome 15 (15q22-q24.1) and is part of the cytochrome P450 family. This catabolizing enzyme has an important role in the activation / deactivation of various chemical agents, including xenobiotics and sex hormones. It is related to the synthesis of cholesterol and steroids, and to the metabolism of drugs, coffee, or different metabolites such as those of tobacco. It is found mainly in extrahepatic tissues such as lung, breast or ovarian follicles, and participates in the metabolism of a large number of xenobiotics as well as one of endogenous substrates. Human cytochrome P450 1A 1 is one of the most important enzymes involved in the human carcinogenesis because it metabolizes several procarcinogens to active carcinogens. There are previous studies that have linked rs2470893 with ovarian cancer. Our aim has been to estimate the association between polymorphism rs2470893 of the CYP1A1 gene on ovarian and endometrial cancer in a Mediterranean population.

Methods: We have carried out an observational study at baseline and longitudinally in the PREDIMED-Valencia study including 696 women at high cardiovascular risk. We prospectively analyzed cancer incidence as a secondary outcome in this study. Lifestyle, clinical and biochemical variables were assessed by standardized methods. DNA was isolated from blood and the selected polymorphisms were determined

Results: We detected 8 new cases of ovarian and endometrial cancer from 2003 to 2014, representing 0.6% and 0.1% respectively, of all cancers. In our study it was observed that the variant rs2470893 was related to ovarian and endometrial cancer. The allelic frequency of the A allele was 0.246. The carriers of the G allele were grouped in front of the AA carriers. When assessing the risk of having suffered from ovarian or endometrial cancer according to the genotype of this variant, it was observed that the individuals carrying the AA allele presented a higher risk OR = 8.7: CI 95% (2.4-31.9); P = 0.001 after adjustment for age, intervention group, tobacco smoking and obesity (BMI $\geq$ 30 Kg/m^2).

Conclusions: rs2470893of the CYP1A1 gene could be associated with ovarian and endometrial cancer in a high cardiovascular risk population.

Clinical trial identification: ISRCTN35739639.

Legal entity responsible for the study: University of Valencia.

Funding: Instituto de Salud Carlos III.

Disclosure: All authors have declared no conflicts of interest.

21P Cisplatin in NIPEC or HIPEC?

I.K. Alvovsky, V.G. Bespalov, G.S. Kireeva

Scientific Laboratory of Cancer Chemoprevention and Oncopharmacology, N.N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russian Federation

Background: Eliminating minimal residual disease in patients with advanced ovarian cancer (AOC) is necessary to prevent recurrencies and could be achieved with hyperthermic intraperitoneal chemoperfusion (HIPEC). Cisplatin comprises the majority of HIPEC regimens due to its known synergic efficacy with hyperthermia. However, emerging report are impugning its role. Our goal was to compare the survival of rats treated with cisplatin by hyperthermic and normothermic intraperitoneal chemoperfusion (HIPEC and NIPEC) and to evaluate, whether the outcome of HIPEC would depend on its opened (oHIPEC) or closed (cHIPEC) delivery.

Methods: A rodent model of ascitic ovarian cancer was used. 1*10^7 tumor cells were inoculated i.p. 48 hours prior to the treatment to 48 female Wistar rats. As indicated by our previous research, this time limit of tumor progression reflects the biological pattern of optimally debulked AOC in women. Each 12 rats were randomized into four groups to receive either cisplatin at a maximum tolerated dose of 20 mg/kg in NIPEC, cHIPEC, and oHIPEC or i.p. 20 mg/kg saline as a control without treatment.

Results: The mean survival in the untreated control was 31.8 days. Cisplatin in NIPEC increased the mean survival by 22 days (P = 0.0007), while in cHIPEC and oHIPEC by 19.9 (P = 0.003) and 31.5 (P = 0.003) days, respectively. Cisplatin in oHIPEC was shown to be the most effective combination. The differences between NIPEC and cHIPEC with cisplatin were not statistically significant.

Conclusions: Our results prompt that NIPEC with cisplatin might be just as effective as cHIPEC in increasing survival in AOC.

Legal entity responsible for the study: Vladimir Bespalov.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

22P Matrix metalloproteinase-mediated regulation of programmed-death ligand in the human head and neck squamous cell carcinoma microenvironment

M. Hirai[1], Y. Kobayashi[2], M.H. Miyazawa[2], H. Kitahara[2], S. Kawashiri[2], H. Nakamura[2]

[1]Oral and Maxillofacial Surgery, Tonami General Hospital, Tonami, Japan, [2]Oral and Maxillofacial Surgery, Kanazawa University Hospital, Kanazawa, Japan

Background: Recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is a devastating malignancy with a poor prognosis. According to recent clinical studies, tumour growth can be effectively reduced and survival can be improved by blocking the programmed death receptor 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway. However, anti-PD-1 treatment is beneficial only for certain patients. Therefore, the mechanisms controlling PD-L1 expression warrant further investigation in order to provide a better understanding of the predicting efficacy of and optimising anti-PD-1 therapy, alone or in combination.

Methods: MMP-mediated regulation of PD-L1 expression was examined in three human HNSCC cell lines (OSC-20, OSC-19 and HOC313). Enzymatic activity of MMP against PD-L1 was evaluated in vitro using purified recombinant proteins or MMP synthetic inhibitors.

Results: PD-L1 protein extracted from the cell membrane was found to be downregulated in OSC-20 cells compared with OSC-19 cells, despite a higher PD-L1 expression in the total cell lysate of the OSC-20 compared with the OSC-19 cells. Several matrix metalloproteinases (MMPs) were found to be upregulated in HNSCC; in particular, MMP-7 and -13 were upregulated in the OSC-20 compared with the OSC-19 cells. Purified PD-L1 was degraded by recombinant MMP-13 and -7. The expression of PD-L1 was significantly restored by a specific inhibitor of MMP-13 (CL82198), which suggested the involvement of MMP-13 in the shedding/cleavage of PD-L1 in the OSC-20 cells. Among the anti-cancer drugs conventionally used in the treatment of patients with HNSCC, paclitaxel increased MMP-13 expression in R/M HNSCC cells (HOC313 cells) co-cultured without/with dendritic cells (DCs).

Conclusions: These results suggest that the shedding/cleavage of PD-L1 by MMP-13 is one of the mechanisms behind the protective effect against invasion and metastasis. Thus, MMP-13 has potential value as a marker predictive of the decreased efficacy of anti-PD-1 therapy. In addition, paclitaxel is a particularly promising candidate for combination therapy in R/M HNSCC with anti-PD-1 therapy.

Legal entity responsible for the study: Graduate School of Medical Science, Kanazawa University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

24P Trametinib synergizes with dexamethasone in KRAS-mutant myeloma cell lines through modulation of NDRG1 and induction of apoptosis

P. Sriskandarajah[1], K. Macleod[2], N. Carragher[2], M.F. Kaiser[3], S.R. Whittaker[1]

[1]Division of Cancer Therapeutics, Institute of Cancer Research, Sutton, UK, [2]Protein and Antibody Microarray Facility, Edinburgh Cancer Research Centre, Edinburgh, UK, [3]Division of Molecular Pathology, Institute of Cancer Research, Sutton, UK

Background: Multiple myeloma (MM) remains incurable despite advances in available therapy. Mutations within the RAS-MAPK pathway are frequently associated with relapsed/refractory disease, with KRAS being particularly prevalent. Increased efforts to target this pathway with the MEK inhibitor, trametinib (Tr) have been limited by toxicities and the development of resistance due to adaptive signalling networks. Dexamethasone (Dex) is a corticosteroid commonly used in clinical practice, to synergistically enhance efficacy of anti-myeloma therapy. Therefore, we hypothesised that the combination of Tr and Dex would yield synergistic activity in KRAS-mutant MM.

Methods: Sensitivity to Tr and Dex was determined via CellTiter-Blue (CTB) assay in the KRAS-mutant multiple myeloma cell lines (MMCLs): MM1R (Dex-refractory) & MM1S (Dex-sensitive). Apoptosis and cell cycle were evaluated by flow cytometry. Reverse phase protein array (RPPA) was employed for quantitative analysis of 60 proteins and validated by Western blotting.

Results: CTB assay demonstrated a dose-dependent reduction in cell proliferation with Tr and Dex individually in MM1S, while MM1R was resistant to both treatments. TrDex demonstrated synergistic cytotoxicity in MM1S using CTB and annexin V staining. An accumulation of sub-G_1 cells was observed during cell cycle analysis in MM1S, confirming increased cell death. These effects were accompanied by activation of pro-apoptotic proteins, such as cleaved PARP and increased BIM. RPPA revealed the following phospho-proteins were downregulated with TrDex in MM1S compared to MM1R: FAK, PYK2, FLT3, NDRG1 and 4EBP1. Changes in phospho-NDRG1 were statistically significant ($P < 0.001$; 2-way ANOVA). This was confirmed by Western blotting, where expression levels were downregulated by TrDex in MM1S but unaffected in the resistant cell line MM1R.

Conclusions: TrDex demonstrates synergistic activity in KRAS-mutant MMCLs by suppression of pro-survival signalling and engagement of apoptotic pathways. Our data support further investigation of this combination in KRAS-mutant MM.

Legal entity responsible for the study: Institute of Cancer Research.

Funding: Cancer Research UK.

Disclosure: P. Sriskandarajah: CRUK funding grant awarded in 2016. All other authors have declared no conflicts of interest.

25P Functional inhibition of TGF-β in colorectal cancer cells and its interaction with AXL receptor

D. Ciardiello[1], G. Martini[2], N. Matrone[1], V. Belli[1], P.P. Vitiello[1], C. Cardone[1], V. Ciaramella[1], G. Barra[1], L. Poliero[1], C. Borrelli[1], T. Troiani[1], D. Melisi[3], F. Morgillo[1], E.F. Giunta[1], V. De Falco[1], F. Ciardiello[1], E. Martinelli[1]

[1]Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [2]Centro Cellex, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [3]Medicina, AOU Integrata Verona "Borgo Roma", Verona, Italy

Background: AXL and transforming growth factor β (TGF-β) are correlated with epithelial to mesenchymal transition, invasiveness, angiogenesis and immune modulation in colorectal cancer (CRC). We have previously demonstrated that targeting AXL caused a significant blockade of cancer cell proliferation and migration. Here we have evaluated the role of TGF-β signalling and the potential interaction between TGF- β and AXL in human CRC cell lines.

Methods: We assessed the expression and activation of TGF-β and AXL in a panel of human CRC cell lines (HCT116, SW480, LOVO, LIM 1215 and SW48) by Western Blot (WB) and Real time PCR. We tested the sensitivity of Galunisertib (LY21209761), a TGF-β R1 inhibitor, in HCT116 and LOVO cells the treatment by using MTT, soft-agar colony forming, cell invasion and wound healing assays. To study the correlation between these two pathways, we generated stable LOVO short hairpin RNA (shRNA)-sh-AXL cells clones, in which AXL expression was decreased, and stimulated both parental and shAXL LOVO cells with TGF-β1.

Results: TGF-β receptors 1 and 2 were expressed in all cell lines, whereas AXL was expressed only in HCT116, SW480, LOVO cells. Treatment with Galunisertib had a modest effect on cancer cell growth, whereas it significantly decreased TGF-β induced cell migration, invasion and colony formation in HCT116 and LOVO cells (that co-expressed both TGF-β receptors and AXL). The stimulation of HCT116 and LOVO cells with TGF-β1 resulted in increased levels of phosphorylated (p) AXL, pAKT, and p38 MAPK proteins. However, in contrast to parental LOVO cells, no increase in p38 MAPK was found in LOVO shAXL clones, upon TGF-β stimulation.

Conclusions: In HCT116 and LOVO cells, TGF-β mediated cell migration, invasion and soft agar colony growth formation were significantly inhibited by Galunisertib treatment. Furthermore, a functional potential cross talk between TGF-β induced signalling and AXL could converge on p38 MAPK activation. In this respect, combined treatments with Galunisertib and AXL inhibitors are ongoing to evaluate their antitumor effects in CRC cells.

Legal entity responsible for the study: Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli.

Funding: AIRC (Associazione Italiana per la Ricerca sul Cancro) MFAG-2015-ID:7778.

Disclosure: All authors have declared no conflicts of interest.

26P Isoform-specific AKT inhibition differentially affects cell functions in pancreatic adenocarcinoma

H. Arasanz[1], M. Gato-Cañas[1], M. Zuazo[2], M. Ibáñez-Vea[2], G. Fernández-Hinojal[3], J. Fernandez-Irigoyen[4], E. Santamaria[4], G. Kochan[2], R. Vera[3], D. Escors[2]

[1]Inmunomodulación, Navarrabiomed / Fundación Miguel Servet, Pamplona, Spain, [2]Immunomodulation-Oncology, Navarrabiomed, Pamplona, Spain, [3]Medical Oncology, Complejo Hospitalario de Navarra, Pamplona, Spain, [4]Proteomics, Navarrabiomed, Pamplona, Spain

Background: AKT/PKB is a protein kinase that plays a key role in cancer, as different oncogenic pathways on it. Three isoforms with a similar structure have been described: AKT1/PKBα, AKT2/PKBβ and AKT3/PKBγ. Although there is evidence that each isoform yields specific functions, which may vary depending on the cell type, the data available about downstream pathways is scarce. Our project evaluates the consequences of the individual inhibition of each isoform in pancreatic adenocarcinoma cells.

Methods: We have individually silenced each AKT isoform short hairpin RNAs (shRNAs) delivered by lentiviral transduction. Cells transduced with an unspecific shRNA were used as controls. Then, high-throughput quantitative proteomic analyses were performed to evaluate the differential signaling routes altered by silencing of each AKT isoform. Lastly, Western Blot and proliferation, apoptosis and chemosensitivity experiments have been completed.

Results: 3930 proteins were identified with a false discovery rate (FDR) lower than 1%. Proteome pairwise comparisons were performed with the cells lines. The specific silencing of each isoform lead to differential protein expression profiles, although KEGG pathway analysis tools revealed that many of the pathways altered were common. Individual silencing of any AKT isoform caused an inhibition of glycolysis and a subsequent increase of mitochondrial activity, as seen by fluorescent mitochondrial staining. AKT silencing increased gemcitabine sensitivity for all isoforms. AKT1 and AKT2 increased 5-FU sensitivity, while AKT3 had a comparable value. Western Blot demonstrated an increase in mTOR expression after AKT1 and AKT2 silencing. p-EIF4B expression was decreased after AKT2 and AKT3 silencing. No differences were observed in ERK expression.

Conclusions: AKT isoforms have specific functions in pancreatic adenocarcinoma. Its silencing drives cancer cells from aerobic glycolysis to mitochondrial dependent metabolism. A deeper knowledge of its downstream molecular pathways might give the rationale for individual pharmacological inhibition and combination with other therapies, thus improving the efficacy of the available treatments.

Legal entity responsible for the study: Immunomodulation Group. Navarrabiomed / Fundación Miguel Servet.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

27P Lymphocytes express receptor tyrosine kinases in patients with renal cell carcinoma and healthy donors

I. Tsimafeyeu[1], M. Volkova[2], A. Olshanskaia[2], G. Raskin[3], S. Aschuba[4], Y. Khochenkova[4], A. Bondarenko[5], D. Khochenkov[4]

[1]Moscow Office, Kidney Cancer Research Bureau, Moscow, Russian Federation, [2]Department of Urology, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [3]Department of Pathology, A.M. Granov Russian Scientific Centre of Radiology and Surgical Technologies, St. Petersburg, Russian Federation, [4]Laboratory of Angiogenesis, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [5]Department of General Medicine, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation

Background: Very little is known about receptor tyrosine kinases (RTK) expression on peripheral blood mononuclear cells (PBMC) in humans including renal cell carcinoma (RCC) patients. The primary objective of study was to evaluate expression levels of major RTKs on PBMC and tumor infiltrating lymphocytes (TIL) isolated from RCC patients. The secondary aim was to compare levels of RTK expression in RCC patients before surgery and on the 180th day after surgery (lymphocyte lifetime) and to compare with expression in healthy donors (HD). In addition, we compared RTK and PD-L1 expression in TIL.

Methods: Tumor and blood samples were obtained from 20 patients with primary RCC immediately after surgical resection. Blood samples were collected from 10 HD. Tumors were harvested into RPMI1640 medium (Gibco) and processed within 4 h. TIL isolation was performed under modified protocol [Baldan 2015]. Isolated TIL and PBMC were prepared for flow cytometry. Cells were double stained with anti-CD45

FITC-conjugated mouse antibody and with PE-conjugated mouse antibodies to VEGFR1-2, PDGFRα-β, FGFR2 (all Sony Biotech) and were analyzed on NovoCyte 2000R flow cytometer (ACEA Biosciences). Expression of RTK was evaluated with NovoExpress Software. 20 tumors from same patients were stained with PD-L1 IHC assay (clone SP142 (Ventana).

Results: PBMC/TIL express RTKs (Table). In HD PBMC express all RTKs in 2-3 times higher than PBMC of RCC patients (all $P < 0.05$). TIL also had lower expression of RTK (all $P < 0.05$). There was no significant recovery of RTK expression on 180th day except of VEGFR2. Level of FGFR2 was lower on TIL ($P = 0.03$). 50% of patients had PD-L1 expression (1-11% of positive TIL). We found negative correlation of PDGFRα, β and PD-L1 expression ($P = 0.04$).

Table: 27P

Expression of RTK, %, mean	PBMC, HD	PBMC, RCC, before surgery	PBMC, RCC, 180 days after surgery	TIL, RCC
VEGFR1	78.1	28.8	43.4	28.1
VEGFR2	79.6	27.1	57.8	44.3
PDGFRα	80.1	44.9	49.1	52.3
PDGFRβ	75.5	62.6	47.4	52.3
FGFR2	72.1	41.4	35.1	23.2

Conclusions: PBMC and TIL had similar low RTK expression levels in RCC patients. Lymphocytes of healthy humans had significantly higher expression of RTK. PD-L1 and PDGFRa-b expression could correlate.

Clinical trial identification: KCRB11022016.

Legal entity responsible for the study: Ministry of Health.

Funding: Kidney Cancer Research Bureau.

Disclosure: All authors have declared no conflicts of interest.

28P Oncogenes analysis using GO-based clustering

D. Babenko[1], Y. Babenko[2]

[1]Research Center, Karaganda State Medical University, Karaganda, Kazakhstan, [2]Dentistry, Karaganda State Medical University, Karaganda, Kazakhstan

Background: New technology, including next-generation sequencing, has been contributing to discover novel genes and a genetic mechanism connected to oncology. Oncogenes are of particular interest to biologists, as they can provide a direct target for small molecule inhibitors. However, recent studies show that tumor suppressors and oncogenes are separable using rates of truncating mutations, mutation clustering, and copy number data. At the same time, existing literature suggested a higher intensity of purifying selection on cancer-related genes. This has led to hypothesize those oncogenes and tumor suppressor genes are more closely related physically, than noncancer-related genes. The aim of this study was to carry out clustering protein genes based on GO-terms and determine cluster structure and oncogene positions on it.

Methods: List of protein-coding genes was obtained with biomaRt Bioconductor package. ClusterProfiler Bioconductor package was used to get gene ontology data of the genes. The association of genes to cancer was calculated with OncoScore Bioconductor package. Data associated with biological processes, cellular components, and molecular functions were presented in a binary format that was used for clustering analysis. SeqSphere software used for generating minimum spanning trees (MST).

Results: 15521 out 19295 protein-coding genes (85.5%) had full information about biological processes, cellular components, and molecular functions. Among 15521 genes (1.5%), 226 genes were high associated with cancer (75 and higher oncoscore). 1441 protein-coding genes had a medium association with cancer (50-74 oncoscore). 5694 genes were between 21 and 49 oncoscores. 7345 genes were not oncogenes (based on oncoscore). In 815 cases it was not possible to determine the oncoscore. MST created on 206 unique GO terms (10% cutoff) of 15521 genes revealed grape-like structure with many clusters. High associated gene to cancer (oncogenes with high oncoscore) was distributed across different clusters and located on the outer layer of clusters.

Conclusions: Cluster analysis of protein-coding genes based on GO-terms (on biological process, molecular functions, and cell localization data) demonstrated cluster (grape-like) structure. Oncogenes were located mostly outside the cluster center.

Legal entity responsible for the study: Dmitriy Babenko, Karaganda State Medical University.

Funding: Ministry of Education and Science of Republic of Kazakhstan.

Disclosure: All authors have declared no conflicts of interest.

29P PNU-74654 enhances the antiproliferative effects of 5-FU in breast cancer and antagonizes thrombin induced cell growth via the Wnt pathway

S. Shahid Sales[1], A. Avan[2], F. Rahmani[3], S.M. Hassanian[2], M. Hashemzehi[2], F. Amerizadeh[2], G. A. Ferns[4], M. Khazaei[5]

[1]Clinical Oncology, Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [2]Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, [3]Department of Medical Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, [4]Division of Medical Education, Brighton & Sussex Medical School, Falmer, UK, [5]Department of Physiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Background: The Wnt/beta-catenin pathway is one of the main pathways that are dysregulated in several malignancies, including breast cancer, and may therefore be a potential therapeutic target. We have investigated the anticancer activity of PNU-74654 in breast cancer, as a Wnt/ β-catenin inhibitor, either alone or in combination with 5-FU in vitro and in vivo.

Methods: Cell viability was assessed in 2 and 3-dimensional (D) cell culture models. The ability of PNU-74654 to inhibit the chemotaxis of cells was investigated using an in vitro migration assay, and the expression of several candidate genes involved in the cell cycle, migration, as well as the markers of Wnt/b-catenin pathway were investigated by qRT-PCR and/or Western blotting as well as cell cycle analysis by flow cytometry. The effect of PNU-74654 on oxidative balance was evaluated by determining the malondialdehyde (MDA) and concentration of total thiols (T-SH), and the activity of catalase (CAT) and superoxide dismutase (SOD). We reconstructed a Boolean network in order to understand dynamic behavior of genes, while the robustness of this model was assessed by Hamming distance.

Results: PNU-74654 suppressed cell growth at an IC50 of 122±0.4 umol/L and synergistically enhanced the antiproliferative activity of gemcitabine by modulating the Wnt pathway. The 3-D cell culture model showed that PNU-74654 caused tumor shrinkage. It reduced the migration of MCF-7 cells (by an 18% reduction in invasive behavior) after treatment with PNU-74654 through perturbation of E-cadherin and MMP3/9. PNU-74654/5-FU combination enhanced the percentages of cells in S-phase, and significantly increased apoptosis. Moreover, our data showed that this agent was able to inhibit the growth of tumor in a xenograft model, although this effect was more pronounced in the animals treated with PNU-74654 plus 5-FU.

Conclusions: The antitumor activity of PNU-74654 were shown in breast cancer.

Legal entity responsible for the study: Mashhad University of Medical Sciences, Mashhad, Iran.

Funding: Mashhad University of Medical Sciences, Mashhad, Iran.

Disclosure: All authors have declared no conflicts of interest.

30P P21 has the potential to become the monitoring marker for the CDK4/6 inhibitors resistance in breast cancer

M. Iida[1], M. Nakamura[1], E. Tokuda[1], T. Niwa[1], T. Ishida[2], S-I. Hayashi[1]

[1]Molecular and Functional Dynamics, Tohoku University Hospital, Sendai, Japan, [2]Breast and Endocrine Surgical Oncology, Tohoku University Hospital, Sendai, Japan

Background: CDK4/6 inhibitors have been widely used around the world for advanced estrogen receptor positive breast cancer patients in the past several years. However, the benefit offered by CDK4/6 inhibitors is individually different, therefore it is imperative need to identify the biomarker and/or monitoring marker.

Methods: We established CDK6 over expression cell lines (MCF7-C6) from MCF-7 by stably transfected CDK6 expression vector. We also established Ribociclib-resistant cell lines (RIBR) after long-term culture under the condition of sufficient doses of Ribociclib from estrogen deprivation-resistant cell lines (EDR) which established from MCF-7 cultured with steroid depleted medium as aromatase inhibitor resistance models. We further established RIBR(-R) cell lines from RIBR by long-term cultured without Ribociclib.

Results: First, we assessed IC50 of Ribociclib in several cell lines. Luminal cell lines exhibited lower Ribociclib IC50 than non-luminal cell lines. Immunoblot analysis of Luminal cell lines showed extremely lower levels of CDK6 compared with others. Then we established MCF7-C6. MCF7-C6 reduced Ribociclib sensitivity equivalent to non-luminal cell lines. Next, we established RIBR to understand the characteristics in acquired resistance. We confirmed RIBR showed higher Ribociclib IC50 than EDR. Surprisingly the expression levels of CDK6 were not reduced in RIBR, indicating that the mechanism of resistance to Ribociclib would be different between MCF-7-C6 and RIBR. Then, we explored the efficacy of other CDK4/6 inhibitors on MCF7-C6 and RIBR. MCF7-C6 and RIBR cells showed cross-resistant not only to Palbociclib but Abemaciclib. The expression levels of p21 were reduced in both cell lines though the mechanisms of resistance to CDK4/6 inhibitors were different. Finally, we established RIBR(-R). RIBR(-R) showed more sensitive to Ribociclib than RIBR. In addition, p21 levels of RIBR(-R) were restored to the same degree as EDR.

Conclusions: Ribociclib sensitivity was proportional to the expression levels of p21, suggesting that p21 levels might be the monitoring marker for the CDK4/6 inhibitors resistance in breast cancer.

Legal entity responsible for the study: Shin-ichi Hayashi.

Funding: Grant-in-aid for scientific research from the Ministry of Education, Science, Sports, Science and Technology of Japan; Grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare of Japan; Program for Promotion of Fundamental Studies in Health Science of the National Institute of Biomedical Innovation (NIBIO); Grant from the Smoking Research Foundation.

Disclosure: S-I. Hayashi: Research grants: Novartis Pharma K.K, AstraZeneca K.K. All other authors have declared no conflicts of interest.

31P Overexpression of NAMPT in adult T-cell leukemia/lymphoma patients and anti-tumor activity of a NAMPT inhibitor in vivo

T. Kozako[1], T. Ohsugi[2], M. Yoshimitsu[3], Y-I. Uchida[3], K. Ishitsuka[3], K. Naho[1], A. Aikawa[1], S-I. Honda[1]

[1]Department of Biochemistry, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan, [2]Department of Hematology and Immunology, Rakuno Gakuen University, Ebethu, Japan, [3]Center for Chronic Viral Diseases, Kagoshima University, Kagoshima, Japan

Background: Adult T-cell leukemia/lymphoma (ATL) is a malignancy of mature T lymphocytes induced by human T-cell leukemia virus (HTLV) that has poor outcomes. New molecular targets for prevention and treatment of ATL are urgently needed. We reported that SIRT1, a nicotinamide adenine dinucleotide (NAD^+)-dependent histone/protein deacetylase, is highly expressed in primary acute-type ATL cells. NAD^+ biosynthesis via nicotinamide phosphoribosyltransferase (NAMPT) modulates SIRT1 activity. We examined the expression and inhibition of NAMPT, a rate-limiting enzyme in NAD^+ biosynthesis, in ATL cells.

Methods: Peripheral blood mononuclear cells from ATL patients were carried out in accordance with the guidelines of the Committees for Ethical Review of Research involving Human Subjects at Kagoshima University Hospital. Cell viability was evaluated in the S1T cell line derived from an ATL patient, MT-2 cell line derived from normal human leukocytes transformed by leukemic T-cells from an ATL patient, and primary ATL cells. Animal experiments were approved by the Animal Care and Use Committee of Rakuno Gakuen University in accordance with the Guide for the Care and Use of Laboratory Animals.

Results: Peripheral blood mononuclear cells from acute-type ATL patients expressed significantly higher NAMPT protein levels than cells from healthy controls. FK866, a NAMPT inhibitor, induced apoptosis in cell lines and fresh ATL cells, accompanied by caspase activation, DNA fragmentation, and mitochondrial transmembrane potential disruption in vitro. A pan-caspase inhibitor failed to prevent the FK866-induced cell death, while FK866 increased endonuclease G, a caspase-independent cell death mediator. Intriguingly, FK866 activated autophagy, revealed by increased LC3-II protein levels. Thus, FK866 simultaneously activated apoptosis and autophagy. Finally, FK866 treatment markedly decreased human ATL tumor xenograft growth in immunodeficient mice.

Conclusions: These results demonstrate that NAMPT inhibition induces autophagy and caspase-dependent and -independent cell death in ATL cells, suggesting a novel therapeutic strategy for patients with this fatal disease.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

32P 9-ING-41, a clinically relevant inhibitor of glycogen synthase kinase-3 (GSK-3), is active pre-clinically in human bladder and renal cell cancers

H. Kuroki[1], T. Anraku[1], V. Bilim[1], M. Tasaki[1], D. Schmitt[2], A. Mazar[3], A. Ugolkov[4], Y. Tomita[1]

[1]Urology, Niigata University Medical and Dental Hospital, Niigata, Japan, [2]Actuate Therapeutics, Fort Worth, TX, USA, [3]Monopar Therapeutics, Wilmette, IL, USA, [4]Developmental Therapeutic Program, Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Background: Glycogen Synthase Kinase-3b (GSK-3b) is a serine/threonine protein kinase that has been established as a therapeutic target in a broad spectrum of human malignancies. We have previously identified aberrant GSK-3b nuclear expression in urothelial cancer (UC) and renal cell carcinoma (RCC), and demonstrated that GSK-3b positively regulated UC and RCC cell survival and proliferation. Our objective was to evaluate the antitumor effects of clinically viable agent 9-ING-41, a maleimide-based ATP-competitive GSK-3 inhibitor, which demonstrated broad spectrum antitumor activity and marked activity in reversing chemoresistance in a variety of human cancers.

Methods: We used flow cytometry, Western immunoblotting, quantitative RT-PCR, BrDU incorporation and MTS assays to examine the pre-clinical antitumor activity of 9-ING-41 in UC (T24, HT1376 and RT4 cell lines) and RCC (ACHN, Caki2, A498 and KRC/Y cell lines).

Results: A dose-dependent decrease in cancer cell proliferation was observed by MTS assay and BrdU incorporation assay with GI50 ranging from 0.7 to 4.7 mM (UC) and 7.2 to 11.5 mM (RCC). Treatment with 9-ING-41 induced prominent cell cycle arrest (predominantly G2 arrest) in UC and RCC cell lines. Expression of cell cycle related proteins, including Cyclin D, and anti-apoptotic proteins, such as XIAP and Bcl-2, were decreased as detected by Western immunoblotting and real time RT-PCR. Treatment with 9-ING-41 significantly potentiated the growth inhibitory effect of cisplatin and gemcitabine in both UC and RCC cell lines.

Conclusions: Our data provide a rationale for the inclusion of patients with advanced and/or chemo-refractory UC or RCC in 9-ING-41 clinical studies.

Legal entity responsible for the study: Hiroo Kuroki.

Funding: D. Schmitt: President, CEO, equity interest: Actuate Therapeutics, Inc. A. Mazar: Equity interest, scientific advisor: Actuate Therapeutics, Inc. A. Ugolkov: Equity interest, consulting scientific Director: Actuate Therapeutics, Inc.

Disclosure: All authors have declared no conflicts of interest.

33P A new natural compound identified through a metabolomic approach has cytotoxic activity against human colorectal cancer cell lines with acquired resistance to cetuximab

V. De Falco, E.F. Giunta, V. Belli, N. Matrone, S. Napolitano, E. Martinelli, P. Vitale, N. Zanaletti, M. Terminiello, P.P. Vitiello, F. Ciardiello, T. Troiani

Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: The discovery of bioactive compounds from natural sources is an important resource to develop new weapons against cancer. In a previous study, we have used a rapid NMR-based metabolomic approach to select plant species belonging to Fabaceae family with anti-proliferative properties. Fourteen species of this family were studied with high-resolution 2D NMR spectroscopy and then several molecules were purified from plant extracts. The family of Fabaceae is widely distributed in the Northern hemisphere and putative pharmacologic effects are described in traditional Chinese pharmacopoeia.

Methods: We analysed the cytotoxic activity of an *Astragalus boeticus* compound on a panel of human colon cancer cell lines sensitive (SW48, GEO and CACO-2) and with acquired resistance to anti-EGFR inhibitors such as cetuximab (SW48-CR, GEO-CR and CACO-2-CR).

Results: Among a panel of human CRC cell lines, three with acquired resistance to cetuximab (SW48-CR, GEO-CR and Caco-2-CR) were highly sensitive to the *Astragalus* compound. The treatment with this compound determines a transition to an epithelial phenotype in all three cell lines with reduction of vimentin and an increase of E-cadherin expression. Moreover, *Astragalus* treatment determines an induction of apoptosis and a significant increase in cell death in SW48-CR, GEO-CR and Caco-2-CR cells, but not in the parental cell lines. These findings were confirmed by western blot assay with activation of caspase cascade only in cetuximab-resistant cells. Moreover, the antiproliferative effect of *Astragalus* compound on cetuximab-resistant cells is mediated by the inhibition of AKT/mTOR signalling pathway. In particular, western blot analyses have shown a significant reduction in the expression of 4-EBP1 and p-4EBP1 in cetuximab-resistant cell lines following *Astragalus* treatment. Moreover, the combined treatment with cetuximab and *Astragalus* induced a synergistic antiproliferative and apoptotic effects with blockade in AKT/mTOR pathway in h cetuximab-resistant cells.

Conclusions: *Astragalus* compound induces antiproliferative activity in a panel of human CRC with acquired resistance to cetuximab by inhibiting AKT/mTOR pathway.

Legal entity responsible for the study: Università degli Studi della Campania Luigi Vanvitelli.

Funding: Università degli Studi della Campania Luigi Vanvitelli.

Disclosure: All authors have declared no conflicts of interest.

34P Multiple myeloma metal levels and proteasome activity

K.U. Stumpf[1], H. Einsele[2], T. Nekova[3]

[1]Biocomposition, Institute of Mineral Analysis, Würzburg, Germany, [2]Medical Policlinic II, University Hospital Wuerzburg, Würzburg, Germany, [3]Hematology, University Hospital Wuerzburg, Würzburg, Germany

Background: The biologically active metal-based compounds are of interest in both prevention and treatment of cancer. Metal-containing complexes are essential for the normal biochemical processes, and due to their reactivity, imbalance in the metal concentration is linked to the development of diverse malignancy. Several proteasome inhibitors contain metal complexes. Bortezomib (a boron complex) is the first successfully used therapeutic proteasome inhibitor in multiple myeloma (MM). However, major clinical limitations of the drug are the severe side effects caused by the inhibition of proteasomal and non-proteasomal activity in normal cells. Here we analyze the associations between individual metals and proteasome activity.

Methods: The study was performed on MM cell lines MM.1S and L363. Chymotrypsin–like (CT-like) proteasome activity is the primary measure of the degradation potential of the proteasome. In order to determine how metals are linked to proteasome activity, we expose MM cells to bortezomib or 5-amino-8-hydroxyquinoline dihydrochloride (5AHQ) proteasome inhibitors. The CT-like activities of β5 and β5i

subunit were measured and evaluated based on a cumulative inhibition of β5 and β5i CT-like sites. Metal content analysis of MM.1S and L363 cells was performed by total reflection X-ray fluorescence spectrometer.

Results: The metal content analysis demonstrated rigorous imbalances for calcium, phosphorus and potassium, moderate to no imbalances for iron and zinc accompanied by 65% MM.1S (54% L363) reduction of CT-like activity under bortezomib. However, under 5AHQ treatment, a decrease in the concentration of phosphorus and potassium was accompanied by minor to no change of iron and zinc levels and an increase of calcium. As metals may positively correlate or be antagonistic to one another, we evaluated the correlations between metals and proteasome activity.

Conclusions: Overall, our analysis suggests that the modulation of metal interactions specific to the proteasome activity is a strategy worth exploring to improve the efficacy of proteasome inhibition therapies.

Legal entity responsible for the study: AG Hematology.

Funding: Wilhelm Sander Foundation.

Disclosure: All authors have declared no conflicts of interest.

35P A translational drug-screening tool for interrogating the effect of anti-TGF-*β* therapy on fibroblast activity and the desmoplastic reaction

N.I. Nissen[1], N. Willumsen[2], N. Gudmann[3], S. Rønnow[3], M. Karsdal[2], D. Leeming[3], J. Sand[3]

[1]Cancer, Nordic Bioscience A/S, Herlev, Denmark, [2]Biomarkers and Research, Nordic Bioscience A/S, Herlev, Denmark, [3]Fibrosis, Nordic Bioscience A/S, Herlev, Denmark

Background: Numerous clinical trials are currently evaluating anti-transforming growth factor beta (TGF-β) therapy for treating lung cancer patients. However, interrogating stromal reactivity, and enhancing the mechanistic understanding of desmoplasia in relation to TGF-β signaling represents unmet medical needs and may allow for discovery of novel TGF-β associated biomarkers for use in the clinical setting. Cancer associated fibroblasts are major contributors to the desmoplastic reaction (ECM deposition) upon TGF-β stimulation. Applying the "Scar-in-a-jar" (SiaJ) model, we evaluated the impact of TGF-β, and inhibitors, on lung fibroblasts' expression of different collagens.

Methods: Primary human healthy lung fibroblasts were cultured for up to 15 days in the presence of ficoll and TGF-β, with or without addition of 1nM-10μM ALK-5/type I TGF-β receptor kinase inhibitor (iTGFβ. ELISAs quantified pro-peptides from type I (PINP), type III (PRO-C3) and type VI (PRO-C6) collagen in cell supernatant as surrogate measures of the TGF-β induced ECM deposition. Cytotoxicity (lactate dehydrogenase (LDH) release) and metabolic activity (AlamarBlue) were evaluated.

Results: Stimulating lung fibroblasts with TGF-β induced PINP, PRO-C3 and PRO-C6 increase up to 8-fold compared to TGF-β ($p < 0.001$). iTGFβ dose-dependently reduced the PINP, PRO-C3 and PRO-C6 increase induced by TGF-β. No cytotoxicity could be detected. The metabolic activity was decreased at 1uM iTGFβ.

Conclusions: The SiaJ model can be used to evaluate the impact of TGF-β, and inhibitors, on lung fibroblasts' viability and expression of different collagens. The findings suggest that SiaJ together with PINP, PRO-C3 and PRO-C6 can be used as a translational drug screening tool for interrogating the effect of anti-TGF-β therapy on fibroblast activity and the desmoplastic reaction.

Legal entity responsible for the study: Nordic Bioscience A/S.

Funding: Nordic Bioscience A/S.

Disclosure: N.I. Nissen, N. Willumsen, N. Gudmann, S. Rønnow, J. Sand: Employee: Nordic Bioscience A/S. M. Karsdal, D. Leeming: Employee and stocks: Nordic Bioscience A/S.

36P Eribulin demonstrate selectively high sensitivity to recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) cells and xenograft tumors

H. Kitahara, Y. Kobayashi, M. Hirai, S. Kawashiri, H. Nakamura

Oral and Maxillofacial Surgery, Kanazawa University Hospital, Kanazawa, Japan

Background: Recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is a devastating malignancy with a poor prognosis. Eribulin (a microtubule inhibitor) reportedly renders breast cancer less aggressive, and less likely to metastasise, by triggering the mesenchymal-to-epithelial (MET) transition. Previously we reported that eribulin-induced MET was associated with re-sensitization of resistant HNSCC cell lines to cetuximab. In this study, we evaluated eribulin activity in preclinical R/M HNSCC models.

Methods: In vitro antiproliferative activities (IC50) were determined in three human HNSCC cell lines (OSC-20, OSC-19 and OLC01) treated with eribulin or other microtubule inhibitors (paclitaxel and vinblastine). The effects of eribulin were evaluated in eribulin-sensitive and -resistant HNSCC xenograft tumors.

Results: Eribulin demonstrate selectively high sensitivity to OLC01 cells (R/M HNSCC) in comparison with other cell lines. Eribulin has sub-0.1 nM growth inhibitory activities in vitro against OLC01 cells as well as marked in vivo activities at 0.1–0.5 mg/kg against OLC01 cells xenografts. Inducible TUBB3 correlates with lower sensitivity to eribulin in HNSCC cells and xenograft tumors.

Conclusions: Understanding the mechanisms involved in the overall drug response to eribulin may help in the design of therapeutic strategies that enhance drug activity and improve benefits of eribulin in R/M HNSCC patients.

Legal entity responsible for the study: Graduate School of Medical Science, Kanazawa University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

37P Tranilast inhibits TGF-beta-induced EMT and invasion/metastasis via the suppression of smad4 in lung cancer cell lines

K. Takahashi, S. Nishikawa, R. Miyata, M. Noguchi, H. Ishikawa, Y. Yutaka, D. Nakajima, M. Hamaji, A. Ohsumi, T. Menju, F. Chen-Yoshikawa, T. Sato, M. Sonobe, H. Date

Thoracic Surgery, Kyoto University-Graduate School of Medicine, Kyoto, Japan

Background: Epithelial-mesenchymal transition (EMT) is a key event in cancer metastasis and promotes cancer cell migration and invasion. Transforming growth factor-beta (TGF-β), a well-known inducer of fibroblast proliferation, plays a crucial role in cancerous EMT via regulating E-cadherin or vimentin expression through TGF-β/Smad signaling. Tranilast is an anti-allergic drug clinically used for the treatment of keloids and hypertrophic scars to inhibit tissue fibrosis. We investigated whether tranilast could inhibit TGF-β-induced EMT in non-small cell lung cancer (NSCLC) cell lines.

Methods: We used A549 and PC14 NSCLC cell lines which are epithelial type cultured under normal conditions, but changes their phenotype into mesenchymal type with TGF-β stimulation. Western blottings were applied to examine epithelial or mesenchymal markers, and signal transductions of TGF-β/Smad pathway in these cell lines exposed to tranilast. To downregulate Smad signaling, siRNA methods were applied. Next, to investigate the capability of in vitro invasion, matrigel invasion assays were performed in which TGF-β was used as a chemoattractant. To develop orthotopic in vivo cancer models, A549 cells mixed with matrigel were injected into left lung of nude mice. Subsequently, mice were treated with or without tranilast for one month, then, the number of micrometastasis in both lungs were counted and compared between the two groups.

Results: In mesenchymal phenotype of A549 and PC14 stimulated with TGF-β, tranilast reinstated EMT via suppressing Smad4. The downregulation of Smad4 by siRNA methods also induced the recovery of EMT in these cell lines, resulting in the inhibition of in vitro invasion. The number of tumor spread through air space (STAS) in lung parenchyma was more suppressed in the tranilast administerd mice group.

Conclusions: Tranilast suppressed TGF-β-induced EMT via the downregulation of Smad4 resulting in the inhibition of in vitro and in vivo invasion/metastasis in lung cancer cell lines.

Editorial acknowledgement: Kissei Pharmaceutical Co., Ltd.

Legal entity responsible for the study: Kyoto University Graduate School, Thoracic Surgery.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

38P Integrin beta-like 1 overexpression stimulates invasiveness of ovarian cancer cells in vitro

A.J. Cortez, K.A. Kujawa, P.A. Tudrej, K.M. Lisowska

Center for Translational Research and Molecular Biology of Cancer, Maria Skłodowska-Curie Institute - Oncology Center, Gliwice Branch, Gliwice, Poland

Background: In our previous microarray study we analyzed gene expression profile of over 100 ovarian cancer samples [1]. We identified two molecular subgroups of high grade serous ovarian cancers (HG-SOC) with distinct gene expression profiles and survival [2]. Among differentially expressed genes was an Integrin beta-like1 gene (ITGBL1). ITGBL1 is a poorly characterized protein, structurally cognate with integrin β. Our aim was to study whether and how ITGBL1 can influence the phenotype of ovarian cancer cells.

Methods: ITGBL1 coding sequence was PCR-amplified from cDNA and cloned into pLNCX2 vector. Retroviral system was used to obtain two ovarian cancer cell lines: OAW42/ITGBL1(+) and SKOV3/ITGBL1(+) with overexpression of ITGBL1. Control cell lines were obtained by transduction with empty vector. A Matrigel cell invasion assay was performed using 24-well transwell inserts (coated with fibronectin and matrigel). Crystal violet staining of invaded cells was performed, then the dye was solubilized with 10% acetic acid and the absorbance was measured at a wavelength of 595 nm.

Results: We compared invasion rate of control OAW42 and SKOV3 cells with that of isogenic cell lines containing ITGBL1 construct. The results indicate that ITGBL1 overexpression increases invasiveness of ovarian cancer cells.

Conclusions: Our results indicate that ITGBL1 may increase ovarian cancer cell invasion rate. Along with our previous reported results that overexpression of ITGBL1 may

increase migration, decrease adhesion [3] and has no effect on proliferation rate [4], these results suggests that ITGBL1 may play an important role in ovarian cancer progression enabling easier spreading of the cells within peritoneal cavity.
[1]K.M.Lisowska, et al. (2014),Front.Oncol. DOI:10.3389/fonc.2014.00006. [2]K.M.Lisowska,et al.(2016),J.Cancer Res.Clin.Oncol.DOI:10.1007/s00432-016-2147-y. [3] A.J.Cortez, et al. (2016), Int. J. Gynecol. Cancer. Vol 26, sup. 3, p. 665 [4] A.J.Cortez, et al. (2017), Int. J. Gynecol. Cancer. Vol 27, sup. 4, p. 1931.

Legal entity responsible for the study: Maria Skłodowska-Curie Institute - Oncology Center, Gliwice Branch.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

39P MiR-449a suppresses endometrial cancer invasion and metastasis by targeting NDRG1

L. Qiu

Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: Endometrial cancer (EC) is the most common gynecologic malignancy in western counties. Generally, a five-year survival of patients with localized disease remains at approximately 96% and this rate drops to 67% and 17% for the patients suffering from regional and distant metastasis, respectively. Therefore, an improved understanding of the molecular mechanisms in metastasis of endometrial cancer has the potential to significantly impact the outcomes for this disease. Studies has outlined the essential roles for miR-449a in regulating pathogenesis of cancers. A number of reports have identified the role of microRNAs in EC, but little is known about miR-449a in it.

Methods: FISH was used to detect the expression of miR-449a in the 55 tissues and IHC was performed to measure the NDRG1 expression in the above samples. The alterations of NDRG1 gene were analyzed by cBioPortal for Cancer Genomics online. The human EC cell lines were cultured in DMEM/F12 medium supplemented with 10% fetal bovine serum and Penicillin/Streptomycin in a humid atmosphere incubator with 5% CO2 at 37 °C. The expression of miR-449a and NDRG1 were assayed by quantitative real time-PCR Wound healing assay, migration and invasion assays were performed to detect the ability of migration and invasion in EC cells. NDRG1 and PTEN/AKT pathway were detected by immunoblotting.

Results: In this study, our analysis found that miR-449a expression is inversely correlated with the stage of endometrial cancer. Overexpression of miR-449a in human EC cells alleviated cell invasion and metastasis in vitro. Conversely, miR-449a knock-down promoted migration and invasion of EC cells. Moreover, we identified N-myc Downstream-Regulated Gene 1 (NDRG1) as a direct and functional target gene of miR-449a in EC cells, and the expression NDRG1 in 55 endometrial cancer specimens were inversely correlated with that of miR-449a. In addition to this, further studies show that down-regulation of NDRG1 inhibited migration and invasion of EC cells through PTEN/AKT pathway.

Conclusions: miR-449a suppresses metastasis of EC cells by directly targeting NDRG1 gene and activation of miR-449a may represent an effective therapeutic strategy in endometrial cancer.

Legal entity responsible for the study: Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine, Shanghai JiaoTong University, China.

Funding: National Natural Science Foundation of China (81272884).

Disclosure: The author has declared no conflicts of interest.

40P Cancer-associated fibroblasts-derived VEGFA mediates the migration of gastric cancer cells through VEGFR1

X. Wang, X. Che, Y. Fan, M. Bai, X. Qu

Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, China

Background: Cancer-associated fibroblasts (CAFs) are major components of the tumor stroma and regulators of tumor progression. CAFs are also involved in the intraperitoneal dissemination of gastric cancer cells. However, the molecular mechanism by which CAFs promote gastric cancer peritoneal dissemination should be further explored.

Methods: 1. Cell migration ability was measured using Transwell assay. 2. Protein expression was analyzed by western blot. 3. Mouse model detects peritoneal metastasis of gastric cancer cells. 4. Affymetrix scanner 3000 was used to analyse the microarray genome-wide expression. 5. Statistical analysis. All values are expressed as means ± SD. The differences of the results between two groups were evaluated by Student's t-test. $P<0.05$ was considered to be statistically significant.

Results: In our study, we found CAFs enhance the migration of gastric cancer cells through the expression of VEGFA. While VEGFA neutralizing antibody bevacizumab markedly attenuated these CAFs-induced phenotypes in gastric cancer cells. Moreover, VEGFA enhances the gastric cancer cells' ability to diffuse and metastasize in the peritoneum. And the Bevacizumab could inhibit peritoneal metastatic nodules. We further found the migration of MGC-803 was increased with VEGFA stimulation, mainly through VEGFR1 but not VEGFR2.

Conclusions: Taken together, these results revealed that the activation of VEGFR1 by CAFs-derived VEGFA enhances the migration of gastric cancer cells. And VEGFA enhances the peritoneal metastasis capacity of gastric cancer cells. Our results suggested that inhibition of VEGFA and its receptor VEGFR1 to control downstream signaling may provide a promising therapeutic target for the treatment of tumors.

Legal entity responsible for the study: Academic Group.

Funding: National Natural Science of Foundation.

Disclosure: All authors have declared no conflicts of interest.

41P Risk prediction of metastasis through study of circulating tumor cells

P. Apostolou, I. Papasotiriou

Research & Development, Research Genetic Cancer Centre S.A., Florina, Greece

Background: The study of circulating tumor cells (CTCs) has rapidly increased in the last decade, as this entity of cells is implicated in cancer prognosis and progression. CTCs constitute a non-homogeneous population of cells, with metastatic ability. The present study tested the gene expression profile of genes involved in metastasis in particular organs, in CTCs from cancer patients representing different cancer types and stages.

Methods: Blood samples were randomly collected from 35 patients, suffering from breast, prostate, ovarian, lung, colorectal, peritoneal, bladder, endometrial and stomach cancer. CTCs were isolated using enrichment protocols and cellular-molecular based assays were used to enumerate and study their expression profiles. qRT-QPCR for genes correlated with risk metastasis in principle (TGFBR2, ITGB5, ITGB6), risk of metastasis to pleura (CCR6), skin (CCR7), lung (IGF2R, ERK1, ERK2), bone (BMPR1A, BMPR1B, BMPR2, CXCR4, BST2), liver (CXCR4, TRAILR2, FAS, MET) and brain metastasis (STAT3, CX3CR1, DSC2) performed by using ACTB as housekeeping gene. All the reactions were performed in triplicates. A normal and a reference cancer RNA was used as control.

Results: Samples mainly from prostate, breast and squamous cancer overexpressed markers involved in general metastasis. These samples were at stage III and IV, and CTCs were 6.7±2.35/ml. For pleura and skin, overexpression was observed in samples with higher CTCs number (8.2±1.3/ml) than in prostate and ovarian cancer, respectively. Markers correlated with liver metastasis were expressed higher in breast and ovarian samples at stage IV. The majority of breast and prostate cancer samples also expressed markers correlated with bone metastasis, while squamous and ovarian cancer samples expressed genes involved in brain metastasis. By contrast, samples with lower CTCs exhibited expression in markers correlated with metastasis to lung (5.8±2.3/ml), involving breast, prostate and ovarian cancer.

Conclusions: Among same cancer type samples, different metastasis profiles were revealed, demonstrating that analysis of CTCs and particularly, their enumeration in comparison with their expression profile might be useful to focus the follow up and screening to specific organs.

Legal entity responsible for the study: Research Genetic Cancer Centre Group Ethic Committee.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

42P First step to metastasis: MiRNAome abnormalities impair cell-cell adhesion and facilitate detachment of breast cancer cells

V. Halytskiy

Molecular Immunology Department, Palladin Institute of Biochemistry of the National Academy of Sciences of Ukraine, Kiev, Ukraine

Background: In order to metastasize, cancer cells must detach from neighboring cells and extracellular matrix. With regard to data that microRNAs (miRNAs) miR-18, miR-19, miR-21, miR-23, miR-29, miR-155, miR-181, miR-206, miR-210, miR-221/222 and miR-375 are usually overexpressed in breast cancer cells, this research aims to identify in what way the abnormality in miRNA signature can contribute to the disintegration of cell-cell contacts.

Methods: MiRNA targets within gene transcripts were predicted in silico using the TargetScan software.

Results: Targets of overexpressed miRNAs miR-18, miR-23, miR-25, miR-150, miR-181, miR-221/222 and miR-372/373 were found in transcript of CDH1 gene encoding E-cadherin. Transcripts of genes F11R and JAM3 encoding junctional adhesion molecules JAM-A and JAM-C carry targets of miRNAs miR-23, miR-29, miR-155, miR-181 and miR-221/222. Binding sites for miRNAs miR-23 and miR-150 were revealed in transcripts of TJP1 and TJP2 genes encoding tight junction proteins ZO-1 and ZO-2. MiRNAs miR-21, miR-29, miR-155 and miR-375 can silence CLDN1 gene encoding claudin 1. Up-regulated miRNAs miR-19, miR-21 and miR-155 can target transcript of CGN gene encoding cingulin. MiRNAs miR-18, miR-29, miR-155, miR-181 and miR-375 suppress OCLN gene coding occludin. Overexpressed miRNAs miR-21, miR-23,

miR-29, miR-155, and miR-221/222 can target transcripts of PVRL1 and PVRL3 genes encoding nectin 1 and 3. In addition, up-regulated miRNAs can silence other genes responsible for cell-cell adhesion - CADM1/3 (encoding nectin-like molecules 2/1), CTNNA1 (alpha-catenin), CTNND1 (p120-catenin) as well as genes encoding tropomyosin 1, vinculin, alpha-actinins.

Conclusions: MiRNAs, hyperexpressed in breast cancer cells, can silence genes encoding E-cadherin and numerous other epithelial junction components. This causes disruption of cell-cell adhesion, and, in addition, affects cell polarity and contact inhibition, predetermines epithelial-mesenchymal transition, detachment, movement and invasiveness of the breast cancer cells.

Legal entity responsible for the study: Palladin Institute of Biochemistry of the National Academy of Sciences of Ukraine.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

43P Extracellular matrix of normal brain tissue is affected by temozolomide during anti-glioblastoma treatment

A. Tsidulko[1], C. Bezier[2], G. de La Bourdonnaye[3], A.V. Suhovskih[1], G. Kazanskaya[4], S. Aidagulova[5], E.V. Grigorieva[1]

[1]Laboratory of Glycobiology, Federal Research Center of Fundamental and Translational Medicine, Novosibirsk, Russian Federation, [2]Molecular and Cellular Biology, Pierre et Marie Curie University, Paris, France, [3]Biochemical Engineering, National Institute for Applied Sciences, Toulouse, France, [4]Department. of Pathomorphology, Meshalkin National Medical Research Center, Novosibirsk, Russian Federation, [5]Department. of Histology, Embryology and Cytology, Novosibirsk State Medical University, Novosibirsk, Russian Federation

Background: Temozolomide (TMZ) is a main drug for chemotherapy of glioblastoma multiforme (GBM). During the treatment, both GBM tumour and surrounding normal brain are exposed to the drug, and its effects on the normal brain tissue are not investigated. Survival and invasion of GBM cells depend not only on their characteristics but also on the structure of extracellular matrix (ECM) of brain tissue, which consists mainly of glycosylated molecules such as proteoglycans (PGs) and glycosaminoglycans (GAGs). Here, we aimed to investigate the effects of TMZ on PGs and GAGs expression in normal brain tissue.

Methods: Two-month-old Wistar rats were used in the study, and effects of TMZ treatment on PGs (syndecan-1, glypican-1, perlecan, decorin, biglycan, lumican, brevican, neurocan, CSPG4/NG2, aggrecan) were studied using real-time RT-PCR and IHC analyses.

Results: Treatment with TMZ had almost no effects on the overall transcriptional activity of the PGs core proteins in normal brain tissue but resulted in a 2-fold increase of GAGs content (both heparin sulfates and chondroitin sulfates). Different TMZ-based drugs demonstrated different effects on the PGs core proteins expression - treatment with some of them resulted in significant decrease in syndecan-1, glypican-1, perlecan and lumican expression. Moreover, treatment with combination of TMZ and dexamethasone, commonly used to treat glioma-induced edema, led to the most dramatic changes in PGs composition in the brain tissue at both core protein and GAG levels.

Conclusions: The obtained results demonstrate that chemotherapy with temozolomide affects proteoglycan composition and ECM structure in normal brain tissue. These changes might be involved in the formation of the tumourigenic niche for the expansion of the residual glioma cells and the disease progression.

Legal entity responsible for the study: Federal Research Center of Fundamental and Translational Medicine.

Funding: Russian Science Foundation (RSF grant 16-15-10243). Tsidulko A. was funded by individual scholarship of Russian Federation President for young scientists (SP-5435.2018.4).

Disclosure: All authors have declared no conflicts of interest.

44P Study of the activation of TLR receptors in neurospheres from glioblastoma cells in vitro

D. Albert Bellver[1], R. Gil-Benso[1], A. Martínez[2], T. San-Miguel[1], L. Muñoz-Hidalgo[1], A. Carratalá[1], D. Gozalbo[2], C. López-Ginés[1], M. Cerdá-Nicolás[1], M.L. Gil[2], J. Megías[1]

[1]Pathology, University of Valencia, Valencia, Spain, [2]Microbiology and Ecology, University of Valencia, Burjassot, Spain

Background: Glioblastoma (GB) is the most aggressive brain tumor known. GB stem cells (GSC) are resistant to ordinary therapy and contribute to the development of recurrences. Toll-like receptors (TLR) are expressed in immunity cells to recognize multiple ligands from multiple infectious agents to unleash the immune response. TLRs are also expressed in neural cells, such as GB and neural stem cells, where its activation may imply cell differentiation. The aim of this study was to prove whether the stimulation of GSC TLRs induces a phenotype more sensitive to therapy and less aggressive.

Methods: Two GB cell lines were used: U-87 and U-118 (ATCC), cultured in the presence of Neurobasal® medium and in the absence of fetal bovine serum. The culture obtained was formed by neurospheres, which include a high proportion of GSC. On the one hand, the enrichment in GSC was confirmed by flow cytometry by the expression of stem cell markers CD133 and CD44. On the other hand, the analysis of TLR expression was performed by RT-PCR. According to its TLR expression, neurosphere cells were exposed to the pertinent TLR ligands for 24 hours in vitro and cultured in the presence or absence of temozolomide (TMZ). After stimulation, the expression of CD133 and CD44 was measured by flow cytometry.

Results: Flow cytometry results showed a higher proportion of GSC in the culture with Neurobasal®. RT-PCR results demonstrated expression in stem cells of the genes corresponding to TLR2, TLR3, TLR4 and TLR6 receptors. Flow cytometry post-stimulation proved a decrease of stem cell markers in the ligands of the TLR2 and TLR4 in both lines. Cultures with TMZ did not show significantly altered expression of GSC, although survival was lower than cultures without TMZ.

Conclusions: These results show a relation between the activation of the TLR and the increase of the differentiation rate in GSCs, especially through TLR2 and TLR4. Based on the results obtained, a new therapy for GB treatment, might be possible, which would include the differentiation of GSC by the exposition to TLR2 and TLR4 ligands, previous or concomitant to chemotherapy.

Legal entity responsible for the study: University of Valencia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

45P 5-fluorouracil-induced up-regulation of exosomal PD-L1 causing immunosuppression in gastric cancer patients

Z. Min, F. Yibo, C. Xiaofang, H. Kezuo, Q. Xiujuan

Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, China

Background: Although 5-fluorouracil chemotherapy has been thought to directly kill cancer cells and even play an immunostimulatory role, accumulating evidence indicates 5-fluorouracil also damages function of T cells through up-regulating programmed death-1-ligand 1(PD-L1), which is a negative regulator of T cell immune ability. Previous study has shown that PD-L1 has exosomal forms secreted in the microenvironment, except for membrane bound forms and extracellular soluble forms. In addition, exosomal PD-L1 retains stronger immunosuppressive activity. However, whether 5-fluorouracil can change the expression of exosomal PD-L1 and induce immunosuppression is unknown.

Methods: We retrospectively detected exosomal PD-L1, by ELISA, in 17 stage III/IV gastric cancer patients before and after 2,4,6,8 repeated cycles of 5-fluorouracil chemotherapy treatment.

Results: Compared with the expression at baseline, exosomal PD-L1 was up-regulated gradually in the plasma of patients when 2,4,6,8 repeated cycles of 5-fluorouracil were administered, accompanied with the decreased amounts of $CD4^+$ and $CD8^+$ T cells. Mechanistically, 5-fluorouracil up-regulated PD-L1 and exosomal PD-L1 in gastric cancer cell lines. Moreover, exosomal PD-L1 derived from gastric cancer cells induced apoptosis of T cells after 48h treatment, which could be reversed by nivolumab.

Conclusions: 5-Fluorouracil up-regulated exosomal PD-L1 which induced apoptosis of T cells and caused immunosuppression in gastric cancer patients.

Legal entity responsible for the study: Academic Group.

Funding: National Natural Science Foundation of China.

Disclosure: All authors have declared no conflicts of interest.

46P Thrombocytosis and leukocytosis: Are they negative prognostic factors in solid tumours?

F. Kohutek[1], B. Bystricky[1], M. Kohutekova[2]

[1]Department of Oncology, Faculty Hospital Trencin, Trencin, Slovak Republic, [2]Department of Otorinolaryngology, Faculty Hospital Trencin, Trencin, Slovak Republic

Background: Induction of thrombocytosis and leukocytosis by tumour is a part of complex propagative strategy of malignancy. Activated leukocytes and thrombocytes produce several cytokines and enzymes that are crucial for tumour growth, invasion and dissemination. Therefore, leukocytosis and thrombocytosis might be a negative prognostic factor in malignancies.

Methods: Thrombocyte and leukocyte count were determined before the beginning of treatment. Patients with recent bleeding, elevated CRP or treated with best-supportive care were excluded. Relationship between thrombocytosis, leukocytosis and known negative prognostic factors was assessed. The impact of thrombocytosis and leukocytosis on progression-free survival (PFS) was determined. Chi- squared test, Kaplan-Meier and Cox- regression statistical analysis were used.

Results: 500 patients with breast cancer (BC), ovarian cancer (OC), colorectal cancer (CrC), head and neck tumours (H&N) or lung cancer (LC) were included to our

retrospective study. Thrombocytosis was more frequent in patients with metastatic cancer (whole population of patients) (17.4%, 95%CI :8.1125-26.7381, p = 0.0001); in patients with CrC (27%, 95% CI: 4.1554-47.9434, p = 0.0111); in patients with OC (27.7%, 95%CI: 6.5334- 46.4296, p = 0.0063) and in patients with H&N (46.9%, 95%CI: -9.5975-72.7755, p = 0.0459). Grading, estrogen- receptor (ER) progesteron-receptor (PR) and her2 status had no impact on frequency of thrombocytosis. Thrombocytosis had no impact on PFS. Leukocytosis was more frequent among patients with metastatic malignancies (10.6 %, 95%CI: 1.4352- 19.9713, p = 0.0174). This result reflected only in the subgroup of patients with H&N (46.9%, 95%CI: -9.5975- 72.7755, p = 0.0459). Grading, PR and her2 status had no impact on frequency of leukocytosis. Leukocytosis was more frequent in BC patients with negative ER status (18.7%, 95%CI: 1.0068- 40.1859, p = 0.0158). Leukocytosis shortened PFS in patients with LC (hazard ratio 2.1126, 95%CI:1.2712- 3.5109, p = 0.0014).

Conclusions: Leukocytosis might be a negative prognostic factor in patients with LC. More studies are needed to identify the subpopulation of leukocytes responsible for this effect.

Legal entity responsible for the study: Faculty Hospital Trencin, Department of Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

47P Evaluation of stemness and proliferation of human breast cancer stem cells (ALDH+) supplemented with heat-activated TGF-beta1 in the secretomes of stem cells from human exfoliated deciduous teeth (SHED)

S.I. Wanandi[1], G. Wideani[2], M. Zainuri[3], R.R. Putri[4], E.W. Bachtiar[5], S.W.A. Jusman[1]

[1]Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [2]Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [3]Doctoral Program in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [4]Center of Biomedical and Basic Technology of Health, National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia, [5]Oral Biology, Faculty of Dentistry, Universitas Indonesia, Jakarta, Indonesia

Background: Our previous studies have reported that the secretomes of umbilical cord- and adipose-derived mesenchymal stem cells (MSCs) affected the stemness properties of human breast CSCs (BCSCs). However, little is known about specific factors in MSC secretomes, particularly those from human exfoliated deciduous teeth, which involved in tumor aggressiveness such as stemness and proliferation of CSCs. This study aimed to evaluate the stemness and proliferation of human BCSCs after supplemented with heated secretomes of stem cells from human exfoliated deciduous teeth (SHED) to activate latent TGF-β1.

Methods: To collect SHED conditioned medium (SHED-CM) containing secretomes, SHED were grown in serum-free a-MEM for 24 and 48 hours, respectively. SHED-CM 24-h was then heated at 80^{0}C for 10 min. Human BCSCs (ALDH+) cultured in DMEM-F12 were supplemented with 50% (v/v) non-heated SHED-CM 24- and 48-h, as well as with heated SHED-CM 24-h followed by 72-h incubation. Control was BCSCs supplemented with non-heated 50% (v/v) a-MEM/DMEM-F12. Following the supplementation, we measured the mRNA expression of TGF-β1 receptor (TβRI), as well as stemness genes ALDH1A1 and OCT4 of BCSCs using qRT-PCR. BCSC proliferation was determined using trypan blue dye.

Results: This study demonstrates that relative mRNA expression levels of TβRI, OCT4 and ALDH1A1 in BCSCs supplemented with non-heated SHED-CM 24- and 48-h were increased compared to their control. Interestingly, the increase of TβRI, OCT4 and ALDH1A1 expressions after TGF-β1 heat activation was significantly higher than in non-heated SHED-CM. Conversely, BCSC proliferation was significantly reduced after supplemented with non-heated SHED-CM 24- and 48-h, but drastically increased higher than control when treated with heated SHED-CM 24-h, suggesting the involvement of other factors in SHED-CM that restrain TGF-β1 signaling and suppress cell proliferation.

Conclusions: Heated SHED secretomes contained activated TGF-β1 that increased the expression of stemness genes, OCT4 and ALDH1A1, as well as proliferation of human BCSCs (ALDH+) via TGF-β1 paracrine signaling.

Legal entity responsible for the study: Septelia Inawati Wanandi.

Funding: Directorate of Research and Community Service, Universitas Indonesia.

Disclosure: All authors have declared no conflicts of interest.

48P Estrogen-related receptor α as a potential molecular target for endometrial cancer therapy

T. Kokabu, T. Mori, H. Matsushima, Y. Tarumi, K. Yoriki, H. Kuroboshi, M. Sawada, S. Umemura, J. Kitawaki

Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Background: Estrogen-related receptor α (ERRα) is considered to be a potential molecular target against several cancer types. We previously demonstrated that ERRα knockdown regulated tumor progression in uterine endometrial cancer. The purpose of this study was to elucidate the effects of XCT790, a selective inverse agonist of ERRα, on endometrial cancer.

Methods: HEC-1A and KLE cells, endometrial cancer cells with high expression of ERRα, and HEC-1A-derived xenograft mouse model were treated with XCT790. Cell proliferation was evaluated with WST-8 and colony formation assays. The cell cycle was examined with flow cytometry, fluorescent immunocytochemistry. The apoptotic effect was determined with TUNEL assay and caspase-3/7 assay. Proteins and mRNA levels were detected by western blotting and real-time PCR.

Results: XCT790 significantly inhibited ERRα-induced transcriptional activity in a dose-dependent manner ($P < 0.01$) without reduction of mRNA level of ERRα. XCT790 suppressed colony formation and cell proliferation in a concentration- and time-dependent manner ($P < 0.01$), without cytotoxicity. Flow cytometry, fluorescence immunocytochemistry, and western blotting indicated that XCT790 induced apoptosis ($P < 0.01$), and caused cell cycle arrest at the mitotic phase. Western blotting revealed that XCT790 inhibited Akt/mTOR signaling pathway without the alteration of the expression level of PI3K. Additionally, XCT790 significantly suppressed tumor progression in the xenograft mouse model ($P < 0.05$). XCT790 induced apoptosis and decreased Ki-67 positive cells in tissue sections ($P < 0.01$).

Conclusions: The findings of the present study suggested that XCT790 could be a novel therapeutic agent in uterine endometrial cancer.

Legal entity responsible for the study: Tetsuya Kokabu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

49P Good tolerability and limited target-specific tissue distribution of an anti-L1CAM antibody administered to cynomolgus monkey indicates favorable safety profile of L1CAM-targeting therapies

J. Gaudreault[1], A. Schmidt[1], P. Altevogt[2], G. Spohn[1]

[1]RD, Elthera AG, Schlieren, Switzerland, [2]Translational Immunology, DKFZ, Heidelberg, Germany

Background: L1 cell adhesion molecule (L1CAM) is a ∼200 kDa transmembrane protein which is overexpressed in several tumor types. Its expression has been shown to be a predictor of poor outcome in several independent publications. Anti-L1CAM antibody therapy, is expected to lead to tumor regression through inhibition of tumor growth, inhibition of migration/cell adhesion, reversal of chemoresistance and cell killing via ADCC. In addition to tumors, L1CAM is expressed in a restricted set of healthy tissues, including the nervous system and kidney tubules. The current study was conducted to investigate the acute tolerability and tissue distribution of an antibody directed against L1CAM and inform about the potential target organs which might be affected by anti-L1 CAM therapy.

Methods: The acute tolerability and biodistribution of an antibody that binds with high affinity to cynomolgus monkey L1CAM was evaluated. The antibody was administered in two IV bolus injections of 20 mg/kg, 24 hours apart to a single cynomolgus monkey. Clinical signs were recorded and the animal was sacrificed 48 hours after administration of the second dose, followed by macropathological inspection and tissue collection. A second untreated control animal was used as control for subsequent analyses. Tissues from both animals were collected, paraffin-blocked, and the presence of tissue-bound anti-L1CAM antibody was detected by immunohistochemistry.

Results: Administration of the anti-L1CAM antibody was well tolerated with no signs of acute local or systemic intolerance observed. In cynomolgus monkey, specific binding was observed in kidney tubules and Kupffer's cells of the liver, while no binding was observed in the central nervous system, peripheral nerves, or any other tissues.

Conclusions: Administration of L1CAM antibody was well tolerated and the observed tissue distribution was consistent with the known expression profile of L1CAM. These data support the safety of anti-L1CAM therapy using an antibody approach.

Legal entity responsible for the study: Elthera AG.

Funding: Elthera AG.

Disclosure: J. Gaudreault, A. Schmidt, P. Altevogt, G. Spohn: Stock ownership: Elthera AG.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii14–viii57, 2018
doi:10.1093/annonc/mdy269

BIOMARKERS

50O Plasma cell-free DNA (cfDNA) assays for early multi-cancer detection: The circulating cell-free genome atlas (CCGA) study

M.C. Liu[1], E. Klein[2], E. Hubbell[3], T. Maddala[3], A.M. Aravanis[3], J.F. Beausang[4], D. Filippova[4], S. Gross[4], A. Jamshidi[4], K. Kurtzman[4], L. Shen[4], N. Zhang[4], O. Venn[4], J. Yecies[4], S. Patel[4], D.A. Smith[5], T. Yeatman[6], M. Seiden[7], A-R. Hartman[4], G. Oxnard[8]

[1]Division of Medical Oncology, Department of Oncology, Mayo Clinic Cancer Center, Rochester, MN, USA, [2]Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA, [3]Clinical Development and Medical Affairs, GRAIL, Menlo Park, CA, USA, [4]Research and Development, GRAIL, Inc., Menlo Park, CA, USA, [5]Research, Compass Oncology, Vancouver, WA, USA, [6]SMC Division of Surgery, Gibbs Cancer Center and Research Institute, Spartanburg, SC, USA, [7]Research and Development, US Oncology Research, The Woodlands, TX, USA, [8]Medicine, Dana-Farber Cancer Institute, Boston, MA, USA

51O Pan-cancer assessment of BRCA1/2 genomic alterations (GAs) by comprehensive genomic profiling (CGP) of tissue and circulating tumor DNA (ctDNA)

N. Agarwal[1], E.S. Sokol[2], P. Lara Jr.[3], J.S. Ross[4], V.A. Miller[2], A.W. Welsh[5], J.P. Gregg[6], G.M. Frampton[2], S.M. Ali[2], J. Chung[2]

[1]Oncology/ Internal Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA, [2]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA, [3]Medicine, University of California, Davis, Sacramento, CA, USA, [4]Medicine, SUNY Upstate Medical University, Syracuse, NY, USA, [5]Medicine, Memorial Sloan Kettering Cancer Center, Lambertville, NJ, USA, [6]Medicine, University of California, Davis, Sacramento, CA, USA

52O Circulating tumour DNA analysis predicts relapse following resection in stage II and III melanoma

L. Tan[1], S.K. Sandhu[1], R. Lee[2], J. Li[3], J. Callahan[4], J. Raleigh[3], A. Hatzimihalis[3], P. Middlehurst[2], M. Henderson[5], M. Shackleton[6], A. Haydon[6], D. Gyorki[5], D. Oudit[7], R.J. Hicks[4], P. Lorigan[8], G.A. McArthur[1], R. Marais[2], S.Q. Wong[3], S-J. Dawson[1]

[1]Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia, [2]Molecular Oncology Group, Cancer Research UK Manchester Institute, Manchester, UK, [3]Cancer Research, Peter MacCallum Cancer Center, Melbourne, Australia, [4]Nuclear Medicine, Peter MacCallum Cancer Center, Melbourne, Australia, [5]Surgical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia, [6]Medical Oncology, The Alfred Hospital, Melbourne, Australia, [7]Surgical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [8]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK

53PD **Association of PD-L1 expression with prognosis among patients with 10 select cancers**

T. Steiniche[1], M. Ladekarl[2], J. Bæhr Georgsen[1], S. Andreasen[3], M. Busch-Sørensen[4], W. Zhou[5], S.K. Pruitt[5], A.K. Joe[5], K-L. Liaw[5]

[1]Institute of Pathology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [3]Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Copenhagen University Hospital, Copenhagen, Denmark, [4]Merck Research Laboratories, MSD Denmark, Copenhagen, Denmark, [5]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA

54PD **Pre-treatment CD4 senescent T cells accurately predicts lack of response to PD-L1/PD-1 immune checkpoint blockade in non-small cell lung cancer and correlates with risk of hyperprogression**

M. Zuazo[1], H. Arasanz[1], M. Gato-Cañas[1], G. Fernández-Hinojal[2], B. Hernández-Marín[2], M. Martínez-Aguillo[2], M. Ibáñez-Vea[1], M.J. Lecumberri Biurrun[2], Á. Fernández de Lascoiti[2], R. Vera[2], G. Kochan[1], D. Escors[1]

[1]Immunomodulation-Oncology, Navarrabiomed / Fundación Miguel Servet, Pamplona, Spain, [2]Medical Oncology, Complejo Hospitalario de Navarra, Pamplona, Spain

55PD **Identification of biological axes associated with stage II/III CRC recurrence risk and outcome after adjuvant therapy revealed a T-effector-independent prognostic role for granzyme B**

M. Das Thakur[1], A. Udyavar[1], T. Sandmann[2], C. Li[1], L.J.W. Bosch[3], W. O'Gorman[1], Y. Li[1], A. Au-Yeung[1], C. Takahashi[1], R. Bourgon[1], A. Daemen[1], P. Hegde[1], C. Bais[1]

[1]Oncology Bomarker Development, Genentech Inc. - Roche - USA, South San Francisco, CA, USA, [2]Denali Therapeutics, South San Francisco, CA, USA, [3]Translational Gastrointestinal Oncology Group Department of Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands

56PD **Analytic validation of tumor mutational burden as a companion diagnostic for combination immunotherapy in non-small cell lung cancer**

D.A. Fabrizio, C. Milbury, W-K. Yip, L. Ramamurthy, X. Bai, V. Pattani, P. Maness, A. Cowen, K. Fedorchak, P. Ma, G.M. Frampton, C. Connelly, Y. Li

Product Development, Foundation Medicine, Cambridge, MA, USA

57PD **Tumor mutational burden and prognosis across pan-cancers**

H. Ding[1], J. Zhao[2], Y. Zhang[2], G. Wang[2], S. Cai[2], F. Qiu[3]

[1]Department of Respiratory Disease, Affiliated People's Hospital of Jiangsu University, Zhenjiang, China, [2]The Medical Department, Shanghai 3D Medicines, Inc., Shanghai, China, [3]Department of Oncology, The First Affiliated Hospital of Nanchang University, Nanchang, China

58PD **Pan-cancer analysis of ret fusions (FN) and rearrangements (RE) by genomic profiling of 158,360 tumors**

L.M. Gay[1], D.C. Pavlick[2], S. Ramkissoon[1], S. Daniel[1], J.K. Killian[1], J-A. Vergilio[1], E. Severson[1], G.M. Frampton[2], J.A. Elvin[1], J.S. Ross[3]

[1]Pathology, Foundation Medicine, Cambridge, MA, USA, [2]Cancer Genomics Research, Foundation Medicine, Cambridge, MA, USA, [3]Medicine, SUNY Upstate Medical University, Syracuse, NY, USA

59PD **Final analysis of serum biomarkers in patients (pts) from the phase III study of lenvatinib (LEN) vs sorafenib (SOR) in unresectable hepatocellular carcinoma (uHCC) [REFLECT]**

R.S. Finn[1], M. Kudo[2], A-L. Cheng[3], L. Wyrwicz[4], R. Ngan[5], J.F. Blanc[6], A.D. Baron[7], A. Vogel[8], M. Ikeda[9], F. Piscaglia[10], K-H. Han[11], S. Qin[12], Y. Minoshima[13], M. Kanekiyo[14], M. Ren[14], R. Dairiki[13], T. Tamai[14], C.E. Dutcus[14], Y. Funahashi[13], T.R.J. Evans[15]

[1]Division of Hematology/Oncology, Geffen School of Medicine, UCLA Medical Center, Santa Monica, CA, USA, [2]Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan, [3]National Taiwan University Hospital, Taipei, Taiwan, [4]Centrum Onkologii-Instytut im., M. Sklodowskiej Curie, Warsaw, Poland, [5]Queen Elizabeth, Hospital, Kowloon, Hong Kong, China, [6]University of, Bordeaux, Bordeaux, France, [7]California Pacific, Medical Center, San Francisco, CA, USA, [8]Hannover Medical, School, Hannover, Germany, [9]Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [10]Medical and Surgical Sciences, University of Bologna, Bologna, Italy, [11]Severance Hospital, Yonsei University, Seoul, Democratic People's Republic of Korea, [12]Nanjing Bayi Hospital, Nanjing, Jiangsu, China, [13]Eisai Co., Ltd., Tsukuba, Ibaraki, Japan, [14]Eisai, Inc, Woodcliff Lake, NJ, USA, [15]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK

60PD **Colon cancer molecular subtype intratumoral heterogeneity and its prognostic impact: An extensive molecular analysis of the PETACC-8**

P. Laurent-Puig[1], L. Marisa[2], M. Ayadi[2], Y. Blum[2], R. Balogoun[1], C. Pilati[1], K. Le Malicot[3], C. Lepage[4], J.F. Emile[5], R. Salazar[6], D. Aust[7], A. Duval[8], J. Selves[9], D. Guenot[10], G. Milano[11], J-F. Seitz[12], J. Taieb[13], V. Boige[14], A. de Reyniès[15]

[1]UMR-S1147, Paris Descartes University, Paris, France, [2]Programme 'Cartes d'Identité des Tumeurs', Ligue Nationale contre le Cancer Paris, France, [3]EPICAD INSERM LNC-UMR 1231, Burgandy University, Dijon, France, [4]Department of Hepato Gastroenterology and Digestive Oncology, University of Burgundy and Franche-Comté, Dijon, France, [5]Anatomie Cytologie Pathologiques, Hopital Ambroise Pare, Boulogne-Billancourt, France, [6]Oncology, Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain, [7]Pathology, Universitätsklinikum Dresden, Dresden, Germany, [8]INSERM UMR1102, Pierre et Marie Curie University, Paris, France, [9]Département de Pathologie, Institut Universitaire du Cancer Toulouse - Oncopole, Toulouse, France, [10]EA3430, Strasbourg University, Strasbourg, France, [11]Biology, Centre Antoine Lacassagne, Nice, France, [12]Oncology, CHU La Timone Enfants, Marseille, France, [13]Department of Gastroenterology and Digestive Oncology, Hôpital Européen Georges-Pompidou, Paris, France, [14]Medicine, Institut Gustave Roussy, Villejuif, France, [15]Biostatistique, La Ligue Contre le Cancer, Paris, France

61PD **Genetic variations within the HER3 gene predict outcome for mCRC patients treated with first-line FOLFIRI/bevacizumab or FOLFIRI/cetuximab: Data from FIRE-3**

M.D. Berger[1], S. Stintzing[2], V. Heinemann[3], S. Cao[4], D. Yang[4], Y. Miyamoto[1], M. Suenaga[1], D.L. Hanna[1], S. Soni[1], A. Puccini[5], R. Tokunaga[1], M. Naseem[1], F. Battaglin[1], M. McSkane[1], W. Zhang[1], H-J. Lenz[1]

[1]Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [2]Department of Medicine III, Ludwig Maximilians University - Grosshadern, Munich, Germany, [3] Department of Medical Oncology and Comprehensive Cancer Center, Ludwig Maximilians University - Grosshadern, Munich, Germany, [4]Preventive Medicine, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [5]Medical Oncology 1, IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

62PD **Could plasma EBV DNA kinetics predict long-term disease-free survival in metastatic nasopharyngeal carcinoma?**

L. Guoying, H. Liang, W-X. Xia, Y-Q. Xiang, X. Lv, X. Guo, Y-H. Yu, S-H. Lv, K-Y. Liu, W-Z. Qiu, X-J. Huang, W-Z. Li

Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China

63PD Predictive and pharmacodynamic biomarkers associated with phase II, selective and orally bioavailable AXL inhibitor bemcentinib across multiple clinical trials

B. Holt[1], D. Micklem[1], A. Brown[1], M. Yule[1], J. Lorens[2]

[1]*BerGenBio ASA, Bergen, Norway,* [2]*Department of Biomedicine, Centre for Cancer Biomarkers, University of Bergen, Bergen, Norway*

64PD Identification and validation of a 23-gene expression signature for subtype classification of medulloblastoma

Q. Xu[1], Q. Wang[2], J. Chen[3], C. Chen[3], Y. Sun[3], L. Chen[3], Q. Ye[4], X. Du[2]

[1]*Institute of Machine Learning and Systems Biology, College of Electronics and Information Engineering, Tongji University, Shanghai, China,* [2]*Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China,* [3]*Research and Development, Canhelp Genomics, Hangzhou, China,* [4]*Department of Pathology, Nanjing Drum Tower Hospital, Nanjing, China*

65PD High tumor mutational burden (TMB) and PD-L1 have similar predictive utility in 2L+ NSCLC patients (pts) treated with anti-PD-L1 and anti-CTLA-4

B.W. Higgs, C.A. Morehouse, P.Z. Brohawn, S. Sridhar, R. Raja, G. Gao, J. Englert, K. Ranade

Translational Medicine, MedImmune, Gaithersburg, MD, USA

66P TCR beta chain convergence defines the tumor infiltrating T cell repertoire of melanoma and non-small cell lung carcinoma

T. Looney[1], G. Lowman[1], L. Miller[1], E. Linch[2]

[1]*Clinical Next-Generation Sequencing Division, Thermo Fisher Scientific, South San Francisco, CA, USA,* [2]*Clinical Next-Generation Sequencing Division, Thermo Fisher Scientific, Carlsbad, CA, USA*

Background: T cell convergence refers to the process whereby antigen-driven selection enriches for T cell receptors having a shared antigen specificity but different amino acid or nucleotide sequence. T cell recruitment and expansion within the tumor microenvironment (TME) may be directed by responses to tumor neoantigen, suggesting that elevated T cell convergence could be a general feature of the tumor infiltrating T cell repertoire. Here we evaluate evidence for T cell convergence in tumor biopsy from

research subjects with melanoma and non-small cell lung carcinoma (NSCLC) and peripheral blood leukocytes (PBL) from healthy donors.

Methods: Total RNA from 63 melanoma and 19 NSCLC tumor biopsy research samples (non-FFPE) was extracted for use in long-amplicon TCRB chain sequencing (mean amplicon of 330bp covering CDR1, 2 and 3) via the Oncomine TCR Beta-LR Research Assay. To evaluate T cell convergence, we searched for instances where TCRB chains were identical in amino acid space but had distinct nucleotide sequences owing to N-addition and exonucleotide chewback within the V-D and D-J junctions of the CDR3. To provide context, we evaluated evidence for T cell convergence in PBL T cell repertoires derived from 16 healthy donors.

Results: Sequencing of melanoma biopsy research samples typically yielded within the range of 2000 to 8000 clones per sample. Convergent T cell receptors were identified in the great majority of melanoma and NSCLC tumor infiltrating T cell repertoires having greater than 100 detected clones (92% and 100%, respectively). The frequency of convergent T cell rearrangements was significantly greater in melanoma and NSCLC tumor biopsies than T cell repertoires derived from healthy PBL research samples.

Conclusions: These data suggest that T cell convergence may be a common feature of the melanoma and NSCLC infiltrating T cell repertoire. Convergence was more frequently observed within the TME than T cell repertoires derived from healthy PBL, consistent with elevated antigen-driven T cell selection within the TME. The finding of elevated T cell convergence in melanoma and NSCLC suggests that convergence may be a hallmark of immunogenic tumors. For research use only.

Legal entity responsible for the study: Thermo Fisher Scientific.

Funding: Thermo Fisher Scientific.

Disclosure: T. Looney, G. Lowman, L. Miller, E. Linch: Employee: Thermo Fisher Scientific.

67P PI3K inhibition and modulation of immune and tumor microenvironment markers by copanlisib in patients with non-Hodgkin's lymphoma or advanced solid tumors

A.H. Awada[1], F. Morschhauser[2], J-P. Machiels[3], G. Salles[4], S. Rottey[5], S. Rule[6], D. Cunningham[7], F. Peyrade[8], C. Fruchart[9], H-T. Arkenau[10], I. Genvresse[11], K. Koechert[11], G. Cisternas[12], C. Granvil[13], C. Pena[14], L. Liu[14]

[1]Department of Medicine, Institute Jules Bordet, Brussels, Belgium, [2]Department of Hematology, CHRU - Hôpital Claude Huriez, Lille, France, [3]Oncology, Cliniques Universitaires St. Luc, Brussels, Belgium, [4]Department of Hematology, Civil Hospices of Lyon, University Claude Bernard Lyon-1, Pierre Benite, France, [5]Department of Medical Oncology, Gent University Hospital, Gent, Belgium, [6]Department of Haematology, Plymouth University, Plymouth, UK, [7]Medicine, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, UK, [8]Medical Oncology, Centre Anticancer Antoine Lacassagne, Nice, France, [9]Department of Clinical Hematology, Centre Francois Baclesse, Caen, France, [10]SCRI, Sarah Cannon Research Institute, London, UK, [11]Pharmaceutical Division, Bayer AG, Berlin, Germany, [12]Oncology, Bayer AG, Berlin, Germany, [13]Clinical Pharmacology, Bayer HealthCare Pharmaceuticals Inc, Whippany, NJ, USA, [14]Clinical Science, Bayer HealthCare Pharmaceuticals Inc, Whippany, NJ, USA

Background: Copanlisib, a pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant activity against α and δ isoforms, shows immune stimulating effects and anti-tumor activity in combination with immune checkpoint blockers in tumor models. Here we explore tumor PI3K signaling and the effects of copanlisib on immune and tumor microenvironment modulation in subjects with NHL and solid tumors (ST) in a phase I pharmacodynamic study (NCT02155582).

Methods: Patients received 0.4 or 0.8 mg/kg (equivalent to a flat dose of 60 mg) copanlisib on an intermittent schedule (QW, IV, 3 wks on/1 wk off). Tumor biopsies were performed at baseline and Day 15. Tumor PI3K isoforms, PTEN, and CD3, CD4 and CD8 tumor infiltrating lymphocytes (TILs) were assessed by IHC. Plasma protein markers were measured using multiplexed immunoassay. Tumor and lymphoma responses were based on RECIST 1.1 and modified Cheson 2007 criteria, respectively.

Results: A total of 61 patients were treated: 33 NHL (20 at 0.4 mg/kg and 13 at 0.8 mg/kg) and 28 ST (14 at 0.4 mg/kg and 14 at 0.8 mg/kg). Among patients treated at 0.8 mg/kg, 2 had CR (PTCL and DLBCL) and 5 had PR (MCL, FL, 2 DLBCL, and endometrial adenocarcinoma); 1 additional PR (DLBCL) occurred at 0.4 mg/kg. Tumor PI3K α was detected in most NHL (18/19) and ST (22/25) samples with comparable intensity. PI3K δ was predominantly present in NHL (18/19). PI3K ß and γ were present in a subset of NHL and ST. PTEN loss was more frequent in ST than NHL. CD3, CD4 and CD8 TIL numbers were higher in NHL than in ST. At 0.8 mg/kg copanlisib decreased tumor pAKT and pS6 in both NHL and ST, and reduced CD4 TILs in NHL (mean -81%, $n = 7$), with little effect on CD8 TILs in both NHL and ST. In plasma, copanlisib decreased cytokine/chemokines (e.g. CCL2, CCL5, CCL17), and factors associated with macrophages (e.g. CD163, CCL4, CCL22) and Treg cells (IL-2Ra). High baseline levels of CD27 and IL2Ra were associated with tumor reduction in NHL ($p < 0.05$, unadjusted).

Conclusions: The high prevalence of the PI3K isoforms – especially α in both NHL and ST and δ in NHL – is consistent with a role for PI3K signaling in immune suppression. The immune modulation profile for copanlisib supports combination studies with immunotherapy.

Clinical trial identification: NCT02155582.

Legal entity responsible for the study: Bayer AG.

Funding: Bayer AG.

Disclosure: I. Genvresse, K. Koechert, G. Cisternas, C. Granvil, C. Pena, L. Liu: Employee: Bayer. All other authors have declared no conflicts of interest.

68P Pan-squamous genomic profiling stratified by anatomic tumor site and viral association

M. Montesion[1], C.H. Chung[2], E.S. Sokol[1], S.A. Khan[3], H. Kang[4], L.A. Albacker[1], J.M. Johnson[5], G.M. Frampton[1], V.A. Miller[6], J.S. Ross[7], S.M. Ali[6]

[1]Cancer Genomics Research, Foundation Medicine, Inc., Cambridge, MA, USA, [2]Department of Head and Neck-Endocrine Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA, [3]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA, [4]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA, USA, [6]Clinical Development, Foundation Medicine, Inc., Cambridge, MA, USA, [7]Pathology, Foundation Medicine Inc., Cambridge, MA, USA

Background: Squamous cell carcinomas (SCC) have diverse anatomic etiologies but may share common genomic biomarkers. We profiled 7,871 unique SCCs across nine anatomic sites to investigate commonality in genomic alterations (GA), tumor mutational burden (TMB), human papillomavirus (HPV) association, and mutational signatures.

Methods: Tissue from over 8,100 unique SCC samples originating from nine anatomic sites (anogenital (anus, cervix, penis, vagina, vulva), esophagus, head and neck, lung, and skin) were sequenced by hybrid capture-based comprehensive genomic profiling to evaluate GA and TMB. About 3% of non-cutaneous SCC samples had UV signatures, indicative of potential primary site misdiagnoses, and were filtered from the analysis. Detection of HPV, including high-risk strains 16, 18, 31, 33, and 45, was implemented through de novo assembly of non-human sequencing reads and BLASTn comparison against all viral nucleotide sequences in the NCBI database.

Results: The proportion of HPV+ patients by anatomic site varied, with the highest being anal (91%) and cervical (83%). The mutational landscape of each cohort was similar, regardless of anatomic origin, but clustered based on HPV status. The largest differences in GA frequency as stratified by HPV- vs. HPV+ were TP53 (87% vs. 12%), CDKN2A (45% vs. 6%), and PIK3CA (22% vs. 33%). The median TMB in cases originating from HPV-associated sites was similar, regardless of HPV status. Higher median TMB was observed in lung and skin cases, which exhibited significant enrichment of mutational signatures indicative of tobacco- and UV-induced DNA damage, respectively.

Conclusions: HPV+ and HPV- SCC populations have distinct genomic profiles and, for the latter, anatomic site is correlated with TMB distribution, secondary to associated carcinogen exposure. As such, biomarkers such as TMB and UV signature can provide unexpected insight into site of origin misdiagnoses and may correlate with benefit from immune checkpoint inhibitors.

Table: 68P

Tumor Site	% HPV+	Median TMB (Interquartile Range)	% TMB >= 10	% TMB >= 20
Anogenital (n = 1213)	76	5 (6)	17	5
Head and Neck (n = 1843)	36	4 (5)	15	5
Esophageal (n = 416)	6	5 (4)	13	2
Lung (n = 3977)	5	9 (8)	43	9
Skin (n = 422)	8	40 (69)	68	62

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: M. Montesion, E.S. Sokol: Employee: Foundation Medicine, Inc. L.A. Albacker, G.M. Frampton, V.A. Miller, J.S. Ross, S.M. Ali: Employee and stock ownership: Foundation Medicine, Inc. All other authors have declared no conflicts of interest.

69P Toward the standardization of bioinformatics methods for the accurate assessment of tumor mutational burden (TMB)

H. Chang, S. Srinivasan, A. Sasson, R. Golhar, D. Greenawalt, S. Kirov, J.D. Szustakowski

Translational Medicine, Bristol-Myers Squibb, Princeton, NJ, USA

Background: TMB has emerged as a predictive biomarker of response to immune checkpoint inhibitors. CheckMate 227 demonstrated that patients with non-small cell lung cancer (NSCLC) with TMB ≥10 mutations/megabase derived enhanced benefit from first-line treatment with nivolumab + ipilimumab vs chemotherapy (Hellmann et al. NEJM 2018). Standardized approaches for the measurement and reporting of TMB are essential for the real-world implementation of TMB. This study aimed to refine a bioinformatic pipeline for mutation calling and annotation of whole exome sequencing (WES) data for TMB assessment.

Methods: In CheckMate 026, TMB was assessed by WES on formalin-fixed, paraffin-embedded tumor samples and matched blood from 312 patients with NSCLC (Carbone et al. NEJM 2017). Data from each sample were aligned to a reference human genome and somatic mutations were called by comparing matched tumor and blood samples using the TNsnv and Strelka algorithms. The somatic mutations were additionally filtered for germline variants in public databases. TMB scores were compared with data from 710 NSCLC samples in The Cancer Genome Atlas (TCGA) dataset. We examined the concordance of TMB estimates using several mutation filtering schemes, with and without matched germline controls.

Results: TMB scores including synonymous, indel, frameshift, and nonsense mutations (all mutations) were ~3-fold higher than matched data filtered for missense mutations only, but values were highly correlated (Spearman's $r = 0.99$). Scores including missense mutations only were similar to those generated from TCGA, but those including all mutations were on average higher. Using public databases for germline subtraction showed a trend for race-dependent increases in TMB scores.

Conclusions: Standardization of bioinformatic analyses is critical to the clinical implementation of TMB assessment. TMB assessment is sensitive to variations in bioinformatic parameters (eg, which type of mutation to include), which may affect the identification of patients likely to respond to immunotherapy. These results show that data from different pipelines are highly correlated, suggesting that reliable assessment of TMB across different centers and platforms is achievable.

Clinical trial identification: NCT02041533.

Editorial acknowledgement: Medical writing assistance was provided by Stuart Rulten, PhD, of Spark Medica Inc. (US), funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: H. Chang, S. Srinivasan, A. Sasson, R. Golhar, D. Greenawalt, J.D. Szustakowski: Employment and stock ownership: Bristol-Myers Squibb. S. Kirov: Stock ownership and compensation: Bristol-Myers Squibb.

70P Prediction of primary resistance to anti-PD1 therapy (APD1) in second-line NSCLC

E.F. Smit[1], J.G. Aerts[2], M. Muller[1], A-L.N. Niemeijer[3], H. Roder[4], C. Oliveira[4], J. Roder[4]

[1]Pulmonary Diseases, The Netherlands Cancer Institute, Amsterdam, Netherlands, [2]Medical Oncology, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Department of Pulmonology and Respiratory Medicine, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [4]Research, Biodesix, Inc., Boulder, CO, USA

Background: APD1, while capable of restoring immunity, does not benefit all patients. While molecular tests like PD-L1 expression and TMB help in enriching response in respective subsets, a test identifying patients showing primary resistance to APD1 which does not require tissue samples could help in optimizing treatment regimens.

Methods: Outcome data (PFS/OS) were correlated with protein profiles from mass spectrometry of the circulating proteome of pretreatment serum from 116 2nd line NSCLC patients treated with nivolumab (development set S) using multivariate machine learning methods related to deep learning. The resulting test stratified patients into three groups: group A having very poor outcomes, group B having intermediate outcomes, and group C having very good outcomes. Development results were obtained using out-of-bag estimators. Two additional patient cohorts treated with nivolumab, V1($N = 58$) and V2($N = 75$), were used for validation.

Results: The proportions of patients in A, B, and C were 41:43:32 in S, 23:18:17 in V1, and 32:19:24 in V2. Median PFS/OS in the poor prognosis group A was 43/132 days in S, 105/189 days in V1, 90/278 days in V2, and in the good prognosis group C 276/528 days in S, 192/459 days in V1, and 155/not reached days in V2. In a comparison with historical controls treated with single agent chemotherapy and analyzed with the same technique, nivolumab appeared substantially superior in the good prognosis group C, while there was no evidence of superiority in the poor prognosis group A. In multivariate analysis including performance status, smoking history, and histology, the test remained an independent predictor of outcome. The patterns of protein expression related to poor prognosis in group A patients were associated with elevated complement, wound healing, and acute phase reactants.

Conclusions: We developed and validated a test stratifying patients into three groups with significantly different outcomes on nivolumab. The poor prognosis group showed little benefit from nivolumab, and other treatments may be needed, while in the good prognosis group outcomes were very good for a 2nd line population. These results emphasize the importance of the host immune response in the prediction of APD1 efficacy.

Legal entity responsible for the study: Biodesix.

Funding: Has not received any funding.

Disclosure: J.G. Aerts: Advisory boards: BMS, MSD, Roche, AstraZeneca, Eli-Lilly, Boehringer Ingelheim, Amphera; Stock owner: Amphera. H. Roder: Officer, salary, stock options: Biodesix. C. Oliveira, J. Roder: Employment, stock options: Biodesix. All other authors have declared no conflicts of interest.

71P Immunomodulatory germline variation impacts the development of multiple primary melanoma (MPM)

R. Ferguson[1], A. Archambault[1], D. Simpson[1], E. Kazlow[1], R. Lax[1], U. Moran[1], M.A. Wilson[2], R. Shapiro[2], A. Pavlick[2], I. Osman[3], D. Polsky[3], T. Kirchhoff[4]

[1]Perlmutter Cancer Center, New York University Medical Center, New York, NY, USA, [2]Department of Medicine, New York University - Perlmutter Cancer Center - Langone Medical Center, New York, NY, USA, [3]Dermatology, New York University Medical Center, New York, NY, USA, [4]Perlmutter Cancer Center, New York University, New York, NY, USA

Background: During their lifetime about 8% of patients with single primary cutaneous melanoma (SPM) will develop multiple primary melanomas (MPM), which are associated with significantly higher mortality compared to patients with SPM. Based on the evidence that the immune system plays a role in regulating melanoma progression we explored whether germline genetic variants controlling the expression of immunomodulatory genes (immunomodulatory quantitative trait loci, eQTLs) discern risk of MPM compared to patients with SPM or healthy controls.

Methods: Previously, we identified 50 eQTLs significantly associated with the expression of 265 immunomodulatory genes using the MuTHer twin cohort. These 50 SNPs were genotyped in 837 SPM and 104 MPM individuals using MassARRAY system. 1047 healthy controls were obtained from a publically available GWAS on CM ascertained at MD Anderson (phs000187.v1.p1). We employed multivariate logistic regression to test the association of SNPs with MPM vs cancer-free controls and MPM vs SPM.

Results: When comparing MPM vs SPM, rs2071304, previously linked to expression of SPI1 in MuTHer data, showed a strong association with reduction of MPM risk ($OR = 0.60$; 95% CI = 0.45-0.81; $p = 0.0007$). Intriguingly, this variant also trended toward significance when comparing MPM vs controls ($OR = 0.61$; 95% CI: 0.44-0.85; $p = 0.003$). Finally, our most significant association when comparing MPM to controls was for rs2276645 ($OR = 0.60$; 95% CI = 0.45-0.81; $p = 0.0008$), an eQTL associated with Zap-70 expression.

Conclusions: Our data, for the first time, indicate that the inherited host immunity impacts risk of MPM in individuals with SPM, highlighting an importance of immune involvement in melanoma progression. The MPM risk-predicting genetic variants identified here or in expanded efforts, currently underway, may eventually lead to a diagnostic tool allowing for enhanced screening and clinical management of patients at risk of MPM, hence reducing elevated MPM-associated mortality. Additionally, our results further support that MPM and SPM may have different genetics underpinnings and should be treated as separate clinical entities.

Legal entity responsible for the study: Tomas Kirchhoff.

Funding: NIH.

Disclosure: D. Polsky: Research grant: BioRad-laboratory reagents: Novartis. All other authors have declared no conflicts of interest.

72P Leukocyte telomere length and recurrence risk after EGFR-TKIs therapy in patients with advanced lung adenocarcinoma

M. Yang[1], J. Li[2], N. Zhang[2], H. Xing[1], J. Liu[1]

[1]Shandong Provincial Key Laboratory of Radiation Oncology, Cancer Research Center, Shandong Cancer Hospital, Jinan, China, [2]Department of Radiation Oncology, Shandong Cancer Hospital, Jinan, China

Background: Gefitinib is currently one of the mostly used epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) recommended for treating non-small cell lung cancer. However, the factors that predict treatment prognosis and drug resistance to EGFR-TKIs remain elusive. The objective of this study is to exam the association between leukocyte relative telomere length (RTL) and prognosis or drug resistance of advanced lung adenocarcinoma to gefitinib treatment.

Methods: In this study, three hundred and sixty-nine patients with stage IIIB or IV lung adenocarcinoma were recruited between January 2009 and June 2013. All patients were treated with gefitinib orally at a daily dose of 250 mg as first-line monotherapy. Leukocyte RTL of each patient was measured using quantitative polymerase chain reaction (qPCR) protocol on an ABI PRISM 7900HT Sequence Detection System (Applied Biosystems) and calculated according to Cawthon's formula. Differences in patients' characteristics were calculated by Pearson's χ^2 tests or Student's t test. Cox proportional hazard regression analyses were used to calculate univariate and multivariate hazard ratios (HRs). Survival differences were examined using the log-rank test. Two-sided $P < 0.05$ indicated a significant difference.

Results: Among 369 patients, EGFR mutations were positive in 181 patients (49.1%). Compared to long RTL, short leukocyte RTL was significantly associated with poor prognosis in all patients after gefitinib treatment (overall survival: 12.9 months vs. 17.8 months, $P = 1.2 \times 10^{-4}$; progression free survival: 7.8 months vs. 13.0 months, $P = 0.043$). Additionally, statistically significant association between short leukocyte RTL and shorten OS still existed among the EGFR mutant patients with gefitinib treatment (HR = 1.65, 95% CI = 1.28-2.12; $P = 0.006$). Besides EGFR mutation status, short RTL also contributed to significantly elevated risk of gefitinib primary resistance (HR = 1.50, 95% CI = 1.05-2.15, $P = 0.027$).

Conclusions: Our results highlight the potential of leukocyte RTL as a novel biomarker in advanced lung adenocarcinoma treated with EGFR-TKIs and the possibility of patient-tailored decisions based on leukocyte RTL.

Legal entity responsible for the study: Ming Yang.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

73P Gene embedding: A novel machine learning approach to identify gene candidates related to immunotherapy responsiveness

C.T. Choy[1], C.H. Wong[2], S.L. Chan[2]
[1]Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China, [2]The Cancer Drug Testing Unit, State Key Laboratory of Oncology in South China, Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

Background: Apart from PD-L1 and mutational load, there are no genetic predictive biomarkers for checkpoint inhibitors treatment. In this study, gene embedding, a machine learning technique, was used to single out related genes of immune checkpoint proteins (i.e. PD-1, PD-L1, CTLA-4) as new potential predictors for such responders.

Methods: TCGA RNASeqV2 level 3 RSEM normalized read counts (January 2016) were downloaded from the Broad Institute TCGA GDAC Firehose. A shallow neural network, aka embedding layers for samples and genes, were trained using log2 transformed data. Neighbors closeness were evaluated by euclidean distance. The model was kept blind from any additional information, including cancer types, protein-protein interactions and gene ontologies.

Results: Gene expressions of 13045 samples from 36 cancer types were embedded into 50-dimension space, while cancer types were learnt by the model without supervision. Immunotherapy responders and non-responders were stimulated from melanoma (SKMC) and lung squamous cell carcinoma (LUSC) data, and hepatocellular carcinoma and prostate cancer data respectively. 9 genes (TNFRSF8, CLEC10A, FCN1, CD8B, SLA2, IL2RA, CTLA4, GZMH), 3 (CD101, LOC154761, RNF152) genes, and 6 (SH2D1A, MEI1, PDCD1, GFI1, SIT1, SIRPG) genes were found to be closely related neighbors with PD-1, PD-L1, and CTLA-4 respectively in responders but not in non-responders. All neighbors were neither co-expressed in SKMC/LUSC dataset nor indicated as interacting partners on existing databases (BioGRID, MINT, iRefWeb, STRING, HPRD and Reactome). 88.8% genes were evidenced as either directly related to checkpoint proteins and/or T cells activation in literature. Further evaluation of the role of identified targets in immune checkpoint blockade therapy would be warranted.

Conclusions: We identified potential biomarker candidates for immune checkpoint blockade therapy by TCGA data mining and demonstrated the utility of gene embedding learned from big gene expression dataset as a powerful tool to uncover gene relationships that may not be discovered otherwise without prior knowledge on functional interactions.

Legal entity responsible for the study: Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong.
Funding: Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong.
Disclosure: All authors have declared no conflicts of interest.

74P Common and rare DPYD variants are predictive for 5FU/capecitabine (5FU) toxicity: The MRC COIN and COIN-B trials

A. Madi[1], D. Fisher[2], T.S. Maughan[3], J.P. Colley[4], A.M. Meade[2], J. Maynard[4], V. Humphreys[4], H. Wasan[5], R.A. Adams[4], S. Idziaszczyk[4], R. Harris[4], R.S. Kaplan[2], J.P. Cheadle[4]
[1]Medical Oncology, Clatterbridge Cancer Center, Wirral, UK, [2]Clinical Trials Unit, MRC, London, UK, [3]CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Oxford, UK, [4]Division of Cancer and Genetics, Cardiff University, Cardiff, UK, [5]Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK

Background: Rare genetic variants in DPYP increase toxicity and screening for them prevents serious complications by upfront reduction in 5FU dose; however, most patients with severe toxicities do not have a rare mutation. We have previously shown that 2 common DPYD variants were associated with toxicity in patients with advanced colorectal cancer treated on COIN & COIN-B (abstract 3509, ASCO 2013): Cys29Arg [rs1801265] (Minor Allele Frequency (MAF) 0.21) and Val732Ile [rs1801160] (MAF 0.04). We have now genotyped 4 rare variants using the same cohort.

Methods: Blood samples were available from 2183 patients treated with first line oxaliplatin-5FU ± cetuximab. We assayed IVS14 + 1G>A [rs3918290], Asp949Val [rs67376798], Lys259Glu [rs45589337] and Ser534Asn [rs1801158] using KASPar. Primary endpoint was dose reduction or delay in chemotherapy in the first 12 weeks of treatment due to any toxicity except neuropathy. Secondary endpoints were grade $\geq$2 versus grade <2 for neutropenia, lethargy, Nausea & Vomiting (N&V), diarrhoea, stomatitis, Hand-Foot Syndrome (HFS) and infection.

Results: Two rare variants were associated with toxicity (OR (95% CI)): Asp949Val with neutropenia 3.2 (1.2-8.2) P = 0.019, N&V 3.4 (1.5-7.3) P = 0.002, diarrhoea 4.6 (2.1-10.1) P < 0.001 and infection 5.5 (1.3-24.2) P = 0.024; IVS14 + 1G>A with lethargy 5.3 (1.9-14.9) P = 0.002, diarrhoea 4.4 (1.7-11.0) P = 0.002, stomatitis 4.6 (1.7-12.6) P = 0.003, HFS 3.8 (1.2- 11.8) P = 0.021 and infection 19.2 (5.0-73.8) P < 0.001. MAF was 0.007 and 0.005, respectively. The effect on toxicity for our 2 common variants was not as marked (OR (95% CI)): Cys29Arg 0.8 (0.7-1.0) P = 0.008 (protective) and Val732Ile 1.6 (1.1-2.1) P = 0.006 for the primary endpoint.

Conclusions: We have validated 2 mutations, Asp949Val and IVS14 + 1G>A, as predictors for 5FU toxicity in a large cohort of patients and recommend they should be screened for. Our data suggest that common DPYD variants are also associated with toxicity but not to the same level seen with rare ones. While the presence of a single common variant is not an indication for dose modification, the presence of multiple variants in a patient might be. Further work is needed to establish what combinations of common DPYD variants would necessitate 5FU dose alteration.

Legal entity responsible for the study: Cardiff University and MRC CTU.
Funding: This work was supported by The Bobby Moore Fund from CRUK, Cancer Research Wales, Tenovus, the Wales Gene Park, and an unrestricted research grant from Merck Serono.
Disclosure: T.S. Maughan, J.P. Cheadle: Part funded by an unrestricted research grant from Merck Serono. All other authors have declared no conflicts of interest.

75P The landscape of NTRK fusions in Chinese patients with solid tumor

Q. Ling[1], B. Li[2], X. Wu[3], H. Wang[4], Y. Shen[5], M. Xiao[6], Z. Yang[6], R. Ma[7], D. Chen[8], H. Chen[9], X. Dong[8], W. Wang[10], M. Yao[7]
[1]Department of Hepatobiliary & Pancreatic Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China, [2]Department of General Medicine, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China, [3]Department of Thoracic Surgery, Nanfang Hospital, Guangzhou, China, [4]Respiratory Oncology Department, Cancer Hospital of Shantou University Medical College, Shantou, China, [5]Department of Gynecology, Zhongda Hospital, Medical School, Southeast University, Nanjing, China, [6]Department of Hepatobiliary & Pancreatic Surgery, Shu Lan (Hangzhou) Hospital, Zhejiang University International Hospital, Hangzhou, China, [7]Medical Department, OrigiMed, Shanghai, China, [8]Department of Pathology, OrigiMed, Shanghai, China, [9]Department of Bioinformatics, OrigiMed, Shanghai, China, [10]Department of Cancer Immunology, OrigiMed, Shanghai, China

Background: NTRK gene fusions resulting in the elevated expression of TRK kinases were discovered in a wide variety of tumor types but generally at a low frequency. TRK inhibitors such as LOXO-101 and entrectinib had remarkable and durable antitumor activities in patients (pts) with TRK fusion-positive cancers, regardless of age or tumor type.

Methods: FFPE tumor samples of over 3700 Chinese solid tumor pts were collected for NGS-based assay. We measured the gene fusions, mutations, and copy number alterations in tumor tissue against matched blood. Pan-Trk IHC testing was performed on five NTRK1 fusions.

Results: 12 pts were idendified as NTRK fusion positive, which accounted to approximately 0.3% of the Chinese solid tumor pts in our cohort. Seven out of 12 pts harbored NTRK1 fusions with 6 partners, and the remaining ones were NTRK3 fusions with 2 partners. The half fusions with novel partner genes or breakpoints were defined as likely fusions. The tumor types of pts with NTRK fusions included NSCLC, colorectal cancer (CRC), prostate cancer and fibrosarcoma. NTRK fusions were more likely t occur in NSCLC and CRC, which accouted for 0.3% and 1.4%, respectively. Three predicted likely fusions and two known fusions were selected to perform pan-Trk IHC assay, and four were IHC positive. One known TPR-NTRK1 fusion not detected by IHC, which highlighted the necessity to use NGS to detect NTRK fusions due to higher sensitivity and capability. NTRK fusions were not always mutually exclusive with driver mutations. Three lung cancer pts with NTRK fusions also harbored EGFR-sensitive mutations.

Table: 75P

Gene fusion	Cancer type	IHC	Pathogenic
NTRK1			
TPM3 exon10-NTRK1 exon8	Colorectal cancer	Positive	Likely
IRF2BP2 exon1-NTRK1 exon8	Prostate cancer	Positive	Likely
PRDX1 exon5-NTRK1 exon12	Lung adenocarcinoma	Positive	Likely
LMNA exon2-NTRK1 exon11	Fibrosarcoma	Positive	Known
TPR exon21-NTRK1 exon 9	Lung adenocarcinoma	Negative	Known
TPM3 exon10-NTRK1 exon8	Colorectal cancer	NA	Likely
AMOTL2 exon6-NTRK1 exon12	Lung adenocarcinoma	NA	Likely
NTRK3			
ETV6 exon5 -NTRK3 exon15	Colorectal cancer	NA	Known
ETV6 exon5 -NTRK3 exon15	Colorectal cancer	NA	Known
ETV6 exon5 -NTRK3 exon15	Squamous cell lung cancer	NA	Known
ETV6 exon4 -NTRK3 exon14	Small cell lung cancer	NA	Known
AKAP13 exon3-NTRK3 exon14	Lung adenocarcinoma	NA	Likely

Conclusions: This study revealed NTRK fuisons in approximately 0.3% of Chinese solid tumor pts for the first time. The NTRK gene fusions more commonly occurred in NSCLC (0.3%) and CRC (1.4%), but may occur with other targetable alterations such as EGFR-activating mutations. NGS panel sequencing showed the advantage of detecting NTRK fusion and providing structure information of partners which could potentially guide more precise treatment options.

Legal entity responsible for the study: OrigiMed.

Funding: Has not received any funding.

Disclosure: R. Ma, D. Chen, H. Chen, X. Dong, W. Wang, M. Yao: Employee: OrigiMed. All other authors have declared no conflicts of interest.

76P Correlative analyses of serum biomarkers and efficacy outcomes in the randomized phase II trial of lenvatinib (LEN), everolimus (EVE), or LEN+EVE in patients with metastatic renal cell carcinoma

C-H. Lee[1], R.J. Motzer[1], H. Glen[2], M.D. Michaelson[3], J. Larkin[4], Y. Minoshima[5], M. Kanekiyo[5], R. Dairiki[5], P. Sachdev[6], C.E. Dutcus[6], Y. Funahashi[5], M.H. Voss[1]

[1]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK, [3]Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA, [4]Department of Medical Oncology, Royal Marsden NHS Hospital, London, UK, [5]Eisai Co., Ltd., Ibaraki, Japan, [6]Oncology Business Group, Eisai Inc., Woodcliff Lake, NJ, USA

Background: In a randomized, 3-arm, phase 2 trial of patients (pts) with metastatic renal cell carcinoma (mRCC) following 1 VEGF-targeted therapy, LEN+EVE improved median progression-free survival (PFS) compared with EVE (hazard ratio [HR] 0.40; 95% confidence interval [CI] 0.24–0.68; $P < 0.001$) or LEN (HR 0.66; 95% CI 0.39–1.10; $P = 0.121$).(Motzer et al. Lancet Oncol 2015) We present biomarker analyses from this study.

Methods: Serum samples collected at baseline were analyzed by Luminex-based xMAP® assays for 40 candidate biomarkers. Baseline biomarker levels were correlated with PFS using Cox regression analysis. Biomarkers with the strongest associations (top 5 ranked by log-rank P-value and HR) with PFS in the LEN+EVE arm were integrated into composite biomarker scores (CBS)(Voss et al. Br J Cancer 2016) All P-values are nominal.

Results: Serum samples from 145 pts (LEN+EVE, n = 49; LEN, n = 50; EVE, n = 46) were analyzed. HGF, MIG, IL-18BP, IL-18, and ANG-2 concentrations demonstrated the strongest correlation with PFS and were selected for the CBS analysis. Associations with PFS are summarized in the table. In the LEN+EVE arm, median PFS for pts with high (3–5) vs low (0–2) CBS was 20.1 vs 5.6 months, respectively (HR 0.28; $P = 0.002$), whereas no significant difference between high vs low CBS was seen in the EVE arm (3.6 vs 5.5 months; HR 1.02; $P = 0.951$). Median PFS differed significantly between treatment arms for pts with high CBS (LEN+EVE vs EVE, 20.1 vs 3.6 months; $P < 0.001$), but not for pts with low CBS (LEN+EVE vs EVE, 5.6 vs 5.5 months; $P = 0.329$).

Table: 76P

	LEN+EVE		EVE		LEN+EVE vs EVE HR (95% CI)
	n	Median PFS (months)	n	Median PFS (months)	
Total	51	14.6	50	5.5	0.40 (CI 0.24–0.68) $P < 0.001$
High CBS	28	20.1	20	3.6	0.19 (0.09–0.41) $P < 0.001$
Low CBS	20	5.6	24	5.5	0.70 (0.34–1.43) $P = 0.329$
High vs low HR (95% CI)	0.28 (0.12–0.63) $P = 0.002$		1.02 (0.52–1.99) $P = 0.951$		

Conclusions: In pts treated with LEN+EVE, high CBS was correlated with PFS benefit; further research is needed to determine if the score can be used to identify pts who may benefit from combination therapy. Altogether, these biomarkers may be predictors of response to LEN+EVE therapy in pts with mRCC.

Clinical trial identification: NCT01136733.

Editorial acknowledgement: Editorial assistance was provided by Oxford PharmaGenesis of Newtown, PA, USA, which was funded by Eisai Inc.

Legal entity responsible for the study: Eisai Inc.

Funding: Eisai Inc.

Disclosure: C-H. Lee: Consulting/advisory role: Exelixis; Research funding: Bristol-Myers Squibb, Eisai, Pfizer. R.J. Motzer: Consulting/advisory role: Eisai, Exelixis, Novartis, Pfizer; Research funding: Bristol-Myers Squibb, Eisai, Genentech/Roche, GlaxoSmithKline, Novartis, Pfizer; Travel, accomodations, expenses: Bristol-Myers Squibb. H. Glen: Consulting/advisory role: Astellas Pharma, Eisai, and Janssen; Research funding: Eisai. M.D. Michaelson: Consulting/advisory role: Exelixis, Novartis, Pfizer; Research funding: Argos Therapeutics, Bristol-Myers Squibb, Eisai, Exelixis, Genentech, Merck, Pfizer, Takeda. J. Larkin: Research funding: Pfizer (institution), Novartis (institution), Bristol-Myers Squibb, Merck Sharp & Dohme; Travel, accomodations, expenses: Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Novartis, GlaxoSmithKline, Genentech, Eisai. Y. Minoshima, M. Kanekiyo, R. Dairiki, Y. Funahashi: Employee: Eisai Co., Ltd. P. Sachdev, C.E. Dutcus: Employee: Eisai Inc. M.H. Voss: Honoraria: Novartis; Consulting/advisory role: Alexion Pharmaceuticals, Calithera Biosciences, Exelixis, GlaxoSmithKline, Natera, Novartis, Pfizer; Research funding: Bristol-Myers Squibb, Genentech/Roche, Pfizer; Travel, accommodations, expenses: Novartis, Takeda.

77P End-to-end learning to predict survival in patients with gastric cancer using convolutional neural networks

A. Meier[1], K. Nekolla[1], S. Earle[2], L. Hewitt[3], T. Aoyama[4], T. Yoshikawa[5], G. Schmidt[1], R. Huss[1], H.I. Grabsch[3]

[1]Research, Definiens AG, Munich, Germany, [2]Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK, [3]Department of Pathology, Maastricht University, Maastricht, Netherlands, [4]Department of Surgery, Yokohama City University Hospital, Yokohama, Japan, [5]Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan

Background: While established deep learning approaches for histopathology usually consist of a two-step process, a cell or region segmentation and subsequent feature calculation, end-to-end learning has been used to predict patient survival directly from digital tissue sections. We aimed to apply a deep learning approach in a series of gastric cancer (GC) tissue microarrays (TMAs) in order to identify regions in the tissue related to a high-risk of poor survival, and subsequently stratify patients into two risk groups.

Methods: Image patches (size 80µm) were extracted from 469 TMA cores constructed from 248 GC resection specimens which were scanned after immunohistochemistry for CD8 and KI67. For each stain, a survival convolutional neural network (CNN) was trained to maximize a log partial likelihood derived from the Cox proportional hazards model [Mobadersany, PNAS, 2018] and to predict patch-based risks for cancer-specific death in a 10-fold pre-validation procedure, creating risk heatmaps for each core. Aggregation from patch to patient level was done by averaging the risks from all patches of each patient.

Results: We generated risk heatmaps comprising on median 1300 image patches per patient for the CD8 and KI67 stained tissue sections. Stratifying patients into low- and high-risk groups by taking the cohort median as threshold led to a significant log-rank test p-value (<0.01). Regarding the Lauren classification, the diffuse type was associated with higher risks than the intestinal type (T-test p-value < 0.015). Visual assessment of the risk heatmaps revealed an association of low-risk regions in CD8-stained sections with clusters of CD8(+) cells and presence of CD8(+) cells in stroma, whereas tumor epithelium and stroma regions with a low density of CD8(+) cells are associated with higher risks.

Conclusions: We applied survival CNNs to IHC stained gastric cancer tissue samples to directly associate image regions with cancer-specific death risks. This information may be used to deepen our knowledge on how tissue morphology relates to survival risk, and to stratify patients into high and low risk groups. Our results will be extended to other biomarkers and will be validated using data from another clinical site.

Legal entity responsible for the study: Heike I. Grabsch.

Funding: Pathological Society of Great Britain and Ireland, Kanagawa Cancer Center.

Disclosure: All authors have declared no conflicts of interest.

78P Detection of targetable kinase fusions in 7260 patients in an integrated cancer system

A. Parikh[1], S.M. Ali[2], A. Moran[3], P. Crilley[1], A.B. Schrock[4], A. Tan[5], P. Reddy[2], V.A. Miller[4], J.S. Ross[6], S. Zook[3], R.H. Alvarez[3], M. Markman[1]

[1]Medical Oncology, Cancer Treatment Centers of America, Philadelphia, PA, USA, [2]Oncology, Foundation Medicine, Boston, MA, USA, [3]Medical Oncology, Cancer Treatment Centers of America, Newnan, GA, USA, [4]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA, [5]Medical Oncology, Cancer Treatment Centers of America, Goodyear, AZ, USA, [6]Pathology Group, Foundation Medicine Inc., Cambridge, MA, USA

Background: Kinase fusions (KF), such as those involving ALK, are eminently targetable genomic alterations (GA) in lung and other cancers, the latter suggested by early clinical evidence (PMID: 29079636). We undertook a review of 7260 patient samples from a tertiary cancer care-focused network of five hospitals assayed with comprehensive genomic profiling (CGP).

Methods: Hybrid capture based CGP was performed on 7260 advanced cancer cases (12/2012-2/2018), with assessment of at least 186 genes (intronic baiting for at least 14) in tissue, and 62 genes (intronic baiting for 6) in circulating tumor DNA samples. Tumor mutational burden (TMB) was determined up to 1.2 Mbp of sequenced DNA.

Results: 77/7260 (1%) samples in this series harbored KF. Patients (pts) with KF+ tumors had a median age of 53 years vs. 56 years in the overall population. The TMB in KF+ cases was 3.51 mut/Mb vs. 4.39 mut/Mb for all cases. KF were found in 55 lung (71%) and 22 (29%) non-lung samples. Of KF+ cases, 71% were non-small cell lung cancer, and the remainder were sarcoma (5%), breast cancer (4%), thyroid (4%), cancer of unknown primary (4%), pancreatic (3%), colorectal (3%) and others (1% each).

Of KF+ non-lung cases, 39% had BRAF fusions, 30% had ALK fusions, 26% had RET fusions, and 4% had ROS1 fusions. One KF+ sarcoma pt received matched targeted therapy with ALK inhibitors including ceritinib and crizotinib. More recently, in 2017 samples alone, 42% (10/24) of KF+ cases were non-lung.

Conclusions: Greater access to CGP has led to increased detection of advanced cancer patients with tumors harboring KF, particularly those with non-lung cancers. The low frequency of the latter is a challenge for clinical investigation. As such, innovative solutions such as basket trial for kinase inhibitors are needed, which may be feasible in an integrated cancer care system with high patient volume.

Legal entity responsible for the study: Ankur Parikh.

Funding: Has not received any funding.

Disclosure: A. Parikh: Consultant: Foundation Medicine, Inc (FMI). S.M. Ali, A.B. Schrock, P. Reddy, V.A. Miller, J.S. Ross: Employee and equity interest: FMI. All other authors have declared no conflicts of interest.

79P Clinical and analytical validation of an FDA approved comprehensive genomic profiling (CGP) assay incorporating multiple companion diagnostics for targeted and immunotherapies

Y. Li[1], J.X. Sun[1], J. Skoletsky[1], C. Milbury[1], C. Burns[1], W-K. Yip[1], N. Dewal[2], J. He[1], J. Tuesdell[3], E. Peters[4], E. Schleifman[5], J. Noe[6], S. Jenkins[7], J.A. Elvin[2], G. Otto[1], D. Lipson[8], J.S. Ross[2], V.A. Miller[2], M. Doherty[1], C. Vietz[1]

[1]Product Development, Foundation Medicine, Inc., Cambridge, MA, USA, [2]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA, [3]Product Marketing, Foundation Medicine, Inc., Cambridge, MA, USA, [4]Companion Diagnostics, Genentech, Inc., San Francisco, CA, USA, [5]Companion Diagnostic Development, Oncology Biomarker Development, Genentech, Inc., South San Francisco, CA, USA, [6]Oncology Biomarker Development, Hoffmann La Roche, Basel, Switzerland, [7]Personalised Medicine and Biomarkers, Astrazeneca, Macclesfield, UK, [8]Foundation Medicine, Cambridge, MA, USA

Background: Due to the compelling predictive value of companion diagnostic (CDx) biomarkers tied to targeted and immune-based therapies, well-characterized robust analytic and clinical validation of genomic assays has become mandatory. An NGS-based CGP (comprehensive genomic profiling) platform was developed in compliance with FDA guidelines for CDx indications.

Methods: DNA extracted from FFPE tumor tissue underwent whole-genome shotgun library construction and hybridization-based capture, followed by sequencing using Illumina HiSeq 4000. Sequence data were processed using a proprietary analysis pipeline designed to identify sub substitutions, indels, copy number alterations, genomic rearrangements, microsatellite instability (MSI), and tumor mutational burden (TMB) in 324 genes.

Results: Clinical validity was demonstrated by establishing statistical non-inferiority between CGP and the respective approved CDx, e.g. cobas EGFR and BRAF mutational testing, ALK rearrangements with FISH and IHC, ERBB2 amplification with FISH, and others. For analytical validity, concordance with an orthogonal NGS platform was 94.6% for substitutions and indels, and within-assay reproducibility had positive percent agreement (PPA) of 99.4%. TMB was analytically validated via concordance with whole-exome sequencing. For the first 616 patients (25% non-small cell lung cancer) assayed in clinical care, 6.8% of cases had TMB exceeding 20 mut/Mb, with 25% of these also harboring microsatellite instability. For 143 NSCLC cases, >50% harbored 10 mut/Mb. Of 354 cases with CDx findings possible, 25.6% had such findings, which were split nearly evenly between indications to benefit from and contraindications to targeted therapies.

Conclusions: We developed a CGP assay and demonstrated clinical and analytical validity for CDx biomarkers for targeted therapy, with clinical validation for TMB in progress via correlation with prospective immunotherapy trials. Initial oncologist feedback indicates impact of assay results on course of treatment decisions in patient care.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: Y. Li: Employee of and stockholder: Foundation Medicine Inc. J.X. Sun: Stockholder: Foundation Medicine Inc. J. Skoletsky, C. Milbury, C. Burns, W-K. Yip, N. Dewal, J. He, J. Tuesdell, J.A. Elvin, G. Otto, D. Lipson, J.S. Ross, V.A. Miller, M. Doherty, C. Vietz: Employee and stockholder: Foundation Medicine Inc. E. Peters, E. Schleifman, J. Noe: Employee and stockholder: Genentech Inc. S. Jenkins: Employee and stockholder: AstraZeneca.

80P SET overexpression promotes colorectal cancer progression and determines poor outcome in patients with localized disease

B. Torrejón[1], M. Pedregal Trujillo[2], A. Santos[1], J. Rubio[2], M. Luque[1], M. Sanz[1], C. Carames[2], S. Zazo[1], J. Madoz-Gurpide[1], F. Rojo[1], J. Garcia Foncillas[2], C. Ion[1]

[1]Molecular Biology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [2]Clinical Oncology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain

Background: SET deregulation is an alteration that determines poor outcome in metastatic colorectal cancer (CRC) patients promoting cell growth and decreasing sensitivity to standard chemotherapeutic agents such as oxaliplatin and 5-fluorouracil. Moreover, this alteration represents a key event to inhibit the tumor suppressor PP2A in metastatic CRC. However, the role of SET in CRC progression and its potential clinical impact in early-stage CRC patients still remain to be investigated.

Methods: In this work, we studied the biological effects of SET on migration using wound-healing and transwell migration assays, and cell invasion ability was determined by colony-forming assays after SET silencing or overexpression. Moreover, we analyzed SET expression by immunostaining in a cohort of 231 CRC patients without metastatic disease at diagnosis. We also quantified the expression of the negative SET regulator miR-199b in a set of CRC patient samples.

Results: We observed that SET deregulation promotes cell migration and markedly affects invasion ability of CRC cells. At the clinical level, SET overexpression was detected in 14.7% of cases. We found this alteration associated with worse ECOG performance status, and with relapse in the subgroup of stage II CRC patients. Moreover, SET overexpression determined significantly shorter overall survival and time to metastasis. Interestingly, its prognostic value was particularly evident in patients older than 70 years. We also identified miR-199b downregulation as a molecular mechanism to deregulate SET in CRC patients with localized disease.

Conclusions: Of importance, our results indicate that SET could serve to anticipate undesirable relapses in stage II CRC patients and define a subgroup of early stage CRC patients that could benefit by the use of SET antagonists or PP2A-activating drugs such as FTY720 in anticancer protocols.

Legal entity responsible for the study: Fundación Jiménez Díaz.

Funding: This work was supported by PI15/00934 and PI16/01468 grants from "Instituto de Salud Carlos III FEDER". BT is supported by Fundación Conchita Rábago de Jiménez Díaz.

Disclosure: All authors have declared no conflicts of interest.

81P The functional MDM4 genetic variant in advanced lung adenocarcinoma patients treated with EGFR-TKIs

N. Zhang[1], M. Yang[2], H. Xing[2], J. Liu[2]

[1]Department of Radiation Oncology, Shandong Cancer Hospital, Ji'nan, China, [2]Shandong Provincial Key Laboratory of Radiation Oncology, Cancer Research Center, Shandong Cancer Hospital, Jinan, China

Background: As a mostly used epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), gefitinib significantly prolongs survival of lung adenocarcinoma patients with EGFR mutations. However, more than 10% of EGFR mutation-positive patients do not respond and a substantial fraction of responded patients progress after 8-12 months' treatment. Identification of new biomarkers for EGFR-TKIs prognosis is vital. The objective of this study is to explore associations between MDM4 genetic variant and survival of lung adenocarcinoma patients treated with gefitinib.

Methods: 384 patients with stage IIIB or IV lung adenocarcinoma were recruited between January 2009 and June 2013. Patients were treated with gefitinib orally at a daily dose of 250 mg as 1st-line monotherapy. MDM4 rs4245739 A>C genotypes were determined using MassArray system. Dual luciferase reporter gene assays evaluated the function of MDM4 rs4245739 genetic variant in lung adenocarcinoma cell lines A549 and H1299. The differences of patient clinical characteristics were calculated by student's t test or χ^2 test. Survival differences were examined by log-rank test. Multivariate Cox regression analysis assessed prognostic factors for PFS or OS. Two-sided $P < 0.05$ indicated a significant difference.

Results: Among 384 patients, EGFR mutations were positive in 181 patients (47.1%). Median progression-free survival (PFS) and overall survival (OS) for all patients with the rs4245739AC genotype were significantly longer than that of the AA carriers (PFS: 22.9vs.10.9 months, $P < 0.001$; OS: 27.3vs.16.5 months, $P = 0.003$). Notably, in the EGFR mutation-positive subgroup, individuals with MDM4 rs4245739AC genotype showed 14.1 months prolonged PFS (28.8 months vs. 14.7 months; $P = 0.022$) and 12.2 months prolonged OS (31.4 months vs. 19.2 months; $P = 0.047$) compared to the AA group. Reporter gene assays showed that the rs4245739A allele leads to significantly increased MDM4 expression in lung adenocarcinoma cells compared to the C allele ($P < 0.05$).

Conclusions: MDM4 rs4245739 genotypes may act as prognostic biomarker for patients' survival to gefitinib therapy and offer help to individualized treatment in lung adenocarcinoma patients with EGFR mutations.

Legal entity responsible for the study: Nasha Zhang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

82P PD-L1 expression on pre-treatment circulating tumour cells, but not serum VEGF, is predictive of response to pembrolizumab in melanoma

M.A. Khattak[1], E.S. Gray[2], A. Reid[2], M. Periera[2], A. McEvoy[2], C. Aya-Bonilla[2], T. Meniawy[3], A. Didan[1], M. Millward[3], M. Ziman[2]

[1]Medical Oncology, Fiona Stanley Hospital, Perth, Australia, [2]School of Medical and Health Sciences, Edith Cowan University, Perth, Australia, [3]Oncology, School of Medicine and Pharmacology Sir Charles Gairdner Hospital, Nedlands, Australia

Background: Immune checkpoint inhibitors including pembrolizumab and nivolumab have revolutionised treatment of melanoma with a small proportion of patients deriving durable disease control lasting up to 5 years. However, majority of patients do

not respond to these drugs that are costly and can lead to substantial toxicity. Therefore, there is an urgent need for biomarkers that can identify patients that will respond to these therapies.

Methods: We used multi-parametric flow cytometry to identify circulating tumour cell (CTC) subpopulations based on the expression of melanoma markers MCAM, MCSP, ABCB5, CD271 and RANK in metastatic melanoma patients prior to commencing treatment with pembrolizumab (n = 40) or with ipilimumab alone or in combination with nivolumab (n = 14). In particular, we evaluated the expression of PD-L1 on CTCs in relation with response to treatment and progression free survival (PFS). Serum vascular endothelial growth factor (VEGF) concentrations were also evaluated.

Results: Pre-treatment serum VEGF concentrations were significantly higher in patients not responding to ipilimumab treatment (alone or in combination with nivolumab) (p = 0.0094). In contrast, serum VEGF was not predictive of response to pembrolizumab. Pre-treatment CTC positivity was not associated with response or PFS in either cohorts. However, PD-L1 expression on CTCs was associated with response to therapy. PD-L1 expression was found in 13 of 16 responders with detectable CTCs, while only 4 of 10 non-responders had PD-L1 detectable on their CTCs (p = 0.0425). Expression of PD-L1 on CTCs was also associated with longer PFS (p = 0.0117).

Conclusions: Our results provide evidence for the first time in melanoma, that detection of PD-L1 on CTCs is predictive of response to pembrolizumab and longer PFS.

Legal entity responsible for the study: Research Governance Office Sir Charles Gairdner Hospital and Fiona Stanley Hospital.

Funding: MSD.

Disclosure: M.A. Khattak, M. Ziman: Research grant: MSD. All other authors have declared no conflicts of interest.

83P Olaparib plus paclitaxel sensitivity in biomarker subgroups of gastric cancer

Y-Z. Liu[1], D. Hodgson[1], G. Locker[2], Z. Lai[3], D. Balcerzak[1], A. Sharpe[1], J.C. Barrett[3], M. Orr[1], T.S. Gutjahr[1], B. Dougherty[3], M.P. Roudier[1], X. Shi[2], R. Miller[4], W.H. Kim[5], X. Zeng[6], A. Ochiai[7], S-A. Im[8], R-H. Xu[9], N. Boku[10], Y-J. Bang[8]

[1]AstraZeneca, Cambridge, UK, [2]AstraZeneca, Gaithersburg, MD, USA, [3]AstraZeneca, Waltham, MA, USA, [4]Ventana Medical Systems, Tucson, AZ, USA, [5]Seoul National University College of Medicine, Seoul, Republic of Korea, [6]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [7]National Cancer Center Hospital East, Chiba, Japan, [8]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, [9]Sun Yat-sen University Cancer Center, Guangzhou, China, [10]National Cancer Center Hospital, Tokyo, Japan

Background: Study 39 (NCT01063517) showed a significant improvement in overall survival (OS) following olaparib plus paclitaxel (OP) vs paclitaxel (P) alone in advanced gastric cancer, with improvements greatest in patients (pts) with low or undetectable tumour ATM protein levels. The Phase III GOLD study (NCT01924533) also showed a survival benefit trend for OP vs P. We investigated biomarker subgroups, candidate genes and homologous recombination repair (HRR) deficiency using predefined and post-hoc exploratory analyses, to determine if a predictive relationship exists between such biomarkers and clinical outcome in gastric cancer pts treated with OP.

Methods: Candidate genes, HRR deficiencies, loss of heterozygosity (LoH) and microsatellite insufficiency (MSI) were assessed in formalin-fixed, paraffin-embedded gastric tumour samples from GOLD by next-generation sequencing. HRR deficiencies were identified as carrying pathogenic mutations in any 15 HRR genes and LoH using allele-specific copy number information coupled with assessed tumour purity. ATM protein level was assessed by immunohistochemistry (IHC). Clinical outcomes analyzed were OS, PFS and ORR.

Results: Efficacy in the genetics evaluable population (n = 400) was broadly consistent with the overall GOLD population (n = 525) for each outcome investigated. ATM-negative patients by IHC had better prognosis independent of treatment. No statistically significant associations with clinical outcomes were identified (Table). Post-hoc exploratory analyses indicated good prognosis (OS) in pts with an ATM mutation, and poor prognosis in pts with CDH1, FGFR2 or KRAS mutations.

Table: 83P

Pre-specified subgroup		Patients/events in OS, PFS, ORR, respectively	OS Hazard ratio [<1 favours OP] (P value)	PFS Hazard ratio [<1 favours OP] (P value)	ORR Odds ratio [>1 favours OP] (P value)
Overall population		525/381, 449, 72	0.80 (0.026)*	0.84 (0.065)	1.68 (0.057)
Evaluable for genetics		400/284, 342, 57	0.80 (0.065)*	0.87 (0.214)	1.40 (0.256)
ATM IHC status†	+ve	324/233, 281, 42	0.79 (0.076)	0.96 (0.737)	1.06 (0.870)
	-ve	76/51, 61, 15	0.72 (0.292)	0.61 (0.081)	3.41 (0.082)
ATM IHC null	Not null	381/273, 327, 52	0.82 (0.094)	0.89 (0.315)	1.25 (0.551)
	Null	19/11, 15, 5	0.55 (0.426)	0.28 (0.090)	6.46 (0.141)
ATM	Wt	378/274, 326, 55	0.80 (0.062)	0.86 (0.175)	1.43 (0.244)
	Mut	22/10, 16, 2	0.83 (0.803)	0.91 (0.875)	0.83 (1.00)
ATM/BRCA	Wt	369/266, 317, 54	0.81 (0.090)	0.85 (0.160)	1.52 (0.185)
	Mut	31/18, 25, 3	0.94 (0.908)	1.11 (0.795)	0.39 (0.578)
HRR	Wt	354/254, 302, 52	0.79 (0.066)	0.83 (0.122)	1.54 (0.177)
	Mut	46/30, 40, 5	1.05 (0.903)	0.96 (0.921)	0.58 (0.659)
ARID1a	Wt	332/232, 287, 46	0.82 (0.133)	0.86 (0.216)	1.28 (0.526)
	Mut	68/52, 55, 11	0.65 (0.326)	0.91 (0.741)	2.06 (0.335)
TP53	Wt	136/90, 113, 17	0.80 (0.322)	0.98 (0.918)	2.03 (0.197)
	Mut	264/194, 229, 40	0.77 (0.074)	0.76 (0.042)	1.16 (0.732)
MSI	Stable	381/269, 325, 53	0.81 (0.081)	0.87 (0.216)	1.32 (0.377)
	High	19/15, 17, 4	0.41 (0.198)	0.83 (0.784)	3.22 (0.582)
LoH score	LOH evaluable ≤6	198/139, 175, 32 137/101,119, 21	0.73 (0.064) 0.73 (0.122)	0.75 (0.062) 0.80 (0.222)	1.11 (0.847) 1.32 (0.638)
	>6	61/38, 56, 11	0.62 (0.175)	0.71 (0.246)	0.84 (1.00)

ATM IHC null, 0% tumour cells expressed ATM; HRR, homologous recombination repair; LoH, loss of heterozygosity; MSI, microsatellite instability status; Mut, mutation; ORR, objective response rate; OS, overall survival; PFS, progression free survival; Wt, wild type Analyses represent the HR for olaparib vs placebo in the stated subgroups *Significant difference for OP vs P was set at P < 0.025 †Assessed using the Ventana ATM (Y170) assay (ATM negative defined as < 25% nuclei staining)

Conclusions: None of the pre-specified molecular subgroups had a better outcome from adding olaparib to paclitaxel than the overall GOLD population. Additional studies are required to understand the OS signal observed with OP treatment in pts with advanced gastric cancer in the GOLD study. Yu-Zhen Liu and Darren Hodgson are joint first authors.

Clinical trial identification: NCT01924533.

Editorial acknowledgement: Claire Routley, Mudskipper Business Ltd.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: D. Hodgson, Z. Lai, D. Balcerzak, A. Sharpe, J.C. Barrett, M. Orr, T.S. Gutjahr, B. Dougherty, X. Shi: Employee and stockholder: AstraZeneca. G. Locker: Employee: AstraZeneca. M.P. Roudier: Employee and shareholder: AstraZeneca. R. Miller: Employee and share/stockholder: Roche. W.H. Kim: Grant: Seoul National University Hospital. S-A. Im: Preclinical research grant: AstraZeneca. N. Boku: Grant and personal fees: Taiho, Ono; Personal fees: Chugai, Eli Lilly. Y-J. Bang: Advisory/consulting role, honorarium, research funding: AstraZeneca. All other authors have declared no conflicts of interest.

84P A diagnostic model for hepatitis B virus-related hepatocellular carcinoma in China: A large-scale, multi-center study

T. Yang[1], H. Xing[1], G. Wang[2], S. Cai[3], F. Shen[4]

[1]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China, [2]Department of Public Health, Peking University Health Science Center, Beijing, China, [3]Department of Public Health, The Second Xiangya Hospital of Central South University, Hunan, China, [4]Department of Hepatobiliary Surgery IV, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China

Background: Almost one third of carriers of hepatitis B virus (HBV) world-wide are in China and more than 80% hepatocellular carcinoma (HCC) in China are associated with HBV infection. So early detection of HCC in HBV-infected patients is necessary. In the present study, we aimed to develop a diagnostic model by combining protein induced by Vitamin K absence or antagonist-II (PIVKA-II) and α-fetoprotein (AFP) for HBV-related HCC.

Methods: We recruited consecutive patients with HBV-related HCC, chronic hepatitis B, HBV-related cirrhosis and healthy controls at 11 hospitals in China from June 2016 to May 2017 for a training cohort. A validation cohort was enrolled at the same sites from FebruaryJune 2017 to September 2017. HCC was defined on the basis of ultrasound, CT, or MRI characteristics and confirmed by histopathology. Serum PIVKA-II level was measured by ARCHITECT immunoassay and AFP was measured with commercially available ELISA. Receiver operating characteristics (ROC) were used to calculate diagnostic accuracy.

Results: The training cohort consisted of 2019 participants, 908 with HBV-related HCC, 289 with chronic hepatitis B, 314 with HBV-related cirrhosis, and 508 healthy controls. The validation cohort comprised 655 participants, 289 with HBV-related HCC, 113 with chronic hepatitis B, 98 with HBV-related cirrhosis, and 155 healthy controls. Levels of PIVKA-II in serum were significantly higher in HBV-related HCC than all controls. ROC curves showed the optimum diagnostic cutoff for PIVKA-II was 44.18 mAU/mL (area under curve [AUC], 0.907 [95% CI 0.892-0.922], sensitivity 81.13%, and specificity 94.97% in the training cohort; 0.909 [0.883-0.934], 79.02%, and 95.46% in the validation cohort). PIVKA-II maintained diagnostic accuracy for patients with HBV-related HCC who were AFP negative. A model combined PIVKA-II, AFP, age, gender and liver cirrhosis improved diagnostic accuracy for HBV-related HCC versus all controls compared with either test alone (0.951 [0.929-0.973] in the training cohort; 0.954 [0.945-0.962] in the validation cohort).

Conclusions: PIVKA-II could complement measurement of AFP in the diagnostic of HBV-related HCC and distinguish HCC from non-malignant chronic liver disease.

Clinical trial identification: NCT03047603.

Legal entity responsible for the study: Eastern Hepatobiliary Surgery Hospital, Second Military Medical University.

Funding: The National Natural Science Foundation of China.

Disclosure: All authors have declared no conflicts of interest.

85P Dissecting gastric cancer biology and how and when to use immunotherapy

M. Das Thakur, K. Okrah, D. Shames, P. Hegde, C. Bais

Oncology Biomarker Development, Genentech Inc. - Roche - USA, South San Francisco, CA, USA

Background: Gastric cancer (GC), is a leading cause of cancer-related death, is a heterogeneous disease where survival depends on factors such as biological differences, MSI status, EBV status, region, ethnicity and patterns of care. The biological context for immune responsiveness and resistance in the clinical are only now starting emerge. Although GC has similar levels of PDL1 IC and TC expression to lung cancer, the approvals and success of immunotherapy in GC to date has been mixed.

Methods: We explored 2 randomized MetMAb trials (Ph3 Study 1 YO28322 and Ph2 Study 2 YO28252) in combination with mFOLFOX6 in metastatic HER2-negative and MET-positive GC. We used Study 1 (n = 146) to uncover novel GC biology using Nanostring based gene expression analyses and Study 2 (n = 70) to confirm the findings. Late Stage GC (Stage IV biopsies) GC from the Study 1 and 2 were compared against early stage GC (Stage I, II and III) in resections from the ACRG GC dataset.

Results: Retrospective analysis revealed key biological differences between early and late stage GC. In 1L mGC with stage IV tissue, unbiased prognostic analyses uncovered genes that grouped into: Immune/Effector T cell genes (Teff), Stromal genes and Differentiation/Proliferation genes as significantly associated with OS. Patients with high Teff genes had poor prognosis (Low/High HR: 0.43, p- value 0.01) and the worst prognosis was seen when both Teff and stromal genes were high. Furthermore, we confirmed these findings in Study 2. We found that EMT, Notch and TGFb pathways interacted with the Teff genes and were all associated with the poor Teff prognosis. Importantly immune/Teff genes have good prognosis in early stage GC and this is largely driven by MSI-H patients. Finally, when assessing what genes changed going from early to late stage, EMT, Notch, Wnt genes played a role in the transition to a more aggressive and metastatic disease.

Conclusions: Although GC has been challenging to treat, it may be possible to increase the success of immunotherapy with carefully tailored combination therapies in the Stage IV setting with molecules that inhibit pathways such as Notch, Wnt and TGFb. Furthermore, it may make a lot of sense to take immunotherapies into Stage I, II and III GC where the immune and Teff gene prognosis is good and the disease is less convoluted.

Clinical trial identification: YO28322: NCT01662869 YO28252: NCT01590719.

Legal entity responsible for the study: Hoffmann-La Roche.

Funding: Hoffmann-La Roche, Genentech.

Disclosure: M. Das Thakur, K. Okrah, D. Shames, P. Hegde, C. Bais: Employee: Hoffmann-La Roche.

86P Longitudinal assessment of multiplex patient-specific ctDNA biomarkers in bladder cancer for diagnosis, surveillance and recurrence

K. Birkenkamp-Demtröder[1], E. Christensen[2], H. Sethi[3], S. Sharma[3], H.-T. Wu[3], A. Taber[2], M. Agerbæk[4], R. Swenerton[3], R. Salari[3], D. Hafez[3], I. Nordentoft[5], P. Lamy[5], R. Srinivasan[3], M. Balcioglu[3], S. Navarro[3], Z. Assaf[3], B. Zimmermann[6], J. Lin[6], J. Bjerggaard Jensen[7], L. Dyrskjøt[2]

[1]Molecular Medicine MOMA, Aarhus University Hospital / Skejby, Aarhus, Denmark, [2]Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark, [3]Natera Inc., San Carlos, CA, USA, [4]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [5]Aarhus University Hospital, Aarhus, Denmark, [6]RND, Natera, San Carlos, CA, USA, [7]Department of Urology, Aarhus University Hospital, Aarhus, Denmark

Background: The use of circulating tumor DNA (ctDNA) as a biomarker for disease staging at diagnosis (DX), treatment response, and recurrence monitoring is an emerging field in many cancer types. In bladder cancer, the utility of ctDNA has shown promising results. Here we present a highly sensitive and specific NGS-based approach to ctDNA monitoring.

Methods: A cohort of 50 patients with locally advanced muscle-invasive bladder cancer treated with neoadjuvant chemotherapy were included prospectively. For each patient, a panel of 16 tumor-specific mutations was designed (Signatera™ RUO) based on whole-exome sequencing of tumor and germline DNA. In total, we analyzed ctDNA from longitudinally collected plasma samples from 386 time points procured at diagnosis, during treatment, at cystectomy (Cx), and during monitoring until disease recurrence or up to 2 years follow-up. Results of ctDNA analyses were compared to radiographic imaging and clinical outcomes. ctDNA from longitudinally-collected urine samples will also be analyzed for treatment response and disease recurrence.

Results: At DX, plasma ctDNA status was strongly prognostic of recurrence-free survival. Specifically, 62% (8/13) of the ctDNA+ patients at DX recurred after neoadjuvant treatment and Cx; conversely, none (0/22) of the ctDNA- patients recurred (log-rank; $p < 0.0001$). In addition, a strong correlation was also observed between presence of ctDNA after CX and disease relapse. Specifically, relapse after Cx was detected in 100% (10/10) of ctDNA+ patients ∼120 days (0–245 days) prior to radiographic imaging, while 0% (0/38) of ctDNA- patients relapsed (log-rank; $p < 0.0001$).

Conclusions: We demonstrate a strong prognostic potential of ctDNA in bladder cancer at time of DX, suggesting a potential role for ctDNA in the staging of bladder cancer. Furthermore, we show ctDNA is detected in all patients with disease recurrence after

Cx. Incorporation of ctDNA analysis into routine follow-up for early detection of relapse may allow earlier initiation of alternate treatment modalities.

Legal entity responsible for the study: The National Committee on Health Research Ethics (#1302183), Denmark.

Funding: Novo Nordisk Foundation, Danish Cancer Society, Natera Inc San Carlos USA.

Disclosure: H. Sethi, S. Sharma, H-T. Wu, R. Swenerton, R. Salari, D. Hafez, R. Srinivasan, M. Balcioglu, S. Navarro, Z. Assaf, B. Zimmermann, J. Lin: Employee, stockownership or options to stock: Natera, Inc. All other authors have declared no conflicts of interest.

87P Distinct functional consequences of HER2 gene amplification in colorectal and lung adenocarcinomas

E.N. Imyanitov[1], T.N. Sokolova[1], G. Raskin[2], A.O. Ivantsov[1], A.G. Iyevleva[1], A.P. Sokolenko[1]

[1]Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, St. Petersburg, Russian Federation, [2]Department of Pathology, A.M. Granov Russian Scientific Centre of Radiology and Surgical Technologies, St. Petersburg, Russian Federation

Background: HER2 oncogene amplification, being accompanied by its overexpression, is an established driver event in breast and gastric carcinomas. The functional role of HER2 in pathogenesis of other tumor types is less defined.

Methods: 2401 archival samples of lung carcinomas (LC) and 1969 samples of colorectal carcinomas (CRC) were subjected to HER2 copy number analysis. Selected tumors with amplification of this oncogene were further subjected to HER2 immunohistochemistry and mRNA quantitation. In addition, the expression levels of some neighbouring genes located in 17q12-21 amplicon were analyzed.

Results: Frequency of HER2 amplification was similar in both groups, being 100/2401 (4.2%) in LC and 84/1969 (4.3%) in CRC, respectively. 10 (82%) out of 12 analyzed HER2-amplified CRCs demonstrated clear evidence for HER2 protein and mRNA overexpression, while this estimate approached to only 3 (27%) out of 11 for LCs. Expression analysis of GRB7, STARD3, and LASP1 revealed a statistically significant correlation between HER2 and STARD3 levels [$r = 0.571$, Spearman test]. High STARD3 expression was observed in HER2-amplified CRCs but not LCs [$p = 0.03$].

Conclusions: HER2 amplification is frequently accompanied by gene overexpression in colorectal but not lung adenocarcinomas. STARD3 gene belonging to 17q12-21 amplicon demonstrates evidence for activation in HER2-amplified colorectal neoplasms and therefore deserves further analysis.

Legal entity responsible for the study: Evgeny Imyanitov.

Funding: Russian Science Foundation.

Disclosure: All authors have declared no conflicts of interest.

88P Role of AR-V7 and AR-FL in resistance to hormonal therapy in mCRPC: Independent actors or reciprocal drivers? A translational study by Meet-Uro group

M. Del Re[1], S. Crucitta[1], A. Sbrana[2], E. Rofi[3], F. Paolieri[3], L. Galli[4], A. Falcone[3], R. van Schaik[5], G. Jenster[6], R. Morganti[2], S. Pignata[7], R. Danesi[1]

[1]Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [2]Medical Oncology 2 Unit, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy, [3]Medical Oncology, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy, [4]UO Oncologia Medica 2 Universitaria, Azienda Ospedaliero-Universitaria Pisana Istituto Toscano Tumori, Pisa, Italy, [5]Clinical Chemistry, Erasmus University, Rotterdam, Netherlands, [6]Josephine Nefkens Institute, Erasmus University, Rotterdam, Netherlands, [7]Urology and Gynecology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy

Background: The androgen receptor splice variant 7 (AR-V7) is strongly associated with resistance to hormonal therapy (HT) in castration-resistant prostate cancer (CRPC), although it is not implemented in clinical practice as a biomarker. The AR-full length (AR-FL) is also overexpressed in CRPC but its role has yet to be clarified. The aim of the present work was to investigate the role of AR-V7 and AR-FL as predictors of resistance to HT in plasma-derived exosomal RNA.

Methods: 6 ml of blood were collected in EDTA tubes before the start of abiraterone/enzalutamide; blood was centrifuged and plasma stored at -80 °C until analysis. Exosomes isolation and RNA extraction were performed using the exoRNeasy kit (Qiagen) as per manufacturer instructions. The analysis of AR-FL and AR-V7 were performed by digital droplet PCR using the One-Step RT-ddPCR kit (BioRad). The absolute target concentration as copies/ml in samples was calculated by ddPCR QuantaSoft and statistical analyses were performed by SPSS v.24.

Results: 52 patients (pts) were enrolled; AR-FL was detected in all pts (median: 700 copies/ml), while 15 subjects (28.8%) were AR-V7 + (median: 310 copies/ml) at baseline. The amount of AR-FL was significantly higher in pts AR-V7+ vs AR-V7- (6700 vs 490 copies/ml, $p < 0.0001$). Median PFS and OS were longer in AR-V7- vs AR-V7+ pts (median PFS 25 vs 4 mo, $p < 0.0001$; median OS 38 vs 9 mo, $p < 0.0001$). A ROC curve was calculated for AR-FL in the overall population and 950 copies/ml was identified as cut-off value. Pts were then stratified across this value and it was found that PFS was 22 mo in pts with <950 AR-FL copies/ml vs 4 mo in pts with ≥950 copies/ml ($p = 0.0003$). In 12/15 AR-V7+ pts the AR-FL expression was ≥950 copies/ml while in 3/15 AR-V7+ pts, AR-FL expression was <950 copies/ml; however, their PFS reflected the AR-V7 better than AR-FL status, being, respectively 6, 10, 4 mo. No other clinical variables were correlated with worse PFS at the univariate analysis (i.e. Gleason score ≤7 vs > 7, age).

Conclusions: This study demonstrates that resistance to HT may be predicted by AR-V7, making it a clinically relevant biomarker. AR-FL over-expression may contribute to hormone resistance although AR-V7 plays a primary role.

Legal entity responsible for the study: Romano Danesi.

Funding: University of Pisa.

Disclosure: All authors have declared no conflicts of interest.

89P Validation of a 90-gene assay for tissue origin diagnosis of brain metastases

Y. Zheng[1], Y. Ding[1], C. Xiao[1], W. Zhong[2], X. Teng[2], Q. Gao[2], Q. Wang[3], Y. Sun[4], C. Chen[4], L. Chen[4], J. Zhu[4], Q. Xu[4], N. Xu[1]

[1]Department of Medical Oncology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China, [2]Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China, [3]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China, [4]Research and Development, Canhelp Genomics Ltd., Hangzhou, China

Background: Brain metastases (BM) are the most common intracranial tumors affecting about 8-10% of all cancer patients. Morphology and immunohistochemical staining are two common approaches used to identify the primary sites of BM samples, but morphology fails to identify poorly differentiated tumors and IHC markers usually lack specificity. About 2% to 14% of BM patients still present with unknown primary sites. A 90-gene assay, proposed in our previous study, is an RNA-based gene expression test to identify the tissue of origin in poorly differentiated and undifferentiated tumors. This study aims to evaluate the performance of the 90-gene assay in determining the primary sites for BM samples.

Methods: The sequence-based gene expression profiles of 708 primary brain tumors (PBT) collected from The Cancer Genome Atlas database were performed by a 90-gene expression signature, with a similarity score for each of 21 tumor types. We used Optimal Binning algorithm to generate a threshold for separating PBT from BM. Eighteen PBT samples from Fudan University Shanghai Cancer Center were analyzed to substantiate reliability of the threshold. In addition, the performance of the 90-gene assay for identifying the tissue of origin was validated in a cohort of 48 BM samples with known origin from The First Affiliated Hospital, Zhejiang University. For each BM sample, the tumor type with the highest similarity score was considered tissue of origin. When a sample was diagnosed as PBT but the similarity score below the threshold, the second prediction was considered as primary site.

Results: A threshold of the similarity score, 70, was identified to discriminate PBT from BM (PBT: ≥ 70, BM: < 70) with an accuracy of 99% (703/708). Eighteen PBT and 44 BM were performed by the 90-gene assay. The results of 18 PBT samples matched reference diagnosis with a concordance rate of 100% and all similarity scores were above 70. Of 44 BM samples, the 90-gene assay accurately predicted primary sites in 89% (39/44, 95%CI: 0.75-0.96) of the cases.

Conclusions: The 90-gene assay showed promising discriminatory ability to separate PBT from BM and identify the primary site of BM. Our findings demonstrated the potential that 90-gene assay can serve as a powerful tool for accurately identifying the tissue of origin for BM samples.

Legal entity responsible for the study: Yulong Zheng.

Funding: Has not received any funding.

Disclosure: Y. Sun, C. Chen, L. Chen, J. Zhu: Employment: Canhelp Genomics Co. Ltd. Q. Xu: Employment, stock ownership: Canhelp Genomics Co. Ltd. All other authors have declared no conflicts of interest.

90P Development of a pan-cancer biomarker panel for improved detection of MSI across all cancer types

J. Bacher[1], R. Halberg[2], P. Ward[3], E. Udho[1], K. Murphy[4], M. Uhr[5], L. Dubeau[3], J. Pettersson[3], D. Storts[1], S. Gallinger[6], D. Buchanan[7], M. Jenkins[7], N. Lindor[8], J. Eshleman[9]

[1]RD Nucleic Acid Technologies Group, Promega Corporation, Madison, WI, USA, [2]Department of Medicine, University of Wisconsin-Madison, Madison, WI, USA, [3]USC Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, [4]Pathology, ProPath, Dallas, TX, USA, [5]RD Protein & Nucleic Acids, Promega Corporation, Madison, WI, USA, [6]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [7]Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia, [8]Health Science Research, Mayo Clinic, Scottsdale, AZ, USA, [9]Pathology, Johns Hopkins University, Baltimore, MD, USA

Background: A new multiplexed biomarker panel is being developed for detection of microsatellite instability (MSI) that is more sensitive than currently available systems. Preliminary research data shows increased MSI sensitivity for colon polyps and

endometrial (EC), skin and prostate cancers. The sensitivity of this Pan-Cancer MSI System is being further verified on 14 different cancer types.

Methods: Selection of the new microsatellite biomarkers was done by screening 160 patients ≤55 years with ≥1 polyp and 100 EC patients ≤ 50 years for MSI. The expanded study uses samples from 100 Lynch syndrome colorectal cancers (CRC), 100 sporadic MSI-High CRC, 100 sporadic MSI stable CRC and 219 extra-colonic cancers obtained from the Colon Cancer Family Registry. DNA samples are being tested for MSI using two pan-cancer systems: Promega's MSI Analysis System version 1.2 and the improved prototype Pan-Cancer MSI System. Mutations in mismatch repair (MMR) and BRAF genes were tested, as well as MMR expression by IHC.

Results: 2.3% of colon polyps were MSI-High for the MSI Analysis System compared to 5.4% with the new prototype Pan-Cancer MSI System. Sensitivity and specificity of the new biomarker panel for detection of MMR deficient lesions was 100% and 96%. Similarly, sensitivity of the new biomarker panel for EC was about 2-fold higher. Allele size changes for MSI-High samples were significantly larger with the new biomarkers making MSI classification highly accurate and robost. The MSI and IHC results were highly correlated. Evaluation of the new biomarker panel is being performed on over 500 cancer samples from 14 different cancer types.

Conclusions: Research results indicate that MSI sensitivity for colonic polyps and many extra-colonic cancers can be increased by at least 2-fold over current MSI systems using the new MSI biomarker panel. The improved sensitivity of the Pan-Cancer MSI System should improve detection of MSI in an expanded number of cancer types and facilitate identification of individuals with both sporadic and hereditary MSI-High cancers.

Legal entity responsible for the study: Promega Corporation.

Funding: Promega Corporation.

Disclosure: J. Bacher: Employee: Promega Corporation. R. Halberg, P. Ward, K. Murphy, J. Eshleman: Corporate sponsored research funds: Promega. E. Udho, M. Uhr: Employee: Promega. D. Storts: Employee and stock ownership: Promega. All other authors have declared no conflicts of interest.

91P bMSI better predicts the responses to immune checkpoint inhibitors (ICI) than MMR/MSI from historical tissue specimens in metastatic gastrointestinal cancer patients

Z. Wang[1], H. Qin[2], M. Wang[3], J. Gong[1], X. Wang[1], J. Li[1], J. Gao[1], Z. Li[4], D. Wang[5], S. Cai[6], Y. Bai[6], L. Xiong[2], F. Li[2], L. Shen[1]

[1]Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China, [2]Research and Development Institute of Precision Medicine, 3D Medicines Inc., Shanghai, China, [3]Oncology Department, Changhai Hospital, Shanghai, China, [4]Department of Pathology, Peking University Cancer Hospital & Institute, Beijing, China, [5]Shanghai 3DMed Clinical Laboratory, 3D Medicines Inc., Shanghai, China, [6]The Medical Department, 3D Medicines Inc., Shanghai, China

Background: Microsatellite instability (MSI) has been approved as the first pan-cancer biomarker in immune checkpoint inhibitors (ICI) therapies. The tumor tissues of most metastatic cancer patients receiving ICI therapies are usually unavailable. However, polymerase chain reaction (PCR) or immunohistochemistry (IHC), the two conventional MSI evaluation methods, could only be applied to the tumor tissues. Hence, we aimed to develop a next-generation sequencing based method to detect MSI from blood circulating tumor DNA (bMSI).

Methods: A training cohort of 40 metastatic cancers patients before first-line treatments were collected to train a linear-based detection model. Then, a validation cohort of 47 metastatic gastrointestinal cancer patients before ICI therapies were collected. The prediction to the responses of ICI by bMSI was compared with that by the mismatch repair (MMR) or MSI from historical tissue specimens.

Results: bMSI showed 87.5% accuracy to predict the MMR/MSI status from tissue specimens in the training cohort, and 95.2% sensitivity in the validation cohort. bMSI-H patients had 31.4% objective response rate (ORR) and 45.7% disease control rate (DCR), which were comparable to the dMMR of historical FFPE specimens (33.3% and 47.6% respectively). However, 57.7% pMMR patients were classified as bMSI-H and showed similar ORR (27%) , DCR (40%) and progress free survival to those of dMMR patients. Furthermore, 17% bMSI-H patients with high bMSI scores (larger or equal to 28) showed 66.7% ORR and 100% DCR. Finally, 91.7% patients with controlled diseases over 6 months showed decreasing bMSI scores, and 60% patients with progressive diseases showed increasing bMSI scores during therapies.

Conclusions: A significant proportion of pMMR metastatic gastrointestinal cancer patients could be rescued by bMSI and get benefits from ICI. bMSI could further classify the patients to three groups and more precisely predict the response of ICI. The level of bMSI is dynamically related to the response during the therapies. bMSI could potentially improve clinical practices in the future.

Legal entity responsible for the study: Peking University Cancer Hospital & Institute.

Funding: National Key Research and Development Program of China (No. 2016YFC0905302).

Disclosure: H. Qin, D. Wang, S. Cai, Y. Bai, Z. Xie: Employee: 3D Medicines Inc. L. Xiong: Employee, stock holder, chairman: 3D Medicines Inc. F. Li: Employee and stock holder: 3D Medicines Inc. All other authors have declared no conflicts of interest.

92P Vall d'Hebron Institute of Oncology (VHIO) immuno-oncology prognostic index (VIO): A new tool for improved patient (pt) selection in phase I (Ph1) trials with immune checkpoint inhibitors (ICI)

C. Hierro[1], I. Matos[1], J. Martin-Liberal[1], M. Ochoa De Olza Amat[1], E. Felip[2], M. Costa Rivas[3], M. Vieito Villar[1], I. Brana[1], A. Azaro[1], M.C. Perez-Gago[1], A. Gros[4], J. Carles[1], A. Oaknin[1], T. Macarulla[1], C. Saura[1], N. pardo[1], E. Muñoz-Couselo[1], J. Tabernero[1], R. Dienstmann[5], E. Garralda[1]

[1]Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [2]Medical Oncology Department, Germans Trias i Pujol Hospital, Catalan Institute of Oncology (ICO)-Badalona, Badalona, Spain, [3]Oncology, Complexo Hospitalario Universitario de Vigo, Vigo, Spain, [4]Tumor Immunology and Immunotherapy, Vall dHebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [5]Oncology Data Science Group (ODysSey), Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: The Royal Marsden Hospital score (RMHs) (albumin <35 g/L, lactate dehydrogenase [LDH]>upper limit of normal [ULN], and >two sites of metastases [met]) is a validated prognostic index for Ph1 pt selection. Recently, a lung immune prognostic index (LIPI) (derived neutrophil/(leukocytes minus neutrophils) ratio [dNLR]>3, and LDH>ULN) proved to be useful for identifying pts with different outcomes under ICI. We aimed to improve pt selection for ICI Ph1 trials by developing a composite VIO that included all clinical-laboratory (CL) variables linked with worse median Overall Survival (mOS).

Methods: Retrospective analysis of pts treated with ICI at VHIO Ph1 Unit from Jan'12 to Oct'17. VIO includes four CL factors previously described (albumin<35g/L, LDH>ULN, >two sites of met, dNLR>3) and a fifth variable (liver met) as per univariate Cox modeling. The following VIO clusters were defined based on Kaplan Meier OS estimates: low risk (0 and 1), intermediate risk (2 and 3) and high risk (4 and 5).

Results: In total, 174 out of 214 pts (81%) treated with ICI (antiPD1/PDL1 ICI in 93%, combination regimens in 53%) had complete CL data for modeling. Most common tumor types were melanoma (22%) and lung (14%). Overall, best response was PD 47%, SD 38%, PR 12%, CR 2% and mOS 9.8 (95% CI 7.3-12.7) months (m). Concordance index of OS models including LIPI, RMHs or VIO scores were 0.62, 0.66 and 0.69, respectively. Estimated mOS in low risk (40.2% of all pts), intermediate risk (50.3%) and high risk (9.2%) were 22.0 m (10.5.4-33.4), 6.7 m (4.1-9.3) and 3.8 m (2.5-5.1), respectively (log rank test, $p < 0.001$). PD as best response was higher in high risk VIO group (81%) as compared to intermediate (50%) and low risk (34%, Chi-square $p = 0.002$). 6m OS rates were 85% (77%-94%), 55% (44%-67%) and 30% (14%-65%) in low, intermediate and high risk VIO groups (log rank test, $p < 0.001$).

Conclusions: Our results suggest that the VIO is a better predictor of OS on ICI in Ph1 trials as compared to existing prognostic scores. The VIO is a helpful tool for identifying Ph1 candidates unlikely to benefit from ICI and with higher chances of death within 6 m of trial recruitment.

Legal entity responsible for the study: VHIO.

Funding: Has not received any funding.

Disclosure: A. Oaknin: Advisory boards: Roche, AstraZeneca, PharmaMar, Clovis Oncology, Tesaro; Travel or accommodation support: Roche, AstraZeneca, PharmaMar. J. Tabernero: Advisory Boards: Bayer, Boehringer Ingelheim, Genentech/Roche, Lilly, MSD, Merck Serono, Merrimack, Novartis, Peptomyc, Roche, Sanofi, Symphogen, Taiho. All other authors have declared no conflicts of interest.

93P Augmenting TNM staging with machine learning-based immune profiling for improved prognosis prediction in muscle-invasive bladder cancer patients

N. Brieu[1], C.G. Gavriel[2], D.J. Harrison[2], G. Schmidt[1], P.D. Caie[2]

[1]Research, Definiens AG, Munich, Germany, [2]School of Medicine, University of St Andrews, St Andrews, UK

Background: Muscle-invasive bladder cancer (MIBC) is a highly aggressive disease whose clinical reporting is based on TNM staging. A more accurate and personalized prognosis could be achieved by profiling the immune contexture alongside clinical TNM staging. This study reports on features captured from the labelling of cells for CD3, CD8 and PD-L1 expression, within both the tumor and stroma of MIBC patients. This data is distilled to identify a novel immune-based prognostic signature which augments TNM staging.

Methods: An image analysis solution was developed to quantify the density of cell populations across immunofluorescence (IF) labelled whole slide images from 105 MIBC patients with known survival data. A regression random forest was used for the detection of nuclei using the Hoechst channel [Brieu et al., ISBI2017] and a convolutional neural network employed for the segmentation of the tumor from the stroma using the pan-cytokeratin channel [Brieu et al., SPIE2018]. The CD3, CD8 and PD-L1 channels were used to classify the cells and calculate their proportion within either the tumor or stroma regions. A decision tree of depth two was trained on these proportions as well as cross-validated. More explicitly, the patients were recursively partitioned during training to maximize at each node their survival difference, leaves showing low survival difference (p-value>0.5) being finally merged.

Results: The method yielded a decision tree which stratified patients into three groups utilizing only two parameters: the proportion of CD8(+) cells in the stroma and the

proportion of PD-L1(+) cells across the whole tissue, which were negatively and positively correlated with cancer-specific death respectively. This method was used to replace TNM stages 1 to 3 while retaining the original stage 4 stratification. Testing for survival curve differences showed that this combined system yielded a higher prognostic value (Chisq=41.5, p-value=5.0x10-9) than the standalone TNM staging system (Chisq=34.9, p-value=1.25x10-7).

Conclusions: Our results suggest that immune profiling derived from image analysis provides additional prognostic value to TNM scoring for MIBC.

Legal entity responsible for the study: University of St Andrews.

Funding: Definiens AG.

Disclosure: N. Brieu, G. Schmidt: Fully employed: Definiens AG, a subsidary of Medimmune and Astrazeneca. C.G. Gavriel: PhD student at the University of St. Andrews; PhD work is funded by Definiens AG. D.J. Harrison: Professor of pathology at the University of St Andrews; Secondary PhD supervisor of C. Gavriel, funded by Definiens AG. P.D. Caie: Senior research fellow at the University of St Andrews; Primary PhD supervisor of C. Gavriel, funded by Definiens AG.

94P HPV circulating tumor DNA as predictive biomarker of sustained response to chemotherapy in advanced anal carcinoma

A. Bernard-Tessier[1], E. Jeannot[1], D. Guenat[2], M. Michel[3], C. Proudhon[3], A. Vincent-Salomon[4], I. Bièche[5], J-Y. Pierga[6], B. Buecher[6], E. Francois[7], S. Kim[8], T. André[9], M. Jary[8], V. Vendrely[10], E. Samalin[11], F. El Hajbi[12], N. Baba-Hamed[13], A. Meurisse[14], F-C. Bidard[15], C. Borg[8]

[1]Biopathology, Institut Curie, Paris, France, [2]Centre National de Référence Papillomavirus, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [3]Circulating Tumor Biomarkers Laboratory, Institut Curie, Paris, France, [4]Pathology, Institut Curie, Paris, France, [5]Pharmacogenomics Unit, Institut Curie, Paris, France, [6]Service d'Oncologie Médicale, Institut Curie, Paris, France, [7]Oncology, Centre Anticancer Antoine Lacassagne, Nice, France, [8]Medical Oncology, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [9]Medical Oncology, Hôpital Saint-Antoine, Paris, France, [10]Oncology Radiotherapy, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France, [11]Medical Oncology, ICM Regional Cancer Institute of Montpellier, Montpellier, France, [12]Medical Oncology, Centre Oscar Lambret, Lille, France, [13]Medical Oncology, Groupe Hospitalier Paris Saint-Joseph, Paris, France, [14]Methodology and Quality of Life in Oncology Unit, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [15]Medical Oncology, Institut Curie, Paris, France,

Background: The Epitopes-HPV02 single arm phase II study (NCT02402842) demonstrated the efficacy of Docetaxel, Cisplatin and 5FU as first line chemotherapy (CT) for advanced squamous cell carcinoma of the anal canal (SCCA), with a 1-year progression-free survival rate (PFS) of 47% (Kim, Lancet Oncol 2018 in press). We previously reported the validity of HPV ctDNA detection and its prognostic value in localized SCCA (Cabel, Clin Cancer Res 2018 in press). This ancillary study reports the impact of HPV ctDNA detection in patients enrolled in the Epitopes-HPV02 trial.

Methods: Per protocol, serum samples (1 ml) were collected twice: before CT and, in non-progressive patients, at CT discontinuation which occurred after 5 months on CT. HPV16 ctDNA was quantified by ddPCR at both time points and correlated with prospectively registered patient characteristics and outcomes; for post-CT survival analyses, a landmark was set at the time of CT discontinuation.

Results: Among 59 patients with HPV16+ advanced SCCA, 52 (88%) had ctDNA detected at baseline (sensitivity: 91.1%; 95%CI[81.1;96.2]) with a median level of 7,148 copies/ml (range: 8.3- 3,147,000). Baseline ctDNA levels were not associated with any of the patient characteristics; ctDNA level below the median at baseline was correlated with a longer PFS (HR = 2.6, 95%CI[1.1;5.9], p = 0.02). Among 38 patients who completed the 5 months CT, residual ctDNA after CT was detected in 14 patients (36.8%; 95%CI[23.4;52.7]) with a median level of 2,662 copies/ml (range: 31.5–211,950). Residual ctDNA detected at CT discontinuation was strongly associated with shorter post-CT PFS (measured from the time of CT discontinuation, median PFS: 5.4 months vs not reached; HR = 6.2, 95%CI[2.3;16.3], p < 0.001) and OS (HR = 9.6, 95%CI[2.0;46.9], p = 0.005).

Conclusions: In this prospective study in advanced SCCA, we observed a strong prognostic impact of HPV ctDNA before 1st line CT and, in non-progressive patients, after 6 months of DCF. With a limited cost and short turnaround, this quantitative assay is a promising tool to optimize the therapeutic management of SCCA with e.g. maintenance anti PD-1/PD-L1 therapy in ctDNA-positive patients after the completion of first line CT.

Clinical trial identification: NCT02402842.

Legal entity responsible for the study: Institut Curie.

Funding: Fondation ARC.

Disclosure: T. André: Honoraria and advisory role: Roche, BMS, Merck & Co. E. Samalin: Honoraria: Sanofi, Bayer, Servier, Roche; Study support: Merck, Bayer; Congress support: Roche, Ipsen. All other authors have declared no conflicts of interest.

95P Predicting toxicity and response to pembrolizumab (P) through germline genomic HLA class I analysis

M. Iafolla[1], C. Yang[2], V. Chandran[3], M. Pintilie[4], A. Hansen[1], P. Bedard[1], S. Lheureux[1], A. Spreafico[1], A. Razak[1], P. Ohashi[5], S. Hakgor[1], A. Giesler[1], T. Pugh[4], L.L. Siu[1]

[1]Medical Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [2]Medical Biophysics, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [3]Laboratory Medicine and Pathobiology, University Health Network, Toronto, ON, Canada, [4]Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [5]Immunology, Campbell Family Institute for Cancer Research, University Health Network, Toronto, ON, Canada

Background: HLA class I-dependent immune activity is linked to autoimmune diseases, and HLA class I-dependent CD8+ T cells are required for immune checkpoint blockade (ICB) anti-tumor activity. It is unknown if HLA class I is predictive of toxicity to ICB.

Methods: 100 patients (pts) with mixed solid tumors received single agent P (anti-PD-1) 200 mg IV Q 3 weeks in the investigator-initiated Phase II trial (INSPIRE study, NCT02644369). Germline whole exome sequencing (WES) of peripheral blood mononuclear cells was analyzed using the Illumina HiSeq2500 platform. Consensus HLA class I alleles were predicted from WES using HLAminer and HLAVBSeq. Using univariate Fisher's exact test and logistic models adjusting for HLA features, heterozygosity of HLA-A, -B and -C, individual HLA alleles and HLA haplotype dimorphism at positions −21M and -21T of the HLA-A and -B leader sequence were analyzed as predictors of: 1) toxicity defined as ≥ Gr 2 immune-related adverse events (irAE) with at least possible attribution to P; and 2) clinical benefit (CBR) defined as either partial response or stable disease lasting ≥ 6 cycles of P.

Results: In the overall cohort of 100 pts, the frequency of irAE and CBR from P was 21% and 25%, respectively. Thus far, 99 patients had their HLA class I genotype determined. Univariate analysis showed heterozygosity of HLA-A, -B and -C, compared to homozygosity of at least one HLA locus, was not predictive of toxicity (≥ Gr 2 irAE 16.7% vs 27.3%, p = 0.29) but did trend to less response (CBR 19.7% vs 36.4%, p = 0.088). Individual heterozygosity of HLA-A, -B or -C, and HLA-A and -B haplotype dimorphism was not predictive of either toxicity or response. HLA-A*02 allele showed a trend to toxicity (≥ Gr 2 irAE 26.8% vs 11.6%, p = 0.079). A pertinent exploratory toxicity model is summarized in the table.

Table: 95P

	Toxicity
A*01 and A*02 (n = 7)	4(57%)
A*01 and no A*02 (n = 13)	2(15%)
A*02 and no A*01 (n = 49)	11(22%)
Neither A*01 nor A*02 (n = 30)	3(10%)

Table Fisher exact p-value=0.0503

Conclusions: This study is the first to assess the association between HLA class I genotype and toxicity to P. There is a possible association of HLA-A*01 and HLA-A*02 with toxicity to P.

Clinical trial identification: Trial protocol number: NCT02644369.

Legal entity responsible for the study: Lillian Siu.

Funding: Merck.

Disclosure: P. Bedard: Research funding: Bristol-Myers Squibb, Sanofi, AstraZeneca, Genentech/Roche, Servier, GlaxoSmithKline, Novartis, SignalChem, PTC Therapeutics, Nektar, Merck, Seattle Genetics. A. Spreafico: Support for clinical trials: Merck, Novartis, BMS. A. Razak: Research funding: Merck, BMS, Pfizer, Karyopharm, Deciphera, Eli Lilly, Boehringer, Boston Biomedicals, Roche, Novartis and Genentech; Consultancy: Eli Lilly, Eisai, Boeringher Ingelheim, Merck. P. Ohashi: Consultancy/advisory: Symphogen Inc., Providence Pharmaceuticals, Inc., Baxalta US. Inc., Lion Biotechnologies, Inc. T. Pugh: Honoraria: Merck, Prosigna, Chrysalis Biomedical Advisors; Consulting: DynaCare Research. Funding: Boehringer Ingelheim; Patents, royalties; other intellectual property: Hybrid-capture sequencing for determining immune cell clonality, combined hybrid-capture DNA sequencing for disease detection. L.L. Siu: Advisory board and funding for clinical trials: Merck. All other authors have declared no conflicts of interest.

96P AXL has a prognostic role in metastatic colorectal cancer (mCRC) and is a predictive biomarker of lack of efficacy of chemotherapy (CT) + cetuximab in RAS wild type (WT) patients (pts)

C. Cardone[1], B. Blauensteiner[2], V. Moreno-Viedma[2], M.C. Paul[2], G. Martini[1], P.P. Vitiello[1], D. Ciardiello[1], C. Borrelli[1], L. Poliero[1], P. Vitale[1], N. Zanaletti[1], V. Famiglietti[1], A.M. Rachiglio[3], D. Rizzi[4], E. Maiello[5], T.P. Latiano[5], N. Normanno[3], M. Sibilia[2], F. Ciardiello[1], E. Martinelli[1]

[1]Medical Oncology, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [2]Institute of Cancer Research, Medical University of Vienna, Vienna, Austria, [3]Cell Biology and Biotherapy Unit, National Cancer Institute 'Fondazione Giovanni Pascale', Naples, Italy, [4]Clinical Research, GOIM Trial Office, Bari, Italy, [5]Oncology, Hospital Casa Sollievo della Sofferenza-IRCCS, San Giovanni Rotondo, Italy

Background: AXL expression promotes tumour growth, angiogenesis, epithelial to mesenchymal transition (EMT), resistance to CT and targeted agents. AXL is overexpressed in CRC. We aimed to evaluate AXL expression in mCRC pts and to correlate it with clinical outcomes.

Methods: AXL expression was assessed by immunohistochemistry in tumor samples of a consecutive series of 109 mCRC pts (75 RAS mutant and 34 RAS WT) treated at our Institution and 68 mCRC RAS WT pts enrolled in CAPRI-GOIM trial. Pts received a first line treatment according to RAS status: RAS mutant pts (n = 75) received CT + anti-angiogenic drugs, RAS WT pts (n = 102) CT + cetuximab.

Results: AXL stained positively in 20/177 samples with different intensity: 13 weak, 5 moderate, 2 intense. In RAS WT cohort 9/102 cases (9%) were positive while in RAS mutant 11/75 (15%). Tumor stroma was assessable in 166 samples. AXL expression was high (moderate + intense) in 47/96 (49%) RAS WT and in 28/70 (40%) RAS mutant cases. No significant correlation was found between AXL expression and clinico-pathological features. In RAS WT cohort, AXL positive pts had a significantly worse median PFS [4.3 m (CI95% 3.2-5.5) vs 12.1 m (CI95% 11.0-13.3) p = 0.001], in RAS mutant no impact on PFS was observed. AXL expression in tumor was a negative prognostic factor in both cohorts although statistical significance was reached only in RAS mutant [median OS: 30.2 m (CI95% 18.4-42.0) vs 20.1 m (CI95% 10.6-29.6) p = 0.007]. Intriguingly, high AXL expression in stroma correlated with lower median OS in both cohorts (Table).

Conclusions: AXL, marker of EMT phenotype, might represent an additional predictive biomarker of lack of efficacy in RAS WT mCRC pts treated with CT + cetuximab. Moreover, its expression in tumor and stroma might have a negative prognostic relevance in mCRC. Targeting AXL could overcome resistance to anti-epidermal growth factor receptor and represent a novel therapeutic strategy in mCRC.

Clinical trial identification: CAPRI-GOIM Trial = EudraCT 2009-014041-81.

Legal entity responsible for the study: Department of Precision Medicine, Università degli Studi della Campania "Luigi Vanvitelli".

Funding: Grant by AIRC = MFAG-2015-ID: 7778.

Disclosure: All authors have declared no conflicts of interest.

97P Multimodal detection of homologous recombination repair gene mutations (HRRm) in a phase II trial of olaparib plus abiraterone in metastatic castrate resistant prostate cancer (mCRPC)

T.H. Carr[1], C. Adelman[1], A. Barnicle[1], I. Kozarewa[1], S. Luke[1], Z. Lai[2], S. Menon[1], S. Hollis[3], B. Dougherty[2], E.A. Harrington[1], J.C. Barrett[2], C. Goessl[2], F. Saad[4], N. Sala[5], N.W. Clarke[6], D. Hodgson[1]

[1]AstraZeneca, Cambridge, UK, [2]AstraZeneca, Gaithersburg, MD, USA, [3]Phastar, London, UK, [4]University of Montreal Hospital Research Centre, Montreal, QC, Canada, [5]Catalan Institute of Oncology, Hospital Josep Trueta, Girona, Spain, [6]The Christie NHS Foundation Trust, Manchester, UK

Background: Study 8 [NCT01972217] was a randomized Phase II trial that tested the hypothesis that the combination of PARP inhibition plus abiraterone benefits unselected patients (pts) with mCRPC. The primary endpoint was progression-free survival. A key secondary objective was to understand the relationship between HRRm status and outcome, which was challenged by low-tissue acquisition and high-test failure. The primary biomarker analysis focused on testing plasma when tumour data were not available and germline mutations were not evident. Here we describe additional analyses of circulating tumour DNA (ctDNA) to further characterize HRRm status and evaluate concordance between different testing modalities.

Methods: Tumour specimens were sequenced via Foundation Medicine. Germline analysis was performed via Color Genomics. An inhouse (RUO) sequencing assay was used for baseline ctDNA analysis. A subset of plasma samples was analyzed via GuardantOMNI™ and a custom assay (Resolution Bioscience). CtDNA libraries were also subjected to shallow whole genome sequencing (~4–5x). From 142 enrolled pts, we obtained HRRm data for 136 (from any source).

Results: Previous tumour/germline analyses identified 8 HRRm pts: 1 somatic, 7 germline (tumour success rate 38/68 [56%]; germline success rate 102/102). CtDNA analyses yielded a success rate of 93% (127/136 pts with plasma analyzed), with tumour variants detectable with high confidence in 79% (100/127). Plasma sequencing identified additional HRRm pts, including homozygous deletions, approximately tripling the number known to have a HRRm. Plasma testing in pts with tumour data revealed high concordance between tumour and ctDNA.

Conclusions: Comprehensive, sensitive sequencing of ctDNA for HRRm is feasible in mCRPC pts with a high success rate. Both targeted and whole genome approaches add value. There was good concordance across testing modalities where gene coverage overlapped, highlighting the considerable value of ctDNA testing in mCRPC where access to tissue of sufficient quality for molecular analysis is challenging, and somatic alterations are common. The first two authors contributed equally.

Clinical trial identification: NCT01972217.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: T.H. Carr, C. Adelman, A. Barnicle, I. Kozarewa, S. Luke, Z. Lai, S. Menon, B. Dougherty, E.A. Harrington, J.C. Barrett, C. Goessl, D. Hodgson: Employee and stockholder: AstraZeneca. S. Hollis: Contracted: AstraZeneca and own stock. F. Saad: Grants and personal fees: AstraZeneca, Janssen, Astellas, Sanofi, Bayer. N. Sala: Personal fees: Astellas, Janssen, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

Table: 96P

Cohort	Median OS (months - CI95%) AXL expression in tumor		Median PFS (months - CI95%) AXL expression in tumor		Median OS (months - CI95%) AXL expression in stroma		Median PFS (months - CI95%) AXL expression in stroma	
N (tumor) / N (stroma)	AXL positive	AXL negative	AXL positive	AXL negative	AXL high	AXL low	AXL high	AXL low
Overall population N = 177 / N = 166	20.1 (12.8-27.4)	36.5 (30.6-42.3) p = 0.02	-	-	25.3 (21.4-29.3)	46.4 (34.6-58.2) p = 0.003	-	-
RAS WT (CT + cetuximab) N = 102 / N = 96	23.0 (0.0- 63.3)	39.8 (30.2– 49.4) p = 0.66	4.3 (3.2- 5.5)	12.1 (11.0– 13.3) p = 0.001	28.8 (17.4- 40.1)	47.7 (29.7– 65.7) p = 0.021	10.7 (8.4- 13.0)	12.4 (9.6– 15.2) p = 0.06
RAS mutant (CT + anti-angiogenic) N = 75 / N = 70	20.1 (10.6- 29.6)	30.2 (18.4- 42.0) p = 0.007	8.9 (5.4- 12.4)	9.1 (7.6- 10.7) p = 0.444	24.2 (18.2- 30.1)	37.7 (16.8- 58.6) p = 0.026	8.9 (6.1- 11.8)	8.6 (7.3- 10.0) p = 0.53

98P Identification of a highly suppressive Treg subset associated to immunotherapy response

E.F. Giunta[1], S. Romano[2], P. D'Arrigo[2], A. Rea[2], M. Tufano[2], G. Matarese[2], C. Procaccini[2], N. Novizio[2], V. Vigorito[2], D. Faicchia[2], G. Argenziano[3], V. De Falco[1], F. Ciardiello[1], M.F. Romano[2], T. Troiani[1]

[1]Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [2]Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università Federico II, Naples, Italy, [3]Dipartimento di Salute Mentale e Fisica e Medicina Preventiva, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: Cancer immunotherapy, particularly monoclonal antibodies against immune checkpoint inhibitors, has shown surprising efficacy in several types of advanced incurable tumors, including malignant melanoma. Tregs, a subset of lymphocytes involved in immune-surveillance and self-tolerance, are usually increased in melanoma patients. Lymphocytes are particularly rich in FKBP51, the intracellular receptor for FK506 and rapamycin. Melanoma aberrantly expresses this immunophilin, which supports cancer resistance and invasion. Recently, our group has shown that melanoma interaction with immune cells, through PD-L1/PD1, generated the splicing of FKBP5 gene inducing a lower molecular weight form (FKBP51s), in both melanoma and lymphocyte. Aim of this study is to assess the role of Treg FKBP51s+ as potential biomarker of response to anti-PD1 drugs.

Methods: Treg FKBP51s+ were measured in peripheral blood by flow cytometry. To date, we have outcomes of 11 patients. For 6 patients, we have collected from 4 up to 16 blood samples, before each anti-PD1 administration, with a total of 80 sample analysis. iTregs were generated by purified CD4+ T lymphocytes from normal donor, stimulated with CD3+CD28+beads. The suppressive capacity was assessed according to the parameters $CD25^{high}$, $Ki67^{high}$ and $p70S6k^{high}$.

Results: In 5 responder patients, Treg FKBP51s+ was 1.2-4.8%; in 5 non-responders, the count was 0.04-0.8%. Interestingly, a patient with count 0.72% developed autoimmune side effects that led to drug discontinuation. Resolution of side effects was accompanied by an increase in Treg FKBP51s+ value to 9.9%. In vitro iTreg generation suggested that FKBP51s was induced in Treg $CD25^{high}$ $Ki67^{high}$ $p70S6k^{high}$, corresponding to a highly metabolically active profile associated with strong suppressive capability. Use of a siRNA for FKBP51s silencing resulted in reduction of this subtype of iTreg.

Conclusions: Our data reinforce the hypothesis that melanoma patients that benefit from immunotherapy are recognizable by an expansion of a Treg subset which plays a central role in tumor immune evasion. This Treg subset is marked by FKBP51s, a splicing protein isoform generated by triggering of surface antigens (PD-L1, PD1) abundantly expressed on highly suppressive Tregs.

Legal entity responsible for the study: Università degli Studi della Campania Luigi Vanvitelli.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

99P A novel framework for evaluating biomarker response relationships in immuno-oncology (IO)

J.L. Evelhoch[1], R. Mogg[1], R. Cristescu[1], D. Aurora-Garg[1], L.Q. Chow[2], S. Loi[3], D.V.T. Catenacci[4], U.A. Matulonis[5], P.A. Ott[6], E.S. Antonarakis[7], C.H. Poehlein[1], A. Joe[1], S.M. Keefe[1], P. Kang[1], V. Karantza[1], J. Cheng[1], E.H. Rubin[1]

[1]Clinical Research, Merck & Co., Inc., Kenilworth, NJ, USA, [2]School of Medicine, University of Washington, Seattle, WA, USA, [3]Translational Breast Cancer Genomics Lab, Division of Research, Peter MacCallum Cancer Center, Melbourne, Australia, [4]Medicine, University of Chicago, Chicago, IL, USA, [5]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [6]Center for Immuno-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [7]School of Medicine, Johns Hopkins University, Baltimore, MD, USA

Background: Unlike biomarkers of dichotomous genetic mutations/fusions required for response, biomarkers for checkpoint inhibitors are continuous biologic variables with context specific cutpoints. Selecting the cutpoint of a continuous biomarker for higher response rate in a given therapy decreases the number of biomarker positive patients (prevalence). To facilitate interpretation of biomarkers in IO, we introduce a framework for understanding how cutpoints, response rate and prevalence are interrelated.

Methods: Objective response rate (ORR) in biomarker positive patients is the product of ORR in all patients and the fraction of responding patients who are biomarker positive (FR+), divided by the prevalence. FR+ depends on the difference in biomarker distributions between responding and nonresponding patients. Biomarker [PD-L1 IHC, tumor mutation burden (TMB), T-cell activated gene expression profile (GEP)] and response data were pooled from 595 patients in 7 clinical trials of pembrolizumab monotherapy across 16 tumor types. A Bayesian model was used to estimate biomarker distributions in responders and nonresponders for each biomarker assuming normality.

Results: ORR prevalence data generated by varying the cutpoint were fit well by the biomarker distribution model for all 3 biomarkers. Individual biomarker ORR prevalence curves and 95% credible intervals overlapped substantially with each other, consistent with indistinguishable areas under the receiver operating characteristics curve (AUROC) for PD-L1, TMB and GEP in this pan tumor population. Thus, although PD-L1 or GEP identify populations only partially overlapping with that of TMB, the predictive ability is similar for all 3 biomarkers.

Table: 99P

Biomarker	Value (95% CI)			
	ORR @ 60% Prevalence	ORR @ 30% Prevalence	ORR @ 10% Prevalence	AUROC
PD-L1	15.5 (12.0, 19.0)	21.5 (15.8, 27.4)	33.6 (22.3, 45.7)	0.69 (0.63, 0.76)
GEP	17.5 (14.1, 21.2)	24.8 (19.2, 30.1)	33.5 (24.2, 44.1)	0.76 (0.70, 0.82)
TMB	15.0 (11.7, 18.6)	21.5 (15.7, 27.7)	35.9 (24.0, 49.0)	0.67 (0.59, 0.74)

CI = Credible interval for ORR and confidence interval for AUROC

Conclusions: A model using biomarker distributions in responding and nonresponding patients accounts for the relationships among cutpoints, response rate and prevalence, and may provide a framework for interpretation of biomarker response data in IO.

Editorial acknowledgement: Joanne Tomassini, Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck Sharp & Dohme, Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Funding: Merck Sharp & Dohme, Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosure: J.L. Evelhoch: Employee and stock owner: Merck Sharp & Dohme Corp. R. Mogg, R. Cristescu, D. Aurora-Garg, C.H. Poehlein, A. Joe, S.M. Keefe, P. Kang, V. Karantza, J. Cheng, E.H. Rubin: Employee and stock owner/stock options: Merck Sharp & Dohme Corp. L.Q. Chow: Advisory board honoraria: Merck & Co., Inc., Sanofi-Genzyme; Institutional grant funding: Merck & Co., Inc., Bristol Myers Squibb, Lily/Imclone; Consulting honoraria: Amgen, Incyte, VentiRx; Institutional research grant and advisory board honoraria: Novartis, Genentech, AstraZeneca, Pfizer, Seattle Genetics. S. Loi: Grants: Merck Sharp & Dohme, Puma Biotechnology, Bristol-Myers Squibb, Novartis, Pfizer; Grants and non-financial support: Roche-Genentech. D.V.T. Catenacci: Consultant: Eli Lilly, Roche/Genentech, Amgen, Taiho, Five Prime Therapeutics; Speaker bureau: Eli Lilly; Institutional research funding: Amgen, Genentech. U.A. Matulonis: Funding: Merck & Co., Inc., Novartis; Consulting/advisor fees: Merck & Co., Inc., Lilly, Geneos, 2X Oncology, Myriad Genetics, Clovis Oncology, Fujifilm. P.A. Ott: Consulting or advisory role: Amgen, Bristol-Myers Squibb, Alexion, CytomX Therapeutics, Celldex, Genentech, Novartis, Pfizer, Neon Therapeutics; Speaking fees: Merck & Co., Inc.; Research funding: Bristol-Myers Squibb, Merck & Co., Inc., Astra Zeneca/MedImmune, Celldex, Neon Therapeutics, Pfizer, CytomX, ARMO BioSciences (to institution). E.S. Antonarakis: Consulting or advisory role: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma, Merck & Co., Inc., AstraZeneca, Clovis Oncology; Travel fees: Sanofi, Dendreon, Medivation; Co-inventor of a biomarker technology that has been licensed to Qiagen; Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Asstellas Pharma, Merck & Co., Inc., AstraZeneca, Clovis Oncology; Research funding: Janssen Biotech, Johnson & Johnson, Sanofi, Dendreon, Aragon Pharma, Exelixis, Millennium, Genentech, Novartis, Astellas Pharma, Tokai Pharmaceuticals, Merck & Co., Inc., AstraZeneca, Clovis Oncology, Constellation Pharmaceuticals (received by institution).

100P Comparison of OncoBEAM and NGS methods to detect plasma EGFR T790M mutations at progression of NSCLC

J. Garcia[1], A. Delherme[1], F. Geigeur[1], P. Merle[2], C. Tissot[3], F.S. Jones[4], D. Edelstein[5], P-J. Souquet[6], C. Rodriguez-Lafrasse[1], S. Couraud[6], L.F. Payen[1], Z. Xu[7]

[1]Biochemistry and Molecular Biology Department of Lyon Sud, Hospices Civiles de Lyon, Lyon, France, [2]Oncology, Centre Jean Perrin, Clermont-Ferrand, France, [3]Oncology, CHU de Saint Etienne, Hôpital du Nord, St. Priest en Jarez, France, [4]Oncology, Sysmex-Inostics, Inc., New York, NY, USA, [5]Oncology, Sysmex Inostics, Baltimore, MD, USA, [6]Oncology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [7]Bio-informatics, Sophia-Genetics, Lausanne, Switzerland

Background: Various methods have been employed to detect plasma EGFR mutations in patients with non-small cell lung cancer patients (NSCLC). Therefore, we evaluated the performance of digital PCR and next generation sequencing (NGS) to detect the p.T790M EGFR mutation in prospectively collected patient samples. Paired plasma samples from patients (CIRCAN cohort) that progressed on first-line EGFR TKI therapy were compared using two platforms: OncoBEAM^{TM}-EGFR (Sysmex Inostics) and NGS (Illumina), utilizing the 56G oncology panel (Swift Biosciences).

Methods: 196 stage 4 NSCLC patients with EGFR alteration under TKI were included from various center. Blood was collected in a routine setting, when physician noted

changes in CT scans that were suspicious of progression. CfDNA analysis is recommended in front line in this setting in France. Replicate plasma samples were analysed using OncoBEAM and NGS. The thresholds for calling EGFR plasma mutations were 0.5% and 0.02% for NGS and OncoBEAM, respectively and were validated using cfDNA reference standards (Horizon Discovery).

Results: OncoBEAM detected the p.T790M mutation in 36/196 patients (18.3%), whereas NGS detected T790M in 20/196 patients (10.2%). The agreement of NGS vs OncoBEAM for T790M detection was 55.6%. The p.T790M-positive samples detected by OncoBEAM but missed by NGS were all found to have low mutant allelic fractions (under 0.35%). With regard to sensitizing EGFR mutations, 28/36 OncoBEAM T790M+ patients had accompanying EGFR mutations, whereas all 20/20 NGS T790M+ samples showed presence of sensitizing mutations. In contrast to OncoBEAM, NGS testing revealed other somatic alterations including ERBB2 amplification, and mutations in TP53.

Conclusions: In conclusion, these findings highlight the value of OncoBEAM^{TM}-EGFR and NGS for detecting T790M at early progression. While less sensitive, NGS provided broader genomic coverage which may reveal diverse mechanisms of resistance. In contrast, OncoBEAM delivers superior sensitivity for focused detection of known resistance alterations such as EGFR T790M. Thus, OncoBEAM may provide the sensitivity required to monitor the kinetics of circulating tumor DNA and correlations with therapeutic response.

Legal entity responsible for the study: Hospices Civils of Lyon.

Funding: Sysmex Innostics / AstraZeneca.

Disclosure: C. Tissot, P-J. Souquet: Membership on pharma advisory board. F.S. Jones, D. Edelstein: Sysmex Innostics. S. Couraud: AstraZeneca, Roche, MSD, Novartis, BMS, Boehringher Ingelheim, Chugai, Pfizer, Lilly, Merck. L.F. Payen: Membership on BMS; Advisory board: AstraZeneca. Z. Xu: Sophia Genetics. All other authors have declared no conflicts of interest.

101P Differential expression of PD-L1 and immune biomarkers by age: Decreased expression in pediatric/AYA patients with advanced cancer

O. Hamid[1], A.M. Vanderwalde[2], C. Szeto[3], S. Reddy[3], S.K. Pal[4]

[1]Research/Immuno-Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA, [2]Hematology/Oncology, University of Tennessee, Memphis, TN, USA, [3]Bioinformatics, NantOmics, Culver City, CA, USA, [4]Medical Oncology and Therapeutics Research, City of Hope, Duarte, CA, USA

Background: The activity of immune checkpoint inhibitors (ICIs) varies substantially at the extremes of age. We interrogated our tissue database (n = 1,467) to determine if expression of checkpoint molecules or variations in tumor mutational burden (TMB) could explain this phenomenon.

Methods: Whole transcriptomic sequencing (RNA-Seq; ~200x10^6 reads/tumor) was performed across 1,467 unselected clinical cases (NantHealth; Culver City, CA), with breast, colon, lung and sarcoma reflecting the most common tumor types assessed. To reflect the extremes of age, patients age < 25 and ≥ 80 were compared to the remainder of the cohort. PD-L1 expression was compared across these age-based subsets, along with CTLA4, TIGIT, FOXP3, LAG3, OX40, TIM3 and IDO expression. Putative markers of ICI resistance (e.g, VEGF-A/B/C) were also explored. Tumor mutational burden (TMB; defined as exonic nonsynonymous mutations/megabase [muts/Mb]) was characterized in each subset.

Results: Median age of the cohort was 59 (range, 2-97). Of 1,467 patients, 84 and 65 were age < 25 and ≥ 80, respectively. In patients < 25, significantly lower PD-L1, CTLA4, FOXP3, OX40, LAG3 and TIGIT levels were observed ($P < 0.001$ for each). No significant differences in IDO, LAG3 or TIM3 were observed in this younger cohort. Older patients had no significant differences in checkpoint molecule expression; curiously, a nonsignificant trend towards increased expression of PD-L1, FOXP3 and LAG3 was observed in the small subset of patients age ≥ 85. No differences in TMB were observed by age. Expression and TMB in each decile of age will be reported.

Conclusions: In pediatric and adolescent and young adult (AYA) patients, lower expression of multiple immune checkpoint molecules may have implications for immune combinatorial strategies. An opposing trend was seen in octagenarians and nonagenarians in our cohort. A detailed further breakdown by histologic subtype will be presented.

Legal entity responsible for the study: Omid Hamid.

Funding: Has not received any funding.

Disclosure: O. Hamid: Consultant: Amgen, Novartis, Roche, BMS, Merck; Speaker: BMS, Genentech, Novartis, Amgen; Contracted research (for institution): AstraZeneca, BMS, Celldex, Genentech, Immunocore, Incyte, Merck, Merck-Serono, MedImmune, Novartis, Pfizer, Rinat, Roche. C. Szeto, S. Reddy: Employee and stockholder: NantOmics LLC. S.K. Pal: Consultant: Pfizer, Inc., Novartis, Aveo Pharmaceuticals, Inc., Myriad Genetics, Genentech, Inc., Exelixis, Bristol-Myers Squibb Company, Astellas Pharma, Inc.; Research/grant support: Medivation, Inc.; Honorarium: Novartis, Medivation, Inc., and Astellas Pharma, Inc. All other authors have declared no conflicts of interest.

102P Potential resistance mechanisms revealed primary resistance to crizotinib in ROS1+ non-small cell lung cancer using next generation sequencing: A multicenter study

Q. Zhang[1], C. Xu[1], W. Wang[2], W. Zhuang[3], Z. Song[2], Y. Zhu[4], Y. Chen[1], G. Chen[1], M. Fang[2], T. Lv[5], Y. Song[5]

[1]Pathology, Fujian Cancer Hospital, Fuzhou, China, [2]Chemotherapy, Zhejiang Cancer Hospital, Hangzhou, China, [3]Medical Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China, [4]Thoracic Disease Center, Zhejiang Rongjun Hospital, Jiaxing, China, [5]Respiratory Medicine, Jinling Hospital, Nanjing, China

Background: Crizotinib have greatly improved the prognosis of ROS1+ lung adenocarcinoma. However, approximately 5% to 10% of patients with ROS1+ non-small-cell lung cancer (NSCLC) have primary resistance to crizotinib treatment. The underlying mechanism is unknown.

Methods: We screened 2617 patients with NSCLC for ROS1 fusion. Among them, 23 patients received crizotinib treatment, and a total of 20 patients with stage IIIb-IV ROS1+ NSCLC were undergoing tumor biopsies or blood withdrawing by the time of primary or acquiring resistance to crizotinib, in including 4 formalin-fixed paraffin-embedded (FFPE) samples, 13 serum samples and 3 serous effusions. We used targeted NGS to detect genes status of patients.

Results: Among 23 patients treated with crizotinib, 73.9% (17/23) developed acquired resistance, and 13.04% (3/23) had primary resistance. Using the specimens at the baseline, there was 1 (33.3%) patient with BCL2L11 loss (BIM deletion polymorphism), 1 (33.3%) patient with PTEN mutation, and 1 (33.3%) patient with KIT mutation. Median PFS was significantly shorter in patients with primary resistance than those with acquired resistance (2.3 vs. 14.5 months, $P < 0.001$).

Conclusions: BCL2L11 loss, PTEN mutation, and KIT mutation might contribute to molecular mechanisms of primary resistance to crizotinib in ROS1+ NSCLC. Further investigations are warranted to overcome these primary resistances.

Legal entity responsible for the study: Quxia Zhang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

103P Prevalence of CLDN18.2, HER2 and PD-L1 in gastric cancer samples

D. Moran[1], D. Maurus[2], C. Rohde[3], A. Arozullah[4]

[1]Oncology Biomarkers, Astellas Pharma US, Inc., Northbrook, IL, USA, [2]Data Science and Biomarker Analysis, BioNTech AG, Mainz, Germany, [3]Medical Oncology, Merck KGaA, Darmstadt, Germany, [4]Development Medical Sciences - Oncology, Astellas Pharma US, Inc., Northbrook, IL, USA

Background: In gastric cancer (GC) there is a need for therapeutic targets/biomarkers beyond HER2 and PD-L1; Claudin 18.2 (CLDN18.2) is a promising target. In healthy tissue, CLDN18.2 is confined to gastric mucosa tight junctions; however, upon malignant transformation, perturbations in cell polarity lead to exposure of CLDN18.2 on the surface of GC cells. In a randomized clinical study (FAST; NCT01630083), patients with CLDN18.2-positive advanced GC and gastroesophageal junction (GEJ) cancers treated with EOX and zolbetuximab (an anti-CLDN18.2 monoclonal antibody) had prolonged survival compared with EOX alone. The CLDN18.2, HER2, and PD-L1 prevalence in global GC/GEJ tissue samples were assessed in this study.

Methods: FFPE GC/GEJ tissue samples were stained using antibodies against CLDN18.2, PD-L1, and HER2. IHC assays were run on an automated platform; HER2 amplification was determined by HER2 CISH. Stained samples were evaluated by a trained pathologist using established scoring criteria.

Results: A total of 298 GC/GEJ tissue samples (North America, n = 100; Asia, n = 100; Europe, n = 98) were assessed; 148 (50%) were histologically classified as intestinal, 123 (41%) diffuse, 18 (6%) mixed, and 9 (3%) other. In American samples, intestinal histology was the most prevalent; diffuse and intestinal were similar within Asian and European samples. Of the 286 evaluable samples, 30% (n = 86/286) were CLDN18.2^{high} (moderate-to-strong CLDN18.2 membrane staining in $\geq$75% of tumor cells). CLDN18.2^{high} prevalence ranged from 24% (n = 22/92) in Asian samples to 34% (n = 33/97) in American samples. CLDN18.2^{high} prevalence was 30% (n = 35/115) in diffuse and 28% (n = 40/145) in intestinal subtypes. HER2+ and PD-L1+ ($\geq$1% membrane-stained tumor cells) occurred in 10% (n = 29/291) and 37% (n = 107/289) of the evaluable samples, respectively. Of CLDN 18.2^{high} samples with evaluable status for HER2, CLDN18.2 overlapped with HER2 in 12% (n = 10/83) of cases.

Conclusions: CLDN18.2 was found globally to be a high prevalence target in GC/GEJ cancer with limited overlap with HER2. In light of the clinical activity observed for zolbetuximab, CLDN18.2 may serve as a therapeutic target for a large subgroup of patients with GC/GEJ cancer.

Editorial acknowledgement: Medical writing and editorial assistance provided by Amlan RayChaudhury, PhD (SuccinctChoice Medical Communications Chicago, IL).

Legal entity responsible for the study: Astellas Pharma, Inc.

Funding: Astellas Pharma, Inc.

Disclosure: D. Moran, A. Arozullah: Employee: Astellas. All other authors have declared no conflicts of interest.

104P Epigenetic markers in circulating cell-free DNA for detection of early stage colorectal cancer

Y. Liu[1], C.K. Tham[2], S. Ong[2], C.L. Tang[1], Y. Zhao[3]

[1]Colorectal Surgery, Singapore General Hospital, Singapore, [2]Medical Oncology, National Cancer Centre Singapore, Singapore, [3]Clinical Research, Singapore General Hospital, Singapore

Background: The detection of early stage colorectal cancer (CRC) significantly improves chances of a cure and is a key factor in reducing CRC mortality rates. Colonoscopy is currently the gold standard for CRC diagnosis, but a somewhat troublesome and invasive procedure makes its acceptance not high in the general public as a screening tool. Epigenetic silencing of tumor-related genes by promoter methylation is common in CRC, but no biomarker has been proven to be individually of sufficient sensitivity or specificity in routine clinical practice. Objective: To identify tumor-derived methylated genes in the serum of stage IIA CRC and assessed their diagnostic potentials for early stage of colorectal cancer.

Methods: In this prospective study, DNA methylation levels were measured by quantitative methylation-specific PCR. Seven genes were screened in an exploratory set of case-control serum samples. Promising methylation markers were selected and verified in the serum of a test set compromising 60 stage IIA CRC and 60 age-gender-matched healthy controls. Receiver operating characteristic curve (ROC) was constructed for assessment of assay performance.

Results: Serum methylation levels of TAC1, EYA4 and SST were significantly higher in stage IIA patients as compared to healthy controls (all $P < 0.001$, Mann-Whitney U test). Area under the receiver operating curve (AUC) using serum methylation of TAC1 and EYA4 was 0.76 [95% confidence interval (CI), 0.68-0.85] and 0.73 (95% CI, 0.64-0.82), respectively. At a specificity of 85%, the assay sensitivity of TAC1 and EYA4 was 58.3% and 43.3%, respectively. Combination of serum methylation levels of EYA4 and SST improved the assay sensitivity to 52.5%. With TAC1 and SST being investigated in tumor DNA as well, we noticed that methylation of both genes in the serum DNA always mirrored that of tumor DNA, exhibiting 100% concordance.

Conclusions: Serum methylation levels of TAC1, EYA4 and SST might be useful for minimally invasive detection of early stage of colorectal cancer. Validation study in larger and independent cohorts is necessary.

Legal entity responsible for the study: Singapore General Hospital.

Funding: National Medical Research Council, Singapore.

Disclosure: All authors have declared no conflicts of interest.

105P Detection and clearance of RET variants in plasma cell free DNA (cfDNA) from patients (pts) treated with LOXO-292

B. Besse[1], V. Subbiah[2], A. Drilon[3], M. Shah[4], L.J. Wirth[5], T.M. Bauer[6], V. Velcheti[7], N. Lakhani[8], V. Boni[9], B.J. Solomon[10], M. Johnson[6], K. Park[11], J. Patel[12], M.E. Cabanillas[13], E. Sherman[3], E. Zhu[14], K. Gordon[14], K. Ebata[14], B. Tuch[14], G. Oxnard[15]

[1]Dept of Cancer Medicine, Gustave Roussy Institut de Cancérologie, Villejuif, France, [2]Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas, MD Anderson Cancer Center, Houston, TX, USA, [3]Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [4]Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA, [5]Cancer Center, Massachuetts General Hospital, Boston, MA, USA, [6]Oncology, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA, [7]Hematology and Oncology Department, Cleveland Clinic, Cleveland, OH, USA, [8]Developmental Therapeutics, START - Midwest, Grand Rapids, MI, USA, [9]Medical Oncology, START Madrid-CIOCC HM Hospital Sanchinarro, Madrid, Spain, [10]Molecular Therapeutics and Biomarkers Laboratory, Peter MacCallum Cancer Center, Melbourne, Australia, [11]Div. of Heamatology/Oncology, Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [12]Thoracic Oncology, University of Chicago, Chicago, IL, USA, [13]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [14]Translational Medicine, Loxo Oncology, Inc, South San Francisco, CA, USA, [15]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: LOXO-292 is a novel, highly-selective, small molecule inhibitor of RET currently in clinical development (Phase 1, NCT03157128) for pts with advanced cancers harboring oncogenic RET alterations (e.g. non-small cell lung cancer [NSCLC], medullary thyroid cancer [MTC], papillary thyroid cancer [PTC], etc.). Here, we update data previously presented at ASCO 2018 on modulation of RET variant allele frequencies (AF) in plasma cfDNA with LOXO-292 therapy.

Methods: Blood was collected pretreatment, after 15 days of treatment, and at each restaging for cfDNA analysis by next-generation sequencing (NGS, Guardant).

Results: As of 4/2/18, 82 pts were enrolled (38 RET fusion NSCLC, 29 RET mutated MTC, 9 RET fusion PTC, 2 RET fusion pancreatic cancer and 4 others) to 8 dose cohorts (20mg QDà240mg BID), and 343 plasma samples were collected. Here we report on 65 pts with plasma NGS results available. Of 62 pts enrolled based on a RET variant detected in a tumor sample, concordant RET alterations were detected in 41 (66%) of the corresponding pre-treatment plasma samples, including 19/30 (63%) pts with RET-fusion NSCLC and 16/21 (76%) pts with RET-mutant MTC. Median AF was higher for MTC (7.03%) than NSCLC (0.51%). In RET alteration-negative pre-treatment samples, peak AF for other detected alterations was generally low (0.28% median), suggesting low tumor DNA shed into plasma. Of 34 pts with a detectable pre-treatment plasma RET alteration and day 15 plasma NGS, RET alteration AF decreased by a median of 96%, with complete clearance in 15 pts (44%). Day 15 plasma clearance was observed at multiple doses, and was more common in RET fusion-positive (67%) than RET-mutant (8%) pts. Data for additional pts will be updated at the time of presentation.

Conclusions: The rapid clearance of RET variants from plasma cfDNA on LOXO-292 supports its observed clinical activity across a range of doses, tumor types and RET alterations. NGS of plasma cfDNA can detect a range of targetable RET variants, though tumor genotyping remains critical if the initial plasma NGS is negative. Serial plasma genotyping warrants continued study as an early pharmacodynamic marker for novel targeted therapies.

Clinical trial identification: NCT03157128.

Legal entity responsible for the study: Loxo Oncology Inc.

Funding: Loxo Oncology Inc.

Disclosure: B. Besse: Grant funding: AstraZeneca, BMS, Boehringer Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Servier, Onxeo, OncoMed, Inivata, OSE Pharma, Loxo. A. Drilon: Honoraria: Foundation Medicine; Pfizer; Advisory board Honoraria from Roche/Genentech, Takeda/Ariad, Loxo Oncology, Ignyta. L.J. Wirth: Personal fees: Eisai Inc., Novartis. B.J. Solomon: Honoraria: Pfizer and Novartis; Consulting or advisory role: AstraZeneca, Roche, Merck, BMS, Novartis. E. Zhu: Employee: Loxo. K. Gordon: Employee and stockholder: Loxo Oncology. K. Ebata: Personal fees and other support: Loxo Oncology, Inc during the conduct of the study; Personal fees and other support: Loxo Oncology, Inc., outside the submitted work. B. Tuch: Employee and share holder: Loxo Oncology. All other authors have declared no conflicts of interest.

106P A prediction panel with DNA methylation biomarkers for lung adenocarcinoma

N. Shen[1], Y. Pan[2], X. Mo[3]

[1]Department of Rehabilitation, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Functional Genome Analysis, Deutsches Krebsforschungszentrum, Heidelberg, Germany, [3]Institute for Pediatric Translational Medicine, Shanghai Children's Medical Center, Shanghai, China

Background: Lung adenocarcinoma accounts for more than 40% of lung cancer incidence. Thus, it is urgent to identify early-stage related markers. In this study, the effectiveness of CpG methylation on predicting lung adenocarcinoma was investigated.

Methods: In total, 1,170 patients with lung adenocarcinoma from four independent databases and one medical center were sorted by three phases. In the discovery phase, 338 lung adenocarcinomas and nonmalignant samples were collected from the GEO databases which used Illumina Infinium HumanMethylation27K BeadChip for the methylation analysis. The K-Means Clustering algorithm was used to select significant CpGs. In the training phase, recursive feature elimination was performed to evaluate the importance of selected CpGs to classification model. In the validation phase, four candidate CpGs were validated using two cohorts ($n = 832$ and $n = 10$). To explore the potential biological function of selected CpGs, GO enrichment analysis was performed using the Database for DAVID version 6.8.

Results: After the selection of CpGs by the K-Means Clustering algorithm, 62 CpGs showed great different methylation profiles between lung adenocarcinomas and adjacent nonmalignant lung tissue ($p < 0.05$). Among these selected CpGs, 95.16% were hypermethylated in the malignant samples comparing to only 4.84% were hypomethylated. With the evaluation of recursive feature elimination, four CpGs corresponding to HOXA9, KRTAP8-1, CCND1, and TULP2 were highlighted as candidate predictors in the training phase. The performance of these four candidate CpGs were validated in two validation cohorts ($p < 0.01$). These disparate hypermethylated genes were significantly enriched in GO biological processes including negative regulation of transcription from RNA polymerase II promoter, DNA-templated transcription, while the hypomethylated gene was obviously enriched with the terms including adenylate cyclase-activating G-protein coupled receptor signaling pathway. The direction of methylation did not affect the enrichments for Out-CpG sites.

Conclusions: A four-CpG-based signature, including HOXA9, KRTAP8-1, CCND1 and TULP2, is useful for the prediction of lung adenocarcinoma.

Legal entity responsible for the study: Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

107P Novel genomic classifier for early stage colorectal cancer patients

E. Letellier[1], M. Schmitz[1], A. Ginolhac[1], E. Koncina[1], M. Marchese[2], L. Antunes[3], S. Rauh[4], S. Haan[1]

[1]Life Sciences Research Unit, University of Luxembourg, Belval, Luxembourg, [2]Biomarker Validation, Integrated Biobank of Luxembourg, Dudelange, Luxembourg, [3]Pathology, Integrated Biobank of Luxembourg, Dudelange, Luxembourg, [4]Hématome Oncologie, Centre Hospitalier Emile Mayrisch CHEM, Esch-sur-Alzette, Luxembourg

Background: Identifying patients at risk of relapse in early colorectal cancer (CRC) stages is an unmet clinical need. Due to the limitations of clinicopathological variables in predicting individual risk of recurrence in CRC patients, genomic information has

increasingly gained prominence as a potential method for patient stratification. We have previously shown that Myosin Vb (MYO5B) expression alone or in combination with the expression of its adapter protein RAB8A shows strong prognostic value in early CRC patients (PMID 29024942).

Methods: We are currently setting up a meta-analysis including multiple CRC datasets, which allows to further validate the prognostic value of the genomic classifier. Additionally, this meta-analysis will determine the predictive value of the classifier on chemotherapy efficiency. Furthermore, pre-analytical and analytical assays will assess the reproducibility, sensitivity and specificity of the biomarker. Finally, we will prospectively collect stage II CRC tumor samples to clinically validate our classifier.

Results: In the follow-up study, we have now validated the prognostic value of the classifier in independent datasets. By multivariate analysis, we show that the gene expression signature is independent of clinicopathological features currently used in the clinics (stage, grading, T3, MSI status among others). Importantly, the identified molecular classifier outperformed the other three molecular tests (Oncotype DX, Coloprint and Oncodefender) that are commercially available but not FDA approved for predicting patient relapse. We will report on the predictive value of our molecular classifier on chemotherapy efficiency. In addition, first results on the pre-analytical and analytical analysis of the classifier will be presented.

Conclusions: Altogether, MYO5B together with RAB8A might allow delineating a high-risk population in early CRC stages. This stratification could potentially help oncologists to choose the best treatment plan, especially for stage II patients, where adjuvant chemotherapy may not always lead to beneficial results, but still results in significant side-effects.

Legal entity responsible for the study: Molecular Disease Mechanisms Group.

Funding: Fonds National de la Recherche, Luxembourg.

Disclosure: All authors have declared no conflicts of interest.

108P Baseline blood immune profiling to predict response to antiPD-1 in patients with advanced non-small cell lung cancer

E. Romano[1], T. Le Bourgeois[1], S. Lopez-Lastra[1], V. Servois[2], S. Beaucaire-Danel[3], C. Daniel[3], J-Y. Pierga[3], F-C. Bidard[3], O. Lantz[1]

[1]Center of Cancer Immunotherapy, Department of Oncology, Institut Curie, PSL Research University, Paris, France, [2]Department of Radiology and Nuclear Medicine, Institut Curie, Paris, France, [3]Department of Oncology, Institut Curie, Paris, France

Background: Immune checkpoint inhibitors have remarkably improved the natural history of patients (pts) with non-small cell lung cancer (NSCLC), with improved clinical responses and overall survival compared to standard therapy. However, over 80% of unselected NSCLC pts do not respond, highlighting the need of theranostic biomarker discovery. In a cohort of NCSLC pts treated with antiPD-1, we investigated blood immune parameters at baseline and pts characteristics as potential theranostic biomarkers.

Methods: Thirty-four pts with locally advanced/metastatic NSCLC received antiPD-1 therapy as ≥ 2 line treatment in a prospective biomarker study (NCT02866149). Peripheral blood mononuclear cells and plasma were analyzed at baseline by multiparametric flow cytometry and Luminex technology, respectively. Primary endpoint was to correlate cellular and soluble immune parameters with clinical outcome based on RECIST criteria.

Results: Baseline $CD3^+/CD14^+$ ratio was a robust predictive biomarker with pts achieving progression free survival (PFS) $\geq$4 months showing an average ratio of 1.91 vs 1.11 in pts with PFS <4 months ($p = 0.003$). Furthermore, we found a strong positive correlation between the proportion of $HLA\text{-}DR^{hi}CD14^+$ monocytes and the PFS ($r = 0.471$), with objective responders showing higher CD86 expression, suggesting an improved antigen-presenting capacity. In addition, pts with a PFS $\geq$4 months, displayed higher proportions of $CCR7^-CD45RA^-$ effector memory $CD8^+$T cells and regulatory $CD4^+$T cells suggesting pre-existing adaptive immune responses. In line with previous reports, our results confirmed the association of baseline plasma albumin with clinical outcome, with levels $\geq$ 3.9 g/dL associated with improved PFS ($p = 0.026$), likely due to the lower plasma levels of the pro-inflammatory mediator IL-6. Finally, soluble CD40 ligand was elevated in pts with reduced PFS, probably in relation with an elevated platelet activation, further supported by a 2-fold increase in plasma concentration of baseline platelet-derived growth factors (PDGFs) in these pts.

Conclusions: Our study identifies promising, predictive, immune-related biomarkers in NSCLC pts treated with PD-1 blockade.

Clinical trial identification: NCT02866149.

Legal entity responsible for the study: Institut Curie.

Funding: Institut Curie.

Disclosure: All authors have declared no conflicts of interest.

109P Evaluation of clinicopathological and molecular criterias for screening of exonucleasic domain POLE (edPOLE) mutated patients in proficient mismatch repair (pMMR) colorectal and endometrial cancers

J. Cohen[1], B.J-C. Rousseau[2], R. Bourgoin[1], C. Tournigand[2], L. Larnaudie[1], A. Dupuy[3], M. Ollier[1], A. Pujals[1]

[1]Departement of Pathology, Centre Hospitalier Universitaire Henri-Mondor, Créteil, France, [2]Service d'Oncologie, Centre Hospitalier Universitaire Henri-Mondor, Créteil, France, [3]U955 Équipe 9, INSERM, Créteil, France

Background: Mismatch Repair Deficiency (dMMR) and edPOLE mutations (mt) are responsible for hypermutated tumoral phenotype. Immunotherapy have shown efficacy in dMMR/high mutation burden patients (pts) and could be also active in edPOLEmt tumors. These mt occur in 6-12% of endometrial cancers (EC) and in 1-2% of Colorectal Cancer (CRC) and are likely infrequent in advanced setting. We aimed to define the most relevant clinicopathogical and molecular criterias to facilitate screening for edPOLE mt pts.

Methods: EdPOLE mutational status was evaluated in cohorts of pMMR CRC and EC using High Resolution Melting PCR on the hotspots described in literature (codons 286, 411 and 459). CRC subcohorts were enriched for BRAF mt, RAS mt, unusual BRAF/RAS mt and young pts ($\leq$40 yrs). Pts harboring a mutated profile were confirmed by Sanger sequencing.

Results: 245 pts were screened: 49 EC and 196 CRC. Among CRC, 41 were BRAF mt (30 V600E, 11 non V600E), 79 were KRAS mt (30 on codon 12/13, 49 other mt), 20 were selected because of the presence of $\geq$ 2 simultaneous BRAF/KRAS/NRAS mt, 30 were BRAF/KRAS/NRAS wild type (wt) and 30 were $\leq$40 yrs. Using our method, 9 edPOLE mt tumors were identified (Table): 4 among EC and 5 among CRC. edPOLE mt EC were all endometrioid ADK. edPOLEmt CRC were all localized in the left colon or rectum with unusual molecular alterations: 1 BRAF (p.D594G), 3 KRAS mt (p.A59T p.A146T et p.N116H) and 1 with two NRAS mt (p.Q61R et p.T58A).

Table: 109P

Tumor subcohort	% of edPOLE mt (n/N)	Clinical and molecular profile of edPOLE mt pts
Whole cohort	3.6 (9/245)	pMMR: 100% (9/9)
EC Endometrioid adenocarcinomas Other histologies	8 (4/49) 13 (4/31) 0 (0/18)	3 codon 286 POLE 0 codon 411 POLE 1 codon 459 POLE
CRC BRAF/KRAS/NRAS wt p.V600E BRAF mt Non p.V600E BRAF mt Codons 12 or 13 KRAS mt Non codons 12 or 13 KRAS mt Multiple BRAF/KRAS/NRAS mt	2.6 (5/196) 0 (0/30) 0 (0/30) 9 (1/11) 0 (0/30) 6 (3/49) 5 (1/20)	Left colon or rectum: 100% (5/5) Age $\leq$ 40 years old: 20% (1/5) 2 codon 286 POLE 1 codon 411 POLE 2 codon 459 POLE

Conclusions: Our screening strategy identified edPOLEmt in 13% of endometrioid ADK and 2.6% of CRC. Pts selection on clinicopathological (histology for EC, young age, left colon or rectum), and molecular criterias (pMMR, unusual BRAF/KRAS/NRAS mt) seem to increase the proportion of edPOLEmt. The use of these criteria in practice could help select patients for edPOLE screening. Additional clinicopathological and molecular data will be shown.

Legal entity responsible for the study: Anaïs Pujals.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

110P Immune prognostic index (IPI) and hyper-progressive disease (HPD) in patients (pts) exposed to targeted agents (TAs) in phase I trials (Ph1T): Can lessons from immune checkpoint inhibitors (ICIs) be translated to other scenarios?

I. Matos Garcia[1], A. Azaro[2], C. Viaplana[3], C. Hierro[4], J. Martin-Liberal[4], I. Brana[5], I. Gardeazabal[1], P. Gomila[6], M. Vieito Villar[4], M. Ochoa De Olza Amat[7], E. Elez Fernandez[7], M. Oliveira[7], A. Oaknin[7], H. Verdaguer[1], A. Navarro Mendivil[2], M. Alsina[8], J. Tabernero[9], T. Macarulla Mercade[1], R. Dienstmann[10], E. Garralda[11]

[1]Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [2]Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain, [3]Oncology Data Science (ODysSey) Group, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Oncology, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [5]Department of Medical Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [6]Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [7]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [8]Medical Oncology, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain, [9]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [10]Oncology Data Science, Vall d'Hebron University Hospital, Barcelona, Spain, [11]Early Drug Development Unit, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain

Background: IPI score (derived neutrophil/(leukocytes minus neutrophils)ratio [dNLR]>3 plus LDH>upper limit normal) is a emerging tool to predict overall survival (OS) with ICIs in different tumor types. HPD has been reported in 15% of pts on ICIs using different criteria, including ours (PD at first restaging with ≥40% increase in sum of target lesions or ≥ 20% with appearance of multiple new lesions; Matos et al, ASCO 2018). We aimed to assess the prognostic value of IPI and the relevance of HPD in pts enrolled in Ph1T with TAs.

Methods: Retrospective analysis of a consecutive cohort of pts treated with experimental TAs at VHIO Ph1T Unit over the last 3 years (we excluded pts in the first dose escalation cohorts of each trial as well as TAs matched to validated biomarkers). Overall survival (OS) was correlated with VHIO HPD criteria and IPI.

Results: In total, 180 pts were treated with TAs (34% FGFR, 26% PI3K, 19% MET, 13% NOTCH, 5% IDH, 3% RAF). In 39% of the cases, TAs were matched to an emerging enrichment molecular alteration. Median age 59y, 58% female, most common tumor types: 20% colorectal, 17% breast, 9% gynecological, 8% biliary tract. Best response was PD in 55%, SD in 41%, PR in 4%. Our HPD criteria was met in 10% of the cases, across all tumor types and targets (highest prevalence in colorectal pts treated with PI3K inhibitors, 5/18, 28%). Median progression-free survival was 1.8 months (m) [95% CI 1.7-2.2], not affected target selected, molecular match or IPI score ($p > 0.2$). Median OS was 7.9 m [6.7-10], significantly different as per IPI score (IPI0 18 m [7.8-NA]; IPI1 7.7 m [6.5-9.9]; IPI2 2.6 m [1.7-NA]; $p < 0.001$). Importantly, in pts with PD as best response while on TAs, HPD did not negatively affect OS ($p = 0.43$).

Conclusions: Our results show that a prognostic score developed in cohorts treated with ICIs also predicts long-term outcome with TAs in Ph1T. HPD criteria can be met with TAs treatment, but the lack of survival impact (different from internal and external cohorts exposed to ICIs) suggests that it is not a relevant clinical finding.

Legal entity responsible for the study: Vall d'Hebron Institute Oncology.

Funding: Has not received any funding.

Disclosure: J. Tabernero: Advisory boards: Bayer, Boehringer Ingelheim, Genentech/Roche, Lilly, MSD, Merck Serono, Merrimack, Novartis, Peptomyc, Roche, Sanofi, Symphogen and Taiho. E. Garralda: Advisory role: Roche, NeoMed Therapeutics, Ellypses Pharma. All other authors have declared no conflicts of interest.

111P Combination of baseline LDH, performance status and age to identify solid tumor patients with higher probability of response to anti-PD1 and PDL1 monoclonal antibodies

M.S. Cona[1], M. Lecchi[2], S. Damian[1], M. Del Vecchio[1], C. Cimminiello[1], S. Cresta[3], M. Duca[3], A. Necchi[1], D. Signorelli[3], M. Poggi[3], D. Raggi[2], R. Ratta[2], P. Verderio[2], F.G.M. de Braud[1], M. Di Nicola[3]

[1]Department of Medical Oncology and Hematology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Department of Applied Research and Technological Development, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Department of Medical Oncology and Hematology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy

Background: The advent of immune check point inhibitors (ICIs) has improved prognosis of various cancers. To better select responding patients (pts) and for a more accurate management of economic resources, biological and biochemical factors have been investigated. To date, no predictive biomarkers have been validated. The aim of this study is to identify manageable and routinely detectable parameters to use in clinical practice to select pts with higher change of response to ICIs.

Methods: 271 consecutive metastatic solid tumor pts treated in our Institute from 2013 to 2017 with ICIs were evaluated for baseline LDH serum level, ECOG score, age, type of ICI, number of metastatic sites, histology and sex. A training and validation set were used to build and test models, respectively. Variables' effects were assessed through odds ratio estimates (OR) and area under the receive operating characteristic curves (AUC), from univariate and multivariate logistic regression models. The validated estimates were used to develop an Excel algorithm to calculate probabilities of response.

Results: As best response, 55.4% of pts achieved disease control and 44.7% had progressive disease. On the training set, LDH, age and ECOG showed a significant OR (p:<.001, 0.009, 0.042, respectively) and were combined in a multivariate model with an AUC of 0.771 (95%CI: 0.701;0.842). These results were statistically validated on the validation set (AUC: 0.685, 95%CI: 0.569;0.801). By fitting the validated model on all pts, the 3 variables retained a significant OR and a satisfactory cross-validated AUC.

Conclusions: We confirm, as reported in literature, that baseline LDH serum levels are inversely associated with response probability. It's reasonable to jointly consider age and ECOG, which give a significant contribution to model performance. The developed algorithm, once validated on an independent prospective series, might be a base to guide physicians in clinical practice to better plan ICI therapy tailored on pts characteristics.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

112P Effects of concomitant genetic alterations on cancer patient overall survival

Y. Wang[1], P. Peng[2], L. Shang[3], Y-A. Dong[4], Z. Yang[5], H. Zhong[6]

[1]Tumor Research and Therapy Center, Shandong Provincial Hospital Affiliated to Shandong University, Ji'nan, China, [2]Oncology Department, Guangdong Second Provixcial General Hospital, Guangzhou, China, [3]Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Ji'nan, China, [4]OrigiMed, OrigiMed, Shanghai, China, [5]Courage, Shu Lan (Hangzhou) Hospital; Zhejiang University International Hospital, Hangzhou, China, [6]Department of Thoracic and Cardiovascular Surgery, People's Hospital of Beihai, The Ninth Affiliated Hospital of Guangxi Medical University, Beihai, China

Background: Genomic alterations have a profound impact on all aspects of cancer biology and therapy. Concomitant mutations involving multiple genes are intrinsically complex, and their relationship with biomarkers such as TMB and clinical outcomes such as drug response is only beginning to be explored. In this study, we systematically analyzed the impact of pairwise co-mutations of common genes on patient overall survival (OS).

Methods: We downloaded the publicly available TCGA datasets and used the LUAD lung adenocarcinoma subset for our pilot study. To limit noise, we restricted our attention to the top 48 most commonly mutated genes among LUAD patients. For each pair of genes g1 and g2 in this list, we compared the survival data of three groups of patients: those with g1 mutations only, those with g2 mutations only, and those with both g1 and g2 mutations. Kaplan-Meyer survival curves were plotted and p-values computed.

Results: We obtained a large number of double mutants (223 out of 1128 possible pairs, ∼20%) with significantly different OS from single mutants. There was a wide spectrum of "co-mutation potential": on one hand, genes such as AHNAK2 and ANK2 readily co-mutated with many other genes, all leading to double mutants with distinguishing OS; on the other hand, genes such as DMD or DNAH9 co-mutated with few or no other genes that led to distinguishing double mutants. In terms of OS, double mutants could be put into three broad categories: those better than either single mutant ("synthetic rescue"), those worse ("synthetic lethal"), and those in between ("averaging"). Surprisingly, many double mutants exhibited synthetic-rescue behaviors. For example, ANK2- and LRP1B-mutant patients had very similar OS, but double-mutants exhibited significantly better OS than either single mutant ($p < 0.001$ in each case).

Conclusions: In our proof-of-concept study we systematically explored the impact of co-mutations on OS. A large number of double mutants exhibited "synthetic rescue" behaviors, and we pinpointed many distinguishing gene pairs for further investigation. It remains to be seen whether co-mutations of the same pair of genes always have the same effect across cancer types, and how they interact with other bio- and clinical markers.

Legal entity responsible for the study: OrigiMed.

Funding: Has not received any funding.

Disclosure: Y-A. Dong: Employee: OrigiMed. All other authors have declared no conflicts of interest.

113P Circulating exosomal integrin αvβ5 predicts liver metastasis and prognosis in human colorectal cancer

D. Chu

Gastroenterology, First Affiliated Hospital of Xi'an Jiaotong University (School of Medicine), Xi'an, China

Background: Ever since the "seed-and-soil" hypothesis, the mechanism of cancer metastatic organotropism is still an unsolved mystery. In colorectal cancer (CRC), there is still no robust metastasis predictive biomarkers for distant organ metastasis, which is the most common cause of deaths. In spite of the function of exosome in RNA and

protein delivery, its clinical significance in CRC metastasis remains uncertain. Here, we evaluated the potential role of serum exosome integrin in CRC metastasis.

Methods: Tissue integrin $\alpha_v\beta_5$ was quantified by quantitative reverse-transcription PCR in 31 pairs of primary CRC and corresponding matched liver metastasis (LM), with non-LM as control. Serum exosomal integrin $\alpha_v\beta_5$ was accessed by ELISA in 126 CRC patients with LM and 166 CRC patients without, as well as when LM was diagnosed in these 166 patients in exploratory cohort. In prospective validation cohort, serum exosomal integrin $\alpha_v\beta_5$ was investigated in 135 initially diagnosed CRC patients without metastasis. CRC-associated metastasis mouse models were established to verify the role of serum exosomal integrin $\alpha_v\beta_5$.

Results: Integrin $\alpha_v\beta_5$ level in LM was significantly increased compared with that in non-LM, which was correlated with its expression in primary CRC. Serum exosomal integrin $\alpha_v\beta_5$ was significantly increased in CRC patients with LM than those without, in a TNM stage-dependent manner. Moreover, it was found that serum exosomal integrin $\alpha_v\beta_5$ in CRC patients was significantly upregulated when LM occurred and associated with unfavorable survival. In validation cohort, increased serum exosomal integrin $\alpha_v\beta_5$ indicated higher risk of LM and unfavorable prognosis. Serum exosomal integrin $\alpha_v\beta_5$ was significantly increased in mice with LM compared with controls.

Conclusions: Our clinical and animal model data indicate that increased levels of serum integrin $\alpha_v\beta_5$ associate with CRC LM and unfavorable survival. These results suggested that circulating integrin $\alpha_v\beta_5$ could be a promising non-invasive predictor for CRC LM and prognosis.

Legal entity responsible for the study: Xi'an Jiaotong University.

Funding: NSFC.

Disclosure: All authors have declared no conflicts of interest.

114P Circulating and tumor-associated caspase-4: A novel diagnostic and prognostic biomarker for non-small cell lung cancer patients?

R. Sorrentino[1], M. Terlizzi[1], C. Colarusso[1], A. Saccomanno[1], R. Salvi[2], R.P. Aquino[1], A. Pinto[1]

[1]Department of Pharmacy, University of Salerno, Fisciano, Italy, [2]Thoracic Surgery Unit, AORN, Monaldi, Naples, Italy

Background: Late diagnosis limits therapeutic options and survival rate of non-small cell lung cancer (NSCLC) patients. Therefore, the identification of biomarkers represents an emerging medical need.

Methods: A highly sensitive and specific ELISA test was developed to identify/quantify a novel/selective diagnostic biomarker for NSCLC patients, caspase-4, which was detected into the plasma and tissues of NSCLC patients. This test was validated by using plasma from 125 NSCLC patients and 79 healthy (non-pathological) subjects. Caspase-4 quantification was also assessed in the lung tumor mass of 98 paired-matched NSCLC patients compared to 10 non-tumor lung tissues (i.e. tuberculosis).

Results: Circulating caspase-4 was detected in both healthy and NSCLC patients; however, at different range values: 2.603-3.372 ng/ml for NSCLC patients (95% CI) compared to 0.3994-0.6219 ng/ml for healthy subjects (95% CI). The sensitivity of the test ranged from 97.07% to 100%; the specificity was 88.1% with a positive predictive value of 92.54%, accuracy of 95.19% and AUC of 0.971. Tissue levels of caspase-4 in the tumor mass showed that 72 (72.7%) out of 99 patients were positive. More importantly, higher levels (cut-off value= 0.307 ng/ml) of caspase-4 in the tumor mass were associated to reduced overall survival (median 0.92 years) compared to NSCLC patients with lower levels (median 3.02 years).

Conclusions: We report for the first time caspase-4 as a novel diagnostic and prognostic biomarker, opening new therapeutic perspectives for NSCLC patients.

Legal entity responsible for the study: ImmunePharma srl.

Funding: Invitalia-Italian Ministry of Economy (MISE).

Disclosure: All authors have declared no conflicts of interest.

115P Smokers and COPD patients have high circulating caspase-4 levels: Is it an alarm?

M. Terlizzi, R. Sorrentino, C. Colarusso, A. Molino, A. Saccomanno, R.P. Aquino, A. Pinto

Department of Pharmacy, University of Salerno, Fisciano, Italy

Background: Lung cancer is the leading cancer-related death disease worldwide. This alerting data is mainly due to late diagnosis of lung cancer, especially non-small cell-lung cancer (NSCLC), limiting the therapeutic options. Therefore, the identification of non-invasive, selective, sensitive and specific biomarker/s represents the emerging medical need for the clinical practice to avoid late diagnosis and ameliorate the personalized therapy with an ensuing higher survival rate. It is well known that smoking and chronic obstructive pulmonary disease represent two high risk factors for NSCLC. Therefore, in this study we aimed to evaluate the levels of a novel diagnostic tool for NSCLC patients in order to understand whether caspase-4 could represent a predictive biomarker.

Methods: In order to evaluate the circulating caspase-4 in the blood, we developed an ELISA test.

Results: Smokers ($\geq$15 cigarettes/day) had higher levels of circulating caspase-4 (95% CI, 1.331-1.94 ng/ml) than healthy subjects (95% CI, 0.395-0.619 ng/ml). Though, these levels were statistically lower than those observed in NSCLC patients. Moreover, there were no statistical differences between the levels of circulating caspase-4 in smokers younger or older than 60 years. Similarly, no gender differences were noted. Similarly, COPD patients, who are smokers and former smokers, had higher levels of circulating caspase-4 (95% CI, 1.703-2.995 ng/ml). According to $\chi 2$ test, the expected frequency of smokers, positive to the circulating caspase-4, who could develop NSCLC is robustly significant (calculated $\chi 2$=82.884 vs tabulated $\chi 2$=3.845, df = 1). Moreover, according to the independence test, smoker who were positive to the circulating caspase-4 are at high risk to develop NSCLC.

Conclusions: In conclusion, we report for the first time that the circulating caspase-4 could represent a predictive diagnostic tool to avoid the occurrence of NSCLC.

Legal entity responsible for the study: ImmunePharma s.r.l.

Funding: Italian Ministry of Economy (MISE) Invitalia.

Disclosure: All authors have declared no conflicts of interest.

116P Genomic characteristics of standardized uptake value of 18F-fluorodeoxy-glucose positron emission tomography in breast cancer

S-K. Kim[1], S.G. Ahn[2], S-H. Leem[3], J. Jeong[2], I-S. Chu[4]

[1]Personalized Genomic Medicine Research Center, Korea Research institute of Bioscience and Biotechnology, Daejeon, Republic of Korea, [2]Department of Surgery, Gananam Severance Hospital, Seoul, Republic of Korea, [3]Department of Biological Science, Dong-A University, Busan, Republic of Korea, [4]Korean Bioinformation Center, Korea Research Institute of Bioscience and Biotechnology, Daejeon, Republic of Korea

Background: Standardized uptake value (SUV), an indicator of the glucose uptake degree in ^{18}F-fluorodeoxy-glucose positron emission tomography (FDG-PET), has been used as a prognostic factor in various malignant tumors. The aim of this study is to identify a molecular signature reflecting prognostic SUV characteristics in breast cancer (BRC).

Methods: We sought to identify a molecular signature associated with SUV by a gene expression profiling using a dataset obtained from 60 BRCs who underwent preoperative FDG-PET. The prognostic value of the signature was verified in three BRC cohorts including TCGA dataset (n = 1,616). Various statistical methods, including log-rank and Cox regression analyses, were applied to estimate an association between the signature and BRC prognosis. To compare somatic variants between two patient subgroups divided by the signature, we obtained predefined gene sets involved in oncogenic or metabolic pathways and estimated a difference of their mutation frequencies between subgroups in the TCGA cohort.

Results: By a gene expression profiling, we defined a signature, namely SUV signature, consisting of 723 genes significantly associated with SUV (Pearson correlation test, $|r| > 0.35$, $p < 0.001$). The patient subgroups classified by the signature [i.e., SUV-high-cluster and SUV-low-cluster] were significantly similar with patient classification by SUV [Fisher exact test, odds ratio 8.02, 95% confidence interval (CI) = 2.45-29.3, $p < 0.001$]. When estimating prognostic value of the SUV signature in three cohorts, the signature showed a strong prediction ability (log-rank tests, each $p < 0.05$) and an independent clinical utility (multivariate Cox regression model, hazard ratio = 1.51, 95% CI = 1.07-2.22, $p = 0.01$) in BRC prognosis. Gene network and mutation analyses revealed that a signaling defined by TP53-FOXM1 and its downstream effectors involved in glycolysis-gluconeogenesis might be important mediators in FDG-PET operation.

Conclusions: Our results uncover genomic and metabolomic characteristics of glucose uptake captured by FDG-PET, supporting an understanding of glucose metabolism as well as a poor prognosis in BRC patients with high SUV.

Legal entity responsible for the study: Korea Research Institute of Bioscience and Biotechnology Gananam Severance Hospital.

Funding: Korea Research Institute of Bioscience and Biotechnology.

Disclosure: All authors have declared no conflicts of interest.

117P Characterization of PD-L1, CD8, CD3, CD68 and PanCK in tumor microenvironment of GI tract tumors with respect to patients' mismatch repair status and anti-PD-1 treatment outcome using 5Plex IHC and whole slide image analysis

W. Zhang[1], M. Khojasteh[2], A. Hubbard[3], J. Martin[4], X. Wang[4], S. Kamthamraju[3], J.L. Munoz-Rodriguez[1], D. Jiang[5], Z. Cai[6], J. Li[6], R. Anders[7], L. Diaz[8], L. Pestic-Dragovich[3], L. Tang[3]

[1]CDx Pharma Service, Roche Tissue Diagnostics - USA, Tucson, AZ, USA, [2]Digital Pathology, Roche Tissue Diagnostics USA, Mountain View, CA, USA, [3]CDx Pharma Service, Roche Tissue Diagnostics - USA, Tucson, AZ, USA, [4]Digital Pathology, Roche Tissue Diagnostics - USA, Mountain View, CA, USA, [5]R&D, Roche Tissue Diagnostics - USA, Tucson, AZ, USA, [6]Biostatistics, Roche Tissue Diagnostics - USA, Tucson, AZ, USA, [7]Pathology, John Hopskin University Hospital, Baltimore, MD, USA, [8]Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center, New York City, NY, USA

Background: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. However, not all patients with mismatch repair deficiency respond to the PD-1 blockade treatment. To understand the different responses, we evaluated tumor

micro-environment such as PD-L1 expression in relationship with tumor infiltrating immune cells.

Methods: FL multiplex IHC for PD-L1, CD8, CD3, CD68, and pan-cytokeratin (panCK) on BenchMark ULTRA instrument stained 54 pre-pembrolizumab treatment patient resection and biopsy specimens including pancreatic, colorectal and cholangiocarcinoma. 17 are mismatch-repair proficient (13 PD, 3 SD, and 1 CR) and 37 deficient (5 PD, 10 SD, 9 CR, and 13 PR). Whole slide images by Zeiss AXIO Z1 were analyzed with in-house dPath automated algorithm. PD-L1+/- T-cells (CD3+), cytotoxic T-cells (CD3+ and CD8+), T helper cells (CD3+ and CD8-), macrophages (CD68+), and tumor cells (panCK+) were identified. Fractions of PD-L1+ phenotypes, area density and spatial relationships of phenotypes in pathologist-annotated tumor/peritumor regions, the panCK+ epithelial tumor and panCK- stroma were computed.

Results: Random forest modelling, logistic regression and Relieff feature selection followed by quadrant discriminant analysis were used to assess the relationship of multiplex IHC readouts to anti-PD-1 treatment responses. Different groupings were used, e.g. PR + CR vs. SD + PD, and PR + CR + SD vs. PD, etc. Fraction of PD-L1+ macrophages and fraction of PD-L1+ T helper cells in tumor region, stroma, and epithelial tumor were identified most important features. Mpx IHC achieves 89% accuracy over 70% with mismatch repair status alone.

Conclusions: Multiplex IHC together with automated image analysis provides a tool to evaluate multiple biomarkers and their special relationships in the tumor micro-environment. In a cohort of 54 patient specimens, exploratory analysis of multiplex IHC data suggests that the knowledge of PD-L1 expression on various immune cell phenotypes aids in better predicting response to anti-PD-1 therapy compared to mismatch repair status alone.

Legal entity responsible for the study: Roche Diagnostics/Ventana Medical Systems, Inc.

Funding: Roche Diagnostics/Ventana Medical Systems, Inc.

Disclosure: W. Zhang, M. Khojasteh, A. Hubbard, X. Wang, J.L. Munoz-Rodriguez, D. Jiang, Z. Cai, J. Li, L. Pestic-Dragovich, L. Tang: Employee: Roche Diagnostics. J. Martin, S. Kamthamraju: Contractor employee: Roche Diagnostics. R. Anders: Financial relationships: Merck, BMS, 5 Prime Therapeutics, FLX Bio, Adaptive Biotech. L. Diaz: Founder: Personal Genome Diagnostics, PapGene, PagerBox.

118P Exhaustion of platelet kinetics and its implication in post-resection HCC recurrence

B. Aryal[1], T. Shimizu[2], J. Kadono[1], A. Furoi[1], T. Komokata[1], K. Gejima[1], M. Yamakuchi[2], T. Hashiguchi[2], Y. Imoto[1]

[1]Cardiovascular and Gastroenterological Surgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan, [2]Department of Laboratory Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

Background: Platelet activation and the release of various growth factors from platelet granules in response to tumor cell profoundly influence tumor biology. Platelet hyperreactivity in cancer patients is a frequently discussed phenomenon; however, cancer patients were also found to have platelet dysfunction. Considerably less is known about exhaustion of platelet kinetics in cancer.

Methods: In this study, we investigated kinetics of intra-platelet growth factors in hepatocellular carcinoma (HCC) recurrence. We prospectively recruited forty patients diagnosed with HCC who were undergoing liver resection. The patients were followed every three months with imagings after the resection. Platelet fractions were separately isolated before and after a month of radical resection of the tumor. Growth factors/cytokines were measured using enzyme-linked immunosorbent assay (ELISA) kits. Follow-up was standardized to two years. HCC recurrence was diagnosed on the basis of imaging.

Results: Fifteen patients developed post-resection HCC recurrence during 2-year follow-up. The concentrations of platelet-alpha granules secreted growth factors [vascular endothelial growth factor-A (VEGF-A), angiopoietin-1(Ang-1)] and dense granules secreted growth factors (serotonin) were significantly depleted in patients with early HCC recurrence. In addition, the post-resection platelet count was also significantly lower in patients with recurrence than those without recurrence. A combined receiver-operating characteristic (ROC) curve generated to determine the cut-off values for these growth factors yielded both specificity and sensitivity of greater than 80%, area under curve (AUC) > 0.8, and $P < 0.001$. Furthermore, in the binary logistic regression model, VEGF-A was able to independently predict early HCC recurrence ($P < 0.05$); accordingly, the disease-free interval was substantially worse in accordance with the exhausted intra-platelet growth factors.

Conclusions: We found a qualitative and quantitative platelet crisis, and its prognostic implication in patients with post-resection HCC recurrence. This study provides an avenue to identify the pathophysiological mechanism of the impaired platelet-kinetics and its relevance in cancer biology.

Legal entity responsible for the study: Bibek Aryal.

Funding: Japan Society for the Promotion of Science (JSPS).

Disclosure: All authors have declared no conflicts of interest.

119P Progastrin, a new blood biomarker for the diagnostic and therapeutic monitoring, in gastro-intestinal cancers: A BIG-RENAPE project

B. You[1], V. Kepenekian[2], A. Prieur[3], M. Caceres[4], L.F. Payen-Gay[5], P. Liaud[3], M. Flaceliere[3], M. Tod[6], L. Villeneuve[7], F. Bibeau[8], L. Bernard[7], P. Jourdan-Enfer[7], N. Medeghri[9], D. Dayde[9], S. Calattini[9], G. Freyer[1], D. Maucort-Boulch[4], D. Joubert[10], O. Glehen[2]

[1]Medical Oncology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [2]Surgical Oncology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [3]ECS-Screening, Lausanne, Switzerland, [4]Biostatistics, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [5]Biology, Hospices Civiles de Lyon, Lyon, France, [6]EMR UCBL/HCL 3738, Université Claude Bernard Lyon 1, Oullins, France, [7]8. Department of Public Health, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [8]Service d'Anatomie Pathologique, CHU de Caen, Caen, France, [9]Plateforme Transversale IC-HCL, Institut de Cancérologie des Hospices Civils de Lyon, Pierre Benite, France, [10]Canton de Vaud, ECS-Screening, Lausanne, Switzerland

Background: Progastrin is abnormally released in the blood of patients with different cancers (colorectal, gastric, ovarian, breast, uterus, melanoma. . .), as the progastrin gene is a direct target of the WNT/ß-catenin oncogenic pathway involved in tumorigenesis of many organs (ASCO 2017, Prieur et al CCR 2017). The value of progastrin as a diagnostic, and as a therapeutic monitoring marker, was assessed in patients treated for peritoneal carcinomatosis from gastro-intestinal (GI) cancers in the prospective BIG-RENAPE study (NCT02823860).

Methods: Patients were enrolled during management of peritoneal carcinomatosis (before or after neo-adjuvant chemotherapy, or surgery) and then regularly sampled for blood. Progastrin was measured using the ELISA DECODE LAB test®. The diagnostic value of progastrin concentrations at inclusion in 190 GI cancer patients (test set) was assessed against 80 samples from French donors (control set with non-cancer subjects). The longitudinal therapeutic monitoring value of progastrin test was also investigated.

Results: The Area Under the ROC curve of prograstrin for cancer diagnosis was 0.87, 95% CI [0.83-092]. Progastrin was significantly elevated at inclusion in all GI tumor subtypes ($p < 0.0001$; median 3.08, 95% CI [1.15-7.23], including colo-rectal & small bowel ($n = 151$; median 2.78) and oeso-gastric ($n = 33$; median 4.75) carcinomas). During monitoring, progastrin levels decreased after neoadjuvant treatment (median value 2.20, $n = 23$), decrease that became significant after surgery ($p < 0.0001$, median value 1.57, $n = 84$), with patients going back to normal value and others not. A trend for better PFS was observed in patients with progastrin decline after surgery. Progastrin baseline value did not correlate with renal function.

Conclusions: Progastrin assay is a simple and inexpensive blood test exhibiting high diagnostic accuracy in patients with GI carcinomas, along with promising therapeutic longitudinal changes across sequential managements. Assessment of progastrin value as a multi-tumor screening assay, and as a monitoring test, is on-going.

Legal entity responsible for the study: BIG-RENAPE.

Funding: ECS-Screening.

Disclosure: A. Prieur, P. Liaud, M. Flaceliere, D. Joubert: Employee: ECS-Screening. All other authors have declared no conflicts of interest.

120P A new biomarker of breast cancer stage and patient response to neoadjuvant chemotherapy: HLA-DR expression in cytotoxic and regulatory T cells

D.P. Saraiva[1], A. Jacinto[1], S. Braga[2], M.G. Cabral[1]

[1]CEDOC, Nova Medical School, Lisbon, Portugal, [2]Instituto CUF de Oncologia, CUF, Lisbon, Portugal

Background: Neoadjuvant chemotherapy (NACT) is the treatment option for locally advanced breast cancer (BC). However, approximately half of the patients have no response. To promptly direct non-responders to personalized therapies, there is an urgency to find a clinical biomarker that could predict treatment response. Tumor infiltrating lymphocytes, namely CD8+ T cells (CTLs) and regulatory T cells (Tregs) are being appointed as biomarkers of response. Nonetheless, tumor cells can escape the immune system by releasing cytokines or expressing immune checkpoint inhibitors, dampening CTLs and increasing Tregs activation. CTLs and Tregs with HLA-DR, a T cell activation marker, by reflecting the tumor immune status, should be a more reliable biomarker of NACT success.

Methods: Fresh biopsies, surgical specimens and blood were collected from 150 BC patients. Immunophenotype was performed by flow cytometry, ELISA and qRT-PCR. Peripheral blood mononuclear cells (PBMCs) were isolated and cultured under canonical stimuli.

Results: 67.3% of BC analysed were ER+, 15.5% HER2+ and 17.2% triple negative. Prior to treatment and independent of BC type, BC with no metastasis in the lymph nodes (53%) have HLA-DR^{hi} CTLs ($p = 0.003$) and HLA-DR^{lo} Tregs ($p = 0.002$), although the average percentage of lymphocytes and myelocytes are similar between more or less advanced disease. Biopsies from NACT responders also have HLA-DR^{hi} CTLs ($p = 0.0006$) and HLA-DR^{lo} Tregs ($p = 0.0002$). A ROC curve revealed a threshold of HLA-DR in CTLs bellow which patients will not respond to NACT. Moreover, HLA-DR+ CTLs express IFN-g, Granzyme B, Perforin, Eomes and TNF-a, essential for CTLs cytolytic activity. HLA-DR+ CTLs negatively correlate with pro-tumorigenesis molecules, such as TGF-b, PD-L1, IL-6, IL-1b and IL-8 ($p < 0.005$); while HLA-DR+

Tregs positively correlate with them. HLA-DR expression in tumor T cells correlates with its level in systemic T cells (CTLs: r = 0.58 p = 0.001; Tregs: r = 0.65 p = 0.0002). PBMCs stimulated in vitro from NACT responders reveal higher IFN-g and lower IL-10 (p = 0.04).

Conclusions: We propose HLA-DR levels in T cells as a biomarker of BC stage and response to NACT, with the advantage of being systemically evaluated.

Legal entity responsible for the study: CEDOC, Nova Medical School.

Funding: Fundação para a Ciência e Tecnologia (FCT), iNOVA4Health.

Disclosure: All authors have declared no conflicts of interest.

121P LungBEAM: A prospective multicenter trial to monitor EGFR mutations using BEAMing technology in stage IV NSCLC patients

P. Garrido Lopez[1], E. Felip[2], L. Paz-Ares[3], M. Majem[4], T. Moran[5], J.L. Gonzalez-Larriba[6], J. Bosch Barrera[7], J.M. Trigo Perez[8], M.R. Garcia Campelo[9], J.M. Sanchez Torres[10], D. Isla[11], N. Vinolas Segarra[12], C. Camps[13], A. Insa Molla[14], O.J. Juan Vidal[15], B. Massuti[16], A. Paredes Lario[17], A. Artal-Cortes[18], M. Lopez-Brea Piqueras[19], J. Palacios Calvo[20]

[1]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [2]Medical Oncology Service (Lung Cancer Unit), Vall d'Hebron University Hospital, Barcelona, Spain, [3]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [4]Medical Oncology Services, Hospital De La Santa Creu I Sant Pau, Barcelona, Spain, [5]Medical Oncology, ICO Badalona, Badalona, Spain, [6]Medical Oncology, Hospital Clinico Universitario San Carlos, Madrid, Spain, [7]Medical Oncology, Catalan Institute of Oncology (ICO)-Hospital Universitari Josep Trueta, Girona, Spain, [8]Medical Oncology, Hospital Universitario Virgen de la Victoria, Málaga, Spain, [9]Medical Oncology, Hospital Universitario a Coruna, A Coruna, Spain, [10]Medical Oncology, Hospital Universitario de La Princesa, Madrid, Spain, [11]Medical Oncology, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain, [12]Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [13]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain, [14]Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain, [15]Medical Oncology, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [16]Oncología Médica, Hospital General Universitario Alicante, Alicante, Spain, [17]Medical Oncology, Hospital Donostia, San Sebastian, Spain, [18]Medical Oncology, Hospital Miguel Servet, Zaragoza, Spain, [19]Medical Oncology, Hospital Universitario Marques de Valdecilla, Santander, Spain, [20]Pathology, Hospital Universitario Ramon y Cajal, Madrid, Spain

Background: Liquid biopsy is a promising approach to improve the management of NSCLC patients, as it offers a minimally-invasive alternative to tumor tissue testing and enables timely monitoring of patients on-therapy. The goal of the present study was to evaluate the clinical value of longitudinal testing of EGFR mutation status in plasma of tissue EGFR mutation-positive NSCLC patients during first-line EGFR TKI therapy across 19 Spanish hospitals to: 1) determine the timing of T790M mutation emergence and 2) monitor EGFR mutation levels in plasma during first-line EGFR TKI therapy with respect to radiological progression.

Methods: Blood samples from 109 therapy-naïve advanced NSCLC patients were collected at baseline and monthly throughout EGFR TKI standard therapy. Results from OncoBEAM EGFR mutation were performed by Sysmex in Hamburg, and compared to those obtained by the EGFR tissue testing obtained at the referring hospital. The times at which T790M were first detected in blood were compared to the date of progression as determined by radiological imaging in standard clinical practice.

Results: At baseline, the initial positive percent agreement (PPA) for EGFR mutation status in 78 out of 109 patients enrolled in this study was 71.6%. From a total of 60 patients out of 89 who completed the study showing either clinical or radiological progression, 20 patients (33.3%) showed presence of the T790M mutation in plasma during follow-up. In 13 of these patients plasma T790M-positivity was detected an average of 14 weeks prior to radiological progression. Furthermore, the clearance of EGFR mutations in plasma at 8 weeks after initiation of EGFR TKI was a favorable indicator for PFS (37.3 weeks with clearance vs 25.5 weeks in patients without clearance). Patients showing EGFR mutation clearance at 8 weeks had an average baseline MAF of 3.6%, whereas patients with detectable mutations at 8 weeks showed an average baseline value of 13% MAF.

Conclusions: Overall, these results show high PPA of plasma and tissue EGFR mutation status at baseline. Early EGFR mutation clearance may be predictive of response to first-line EGFR TKI therapy. Plasma detection of T790M mutation anticipates clinical progression.

Clinical trial identification: SYS-ONC-2015-01.

Legal entity responsible for the study: Sysmex Inostics GmbH.

Funding: Sysmex Inostics GmbH.

Disclosure: All authors have declared no conflicts of interest.

122P Immune checkpoints and liver resection after neoadjuvant chemotherapy including bevacizumab in patients with colorectal liver metastases

S. Stremitzer[1], A. Graf[2], B. Neudert[3], M. Herac[3], A. Beer[3], C. Schwarz[1], F. Wrba[3], K. Kaczirek[4], J. Stift[3]

[1]Department of Surgery, Medical University of Vienna, Vienna, Austria, [2]Center for Medical Statistics, Informatics and Intelligent Systems, Medical University Vienna, Vienna, Austria, [3]Clinical Institute of Pathology, Medical University Vienna, Vienna, Austria, [4]Department of Surgery, Vienna General Hospital (AKH) - Medizinische Universität Wien, Vienna, Austria

Background: Liver resection after neoadjuvant chemotherapy including bevacizumab offers the possibility of cure in patients with colorectal liver metastases. The clinical value of immune checkpoint expression as prognostic biomarker is unclear.

Methods: Expression analyses of IDO-1, PD-L1 and CTLA-4 were performed by immunohistochemistry in resected colorectal liver metastases in patients who underwent liver resection after neoadjuvant chemotherapy including bevacizumab (2005-2011). Association of expression of immune checkpoints in tumor cells and immune cells with response, RFS and OS was investigated.

Results: One hundred forty-six patients were enrolled [88 (60.3%) male/58 (39.7%) female, median age 63.0 years (31.0-80.4)]. High expression of CTLA-4 in tumor cells was associated with shorter OS (median OS 48.2 months versus not reached, HR 2.04, P = 0.028). High expression of IDO-1 and PD-L1 in immune cells was associated with longer OS (not reached versus 47.1 months, HR 0.43, P = 0.016 and not reached versus 47.1 months, HR 0.41, P = 0.017). Results of IDO-1 remained significant in multivariable analysis (HR 0.29, P = 0.006). Low expression of CTLA-4 in tumor cells was associated with better histologic response (26 major, 19 partial, 18 none versus 14 major, 23 partial, 30 none, P = 0.032). No association of expression was found with RFS and radiologic response.

Conclusions: The clinical meaning of immune checkpoint expression and its association with response and survival were dependent on the expressing cell types. IDO-1 and CTLA-4 may be new prognostic and/or predictive biomarkers in patients with colorectal liver metastases. The role of immune checkpoint inhibitors in a multidisciplinary treatment approach remains to be elucidated.

Legal entity responsible for the study: Stefan Stremitzer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

123P Gene expression (GE)-based biomarkers associated with nivolumab response in a real-life cohort of patients with metastatic non-small cell lung cancer (mNSCLC)

N. Radosevic-Robin[1], S. Ong[2], S.E. Warren[3], M. Kossai[1], C. Godfraind[4], M. Masson[5], H. Janicot[6], P. Merle[6], P. Dubray-Longueras[5], X. Durando[5], P. Morel[7], A. Cesano[7], F. Penault-Llorca[1]

[1]Pathology, Centre Jean Perrin, Clermont-Ferrand, France, [2]Bioinformatics, NanoString Technologies, Inc., Seattle, WA, USA, [3]Biology, NanoString Technologies, Inc., Seattle, WA, USA, [4]Pathology, University Hospital Center of Clermont-Ferrand, Clermont-Ferrand, France, [5]Medical Oncology, Centre Jean Perrin, Clermont-Ferrand, France, [6]Pneumology, University Hospital Center of Clermont-Ferrand, Clermont-Ferrand, France, [7]Medical Affairs, NanoString Technologies, Inc., Seattle, WA, USA

Background: Robust and versatile biomarkers are urgently needed to identify cancer pts who are likely to benefit from immune checkpoint inhibitors (ICI). The Tumor Inflammation Signature (TIS) is an 18-gene signature measuring the suppressed adaptive immune response necessary for pts clinical benefit from ICI (Ayers, J Clin Invest 2017). This retrospective study evaluated the performance of TIS and additional GE signatures assessing pathways associated with immune evasion in mNSCLC pts, treated with nivolumab as per label (2nd+ line), in two French cancer centers.

Methods: RNA from primary FFPE tumor samples from 77 immunotherapy-naïve mNSCLC pts, treated with nivolumab monotherapy, was profiled with a β-version of the NanoString® IO 360 GE panel, which includes the TIS and other tumor and immune biology signatures. The statistical analysis treated associations of GE and clinical response.

Results: In the whole cohort analysis, samples from pts who experienced clinical benefit showed an "inflamed" phenotype. Specifically, TIS was significantly higher in the responder group compared to non-responders (p = 0.005, non-adjusted). A similar association was observed for myeloid and macrophage scores (p = 0.001 and p = 0.002, respectively) as well as for PDCD1 (PD1), CD274 (PDL1), and CTLA4 (p = 0.05, 0.001, 0.02, resp.). In a subtype analysis, squamous carcinomas showed a less inflamed phenotype than adenocarcinomas but had elevated proliferation, glycolysis and hypoxia scores, as well as increased ARG1 and NOS2. In contrast, in the independent subtype analysis, both TIS and additional immune signatures remained associated with clinical response.

Conclusions: TIS and other immune signatures predicted response to nivolumab single agent in a real-life cohort of pts, in both adeno- and squamous mNSCLC. Thus, assessing GE patterns can give insight into different mechanisms of immune evasion operating at the single patient level. Additional analyses of this cohort, evaluating the

NanoString® IO 360 signatures and single gene expressions, with regard to various other clinical and molecular tumor features, will be presented.

Legal entity responsible for the study: NanoString Technologies, Inc.

Funding: NanoString Technologies, Inc.

Disclosure: S. Ong, S.E. Warren, P. Morel, A. Cesano: Employee and stockholder: NanoString. All other authors have declared no conflicts of interest.

124P Association of microRNA-21 (miR-21) with efficacy of cetuximab (cet) and bevacizumab (bev) in patients with metastatic colorectal cancer (mCRC) within the FIRE-3 study (AIO KRK-0306)

L. Miller-Phillips[1], L. Fischer von Weikersthal[2], F. Kaiser[3], S-E. Al-Batran[4], T. Heintges[5], D. Neureiter[6], C. Kahl[7], F. Kullmann[8], M. Moehler[9], W. Scheithauer[10], C. Vazart[11], K. Fontaine[11], S. Held[12], D.P. Modest[1], J. Neumann[13], A. Jung[13], T. Kirchner[13], V. Heinemann[1], S. Stintzing[1]

[1]Department of Medicine III, University Hospital, LMU Munich, Munich, Germany, [2]Health Center, Health Center St. Marien, Amberg, Germany, [3]Studien GbR, VK&K, Landshut, Germany, [4]Department of Hematology and Oncology, Nordwest-Krankenhaus, Frankfurt am Main, Germany, [5]Department of Medicine II, Staedtische Kliniken Neuss, Neuss, Germany, [6]Institute of Pathology, Paracelsus Medical University Salzburg, Salzburg, Austria, [7]Haematology and Oncology, Klinikum Magdeburg, Magdeburg, Germany, [8]Department of Medicine I, Klinikum Weiden, Weiden in der Oberpfalz, Germany, [9]Department of Medicine I, Universitiy Hospital, Mainz, Germany, [10]Department of Internal Medicine I & Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, [11]R&D, IntegraGen SA, Évry, France, [12]Statistik, Clinassess, Leverkusen, Germany, [13]Institute of Pathology, Ludwig Maximilians University, Munich, Germany

Background: FIRE-3 compared first-line therapy with FOLFIRI plus either cet or bev in KRAS exon 2 wildtype (wt) patients with mCRC. Identification of RAS mutations as a predictor for the efficacy of EGFR-antibody therapy raised the question of whether miR-21 as a potential regulator of the EGFR dependent pathway influences therapy outcome.

Methods: A reverse-transcription quantitative polymerase chain reaction (RT-qPCR) assay was used to identify quantitative miR-21 expression in formalin-fixed paraffin-embedded (FFPE) tumor samples of FIRE-3 patients. The median of miR-21 expression within the FIRE-3 population was determined and subsequently used to segment the population into low and high miR-21 expression groups. Overall response rate (ORR) between treatment groups was compared using Fisher's exact test. Median progression free (PFS) and overall survival (OS) were calculated using Kaplan-Meier estimation and compared through log-rank test.

Results: RAS wt population with low miR-21 expression (n = 146) showed a significantly higher ORR when cet instead of bev was added to FOLFIRI chemotherapy (80.0% vs. 57.9%; p = 0.005). High miR-21 expression in RAS wt population (n = 149) showed no significant difference in ORR between treatment groups (74.6% vs. 64.0%; p = 0.21). ORR of RAS mutated patients with high miR-21 expression (n = 48) showed no significant difference between cet or bev when added to FOLFIRI (38.1% vs. 59.3%; p = 0.24). ORR (50.0% vs. 48.3%; p > 0.99) also showed no significant difference in RAS mutated patients with low miR-21 expression (n = 59). The following table presents statistical results of PFS and OS by comparing FOLFIRI plus cet versus FOLFIRI plus bev depending on RAS and miR-21 status.

Table: 124P

	RAS wt		RAS mut	
	low miR-21 (n = 166)	high miR-21 (n = 167)	low miR-21 (n = 67)	high miR-21 (n = 62)
PFS (months)	10.6 vs. 10.3 p = 0.3	10.1 vs. 9.9 p = 0.5	8.5 vs. 12.2 p = 0.3	7.7 vs. 8.9 p = 0.044
OS (months)	35.8 vs. 25.9 p = 0.005	24.5 vs. 23.8 p = 0.4	20.2 vs. 26.0 p = 0.4	16.4 vs. 20.2 p = 0.2

Conclusions: Along with RAS status, miR-21 expression level may be a promising predictive biomarker for anti-EGFR-therapy.

Clinical trial identification: NCT00433927; Study Start Date: January 2007; First Posted: February 12, 2007.

Legal entity responsible for the study: University Hospital, LMU Munich.

Funding: Merck.

Disclosure: C. Vazart, K. Fontaine: Employee: Integragen. D.P. Modest: Honoraria and advisory boards: Amgen, Bayer, Merck, MSD, Roche, Servier, Taiho, BMS, Sirtex; Travel support/research funding: Amgen, Bayer, Merck, Roche, Servier. V. Heinemann: Advisory boards: Merck KgaA, Roche AG, Amgen, Sanofi, Lilly, Sirtex, Boehringer Ingelheim, Taiho, Servier; Honoraria for talks: Merck KgaA, Roche AG, Amgen, Sanofi, Sirtex, Servier, MSD; Travel expenses to meetings: Merck KgaA, Roche AG, Amgen, Sirtex, Servier, MSD, BMS; Funding of research activity: Merck KgaA, Pfizer, Amgen, Roche, Servier, Sirtex. S. Stintzing: Honoraria for talks and travel support: Amgen, Bayer, Roche, Merck KgaA, SANOFI, Lilly, Takeda. All other authors have declared no conflicts of interest.

125P Molecular heterogeneity assessment by NGS in non-small cell lung cancer (NSCLC) harboring EGFR mutations: Results of the French Cooperative Thoracic Intergroup (IFCT) Biomarkers France study

H. Blons[1], J-B. Oudart[1], J-P. Merlio[2], S. Hominal[3], F. de Fraipont[4], D. Debieuvre[5], F. Escande[6], C. Audigier Valette[7], P-P. Bringuier[8], S. Moreau Fraboulet[9], L. Ouafik[10], D. Moro-Sibilot[11], A. Lemoine[12], A. Langlais[13], P. Missy[14], F. Morin[14], P-J. Souquet[15], F. Barlesi[16], J. Cadranel[17], M. Beau-Faller[18]

[1]Biochimie UF de Pharmacogénétique et Oncologie Moléculaire, APHP, HEGP, Paris, France, [2]EA 2406 Histologie et Pathologie Moléculaire des Tumeurs, Université de Bordeaux, Bordeaux, France, [3]Service Cancérologie-Oncologie, Centre Hospitalier Annecy Genevois, Metz-Tessy, France, [4]Molecular Genetic, Oncology, CHU Grenoble Alpes, Grenoble, France, [5]Service de Pneumologie, Hôpital Emile Muller, GHRMSA, Mulhouse, France, [6]Centre Biologie et Pathologie, CHRU Lille, Lille, France, [7]Service de Pneumologie, Hospital Sainte Musse, Toulon, France, [8]Centre de Biologie et Pathologie Est, Service d'Anatomie et de Cytologie Pathologique, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France, [9]Pneumologie, Hopital Foch, Suresnes, France, [10]Service de Transfert d'Oncologie Biologique, APHM, Marseille, France, [11]Thoracic Oncology Unit, CHU de Grenoble, La Tronche, France, [12]Biochimie et Oncogénétique, Hopital Paul Brousse, Villejuif, France, [13]Department of Biostatistics, IFCT, Paris, France, [14]Clinical Research Unit, IFCT, Paris, France, [15]Service de Pneumologie, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [16]Service d'Oncologie Multidisciplinaire et Innovations Thérapeutiques, Aix-Marseille Université; Assistance Publique Hôpitaux de Marseille, Marseille, France, [17]Service de Pneumologie, Hôpital Tenon GH-HUEP, Paris, France, [18]Laboratoire de Biologie Moléculaire & Plate-Forme de Génomique des Cancers d'Alsace, Hôpital de Hautepierre & Institut Régional du Cancer, Strasbourg, France

Background: NSCLC is characterized by genome alterations that promote cancer cell growth. TO what extent co-mutations cooperate with the EGFR driver and explain the variable response to EGFR TKI is not well understood. Here, we screened additional co-mutations (ACMs) and evaluate their clinical impact in patients (pts) with advanced NSCLC.

Methods: We identified 204 pts with EGFR mutated tumors from the IFCT Biomarkers France study cohort with available tumor DNA who received first or second line first-generation EGFR-TKIs. Samples were assessed by NGS using the AmpliSeq Cancer Hotspot Panel v2. Among the 204 samples, 167 were fully contributive.

Results: EGFR mutations were: classical with del 19 (74; 44%) and L858R (59; 35%), complex (17; 10%) including T790M (9; 5%) or uncommon (17; 10%). EGFR was amplified in 27 (17%) samples. ACMs were identified in 120 (72%) samples with an average of mutations at 2.9 (2-8). Recurrent ACMs (more than 6 samples) were in TP53 (84; 50.3%), CTNNB1 (16; 10%), PI3KCA (15; 9%), RB (12; 7%), APC (10; 6%), PTEN (8; 5%) and ATM (7; 4.5%). EGFR complex mutations were more frequent in smokers (p = 0.01) whereas RB1 mutations were more frequent in non-smokers (p = 0.03). CTNNB1 mutations were mutually exclusive with TP53 (p = 0.01) or PI3KCA (p = 0.05) mutations. High EGFR variant allelic fraction was associated to EGFR amplification (p < 0.001) suggesting mutant allele amplification and to TP53 mutations (p = 0.003). Non-classical or complex EGFR mutations were linked to rapid (< 3 months) versus normal (3-20 months)/slow (> 20 months) progression (p = 0.07 and p = 0.05 respectively). In the non-T790M group, ATM and PTEN mutations were negative predictors of first-line TKI efficacy (mPFS 3.7 versus 8.9 months, HR 2.85, 95CI% 1.14-7.15 and mPFS 5.6 versus 9.0 months, HR 2.46, 95CI% 1.16-5.9, respectively).

Conclusions: EGFR mutated NSCLC have heterogeneous molecular profiles. This work suggests that PTEN and ATM mutations could limit EGFR inhibitor efficacy. However, large series of EGFR mutated NSCLC will be needed to validated links between clinical outcomes and specific EGFR altered pathways.

Legal entity responsible for the study: IFCT.

Funding: AstraZeneca: INCa (French NCI); IFCT (Alain Depierre Research Award 2015).

Disclosure: D. Debieuvre: Consulting: Roche; Honoraria: AstraZeneca, Chugaï, Lilly, Roche, Novartis, Pfizer, MSD, BMS; Grants: Roche, AstraZeneca, Lilly, BMS, Boehringer Ingelheim, Chiesi, Chugaï, Janssen, Pfizer, MSD, Novartis, GSK, Sandoz; Board: Roche, Boehringer Ingelheim, Pfizer, MSD, BMS, Novartis; Conferences: Roche, Boehringer Ingelheim, Novartis, Pierre Fabre, Pfizer, MundiPharma, BMS. C. Audigier Valette: Clinical trials (PI): AstraZeneca, Boehringer Ingelheim, BMS, Novartis, Roche; Consulting: AstraZeneca, Boehringer Ingelheim, BMS, Lilly, Novartis, MSD, Pfizer, Roche; Conferences: AstraZeneca, Boehringer Ingelheim, BMS, Lilly, Novartis, Pfizer, Roche. S. Moreau Fraboulet: Personal fees and non-financial support: Novartis; Non-financial support: Lilly. D. Moro-Sibilot: Personal fees: Roche, Eli Lilly, Pfizer, Novartis, AstraZeneca, BMS, MSD, Boehringer Ingelheim. A. Lemoine: AstraZeneca, Boehringer, Roche. F. Barlesi: Personal fees: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer. J. Cadranel: Clinical research (PI): AbbVie, AstraZeneca, Bayer, Boehringer–Ingelheim, BMS, MSD, Novartis, Roche, Takeda; Consulting: AstraZeneca, Boehringer Ingelheim, BMS, Lilly, Novartis,

MSD, Pfizer, Roche; Conferences: AstraZeneca, BMS, MSD, Pfizer. M. Beau-Faller: Board: BMS, Boehringer-Ingelheim, AstraZeneca; Non-financial support: AstraZeneca, Roche. All other authors have declared no conflicts of interest.

126P Simultaneous identification and profiling of tumor-specific T cells by mass cytometry

M. Fehlings, E. Newell

*SIgN, A*STAR, Singapore*

Background: immunoSCAPE leverages the high-dimensional immune profiling capabilities of mass cytometry combined with a unique technology for the identification of antigen-specific T-cells to support the development of immunotherapy strategies in cancer and immune-related diseases. In cancer, there is now strong evidence that immunotherapy-mediated tumor rejection can rely on tumor-specific (neoantigen-specific) $CD8^+$ T-cells. Consequently, the discovery of neoantigens becomes valuable for personalized cancer immunotherapies. Although in silico pipelines exist, that are capable of predicting non-synonymous mutations potentially giving rise to tumor-specific neoantigens, it is not clear how accurate these methods are in identifying immunogenic and therapeutically relevant epitopes, since T-cell epitope usage can be influenced by many factors. Moreover, analysis of T-cells in cancer patients is challenging as it requires detecting rare antigen-specific T-cell populations in samples that are usually limited in volume and availability.

Methods: By applying cytometry by time of flight in conjunction with combinatorial peptide-MHC tetramer staining and high-performance dimensional analysis tools, we are able to map broadly MHC-class I epitope with a high sensitivity for rare antigen-specific T-cells and perform concurrently in-depth characterization of these cells.

Results: We will show here the application of this technology in the context of immunotherapy, through the example of a murine in vivo tumor model responsive to checkpoint blockade inhibitors, as well as through the analysis of different human cancer samples.

Conclusions: Together, by providing insights into the nature of neoantigen-specific T-cells, immunoSCAPE's unique target discovery and high-dimensional immune profiling platform is a valuable tool for the development of novel diagnostic biomarkers and therapeutic strategies at different stages of drug development.

Legal entity responsible for the study: A*STAR / Singapore Immunology Network and immunoSCAPE.

Funding: immunoSCAPE.

Disclosure: E. Newell: Board director and shareholder: immunoSCAPE Pte. Ltd. All other authors have declared no conflicts of interest.

127P Over-expression of S100B protein as a serum marker of brain metastasis in non-small cell lung cancer and its prognostic value

L. Chen, Y. Zhao, X. Hu, H. Wu, J. Liu, X. Mu

Oncology, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China

Background: Validated serum biomarkers for patients suffering from non-small cell lung cancer (NSCLC) brain metastasis are urgently needed for early diagnosis, treatment monitoring, and prognostic classification in daily clinical practice and trials. Serum S100B was reported to be a marker of leaky blood-brain barrier (BBB), which was often caused by brain tumors. This study aimed to investigate the role of S100B and S100B antibody in the early detection of NSCLC brain metastasis and the prognostic significance.

Methods: 100 patients with NSCLC brain metastasis, 50 patients of stage IV NSCLC without brain metastasis, and 50 patients with cerebrovascular diseases were enrolled in this prospective study. S100B and S100B antibody were measured in serum samples of all patients before and after treatment by ELISA, and the correlations with brain metastasis were assessed by ANOVA. Kaplan-Meier survival analyses and COX regression were used to unveil the prognosis significance.

Results: The results showed that serum S100B correlated significantly with NSCLC brain metastasis ($p < 0.001$), but not S100B antibody ($p > 0.05$). When evaluated by the ROC curve, at the cutoff point 13.83 pg/ml, the sensitivity and specificity were 94% and 93%, respectively (AUC= 0.938, $p < 0.001$). The PFS and OS of NSCLC patients with brain metastasis were significantly shorter in the patients with high levels of serum S100B. In addition, S100B was an independent prognostic factor.

Conclusions: In conclusion, serum S100B was a sensitive and specific marker for early detection of brain metastasis in NSCLC and could be used as a surveillance tool for prognosis evaluation.

Legal entity responsible for the study: Affiliated Cancer Hospital of Zhengzhou University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

128P Differential gene expression profiles in poor vs good responders to maintenance vinflunine in patients (p) with advanced urothelial carcinoma (aUC): Preliminary results of biomarker analyses from the MAJA trial (SOGUG 2011/02)

J.L. Ramirez[1], A. Font Pous[2], J. Garcia-Donas[3], B. Perez Valderrama[4], I. Aguirre Egaña[5], L. Nonell[6], V. Ruiz de Porras Fontdevila[7], M. Mallo[8], D. Balañá[1], J.A. Virizuela[9], U. Anido[10], M.M. Llorente Ostiategui[11], M.A. Gonzalez del Alba Baamonde[12], N. Lainez[13], B. Mellado[14], M.A. Climent Duran[15], J. Bellmunt[16]

[1]Cancer Molecular Biology Laboratory, Catalan Institute of Oncology (ICO) - Germans Trias i Pujol Health Sciences Research Institute (IGTP), Badalona, Spain, [2]Medical Oncology, Institut Català d' Oncologia, Badalona, Spain, [3]Genitourinary, Ginecologycal, Skin and Rare Tumors Unit, Hospital Madrid Norte San Chinarro Centro Integral Oncologico Clara Campal, Madrid, Spain, [4]Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain, [5]Programa de Medicina Predictivia i Personalitzada del Càncer, Catalan Institute of Oncology (ICO) - Germans Trias i Pujol Health Sciences Research Institute (IGTP), Badalona, Spain, [6]Microarrays Analysis Department, Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain, [7]Resistance, Chemotherapy and Predictive Biomarkers Department, Catalan Institute of Oncology (ICO) - Germans Trias i Pujol Health Sciences Research Institute (IGTP), Badalona, Spain, [8]Josep Carreras Leukaemia Research Institute, Catalan Institute of Oncology (ICO) - Germans Trias i Pujol Health Sciences Research Institute (IGTP), Badalona, Spain, [9]Medical Oncology, Hospital Virgen Macarena, Seville, Spain, [10]Medical Oncologist, CHU Santiago, Santiago, Spain, [11]Oncología, Hospital General de Elda, Elda, Spain, [12]Medical Oncology, Hospital Universitario Son Espases, Palma de Mallorca, Spain, [13]Medical Oncology, Complejo Hospitalario de Navarra, Pamplona, Spain, [14]Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [15]Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [16]Medical Oncology, Hospital del Mar, Barcelona, Spain

Background: Vinflunine is an antimicrotubule agent approved by the EMA for second-line treatment in p with aUC. However, no molecular biomarkers are currently available that can predict response to vinflunine in aUC. In the randomized phase II MAJA trial (NCT01529411) in p with aUC with disease control after a platinum-based regimen, maintenance vinflunine conferred a significant improvement in progression-free survival compared to best supportive care (Garcia-Donas et al. Lancet Oncol 2017). Pre-planned gene expression analyses aimed to identify biomarkers to predict response to maintenance vinflunine.

Methods: In the MAJA trial, 44 p received vinflunine. We have compared the gene expression profiles of eight poor responders to vinflunine (<4 cycles) and nine good responders (>12 cycles). RNA was isolated from FFPE tumor tissue collected during screening using the Covaris kit and gene expression levels were analyzed with Clariom S array (Thermo Fisher). Differential expression (DE), defined as $p < 0.05$ and $|FC| > 1.5$, was determined with linear models for microarray data included in the limma and sva packages. Pre-ranked Gene Set Enrichment Analysis (GSEA) was used for the functional classification of the DE genes.

Results: Hierarchical clustering of genes showed a DE between good and poor responders. DE were found in 31 genes, 13 of them were unregulated in good responders and 18 were unregulated in poor responders. In good responders, GSEA revealed overexpression of 72 genes related to G2M-checkpoint and of 61 genes related to E2F transcription factor. In poor responders, 73 genes related to epithelial-mesenchymal transition and 39 related to IL6/JAK/STAT3 were downregulated. We are currently validating these genes using qPCR to determine a gene expression profile associated with response to maintenance vinflunine.

Conclusions: Our preliminary results suggest that microarray analysis could identify a gene expression signature to predict response to maintenance vinflunine, which will be useful in selecting treatment for p with aUC. Complete results of the analyses will be reported.

Clinical trial identification: NCT01529411; EudraCT: 2011-001271-39.

Legal entity responsible for the study: Spanish Oncology Genitourinary Group.

Funding: Spanish Oncology Genitourinary Group.

Disclosure: All authors have declared no conflicts of interest.

129P Pre-diagnostic measurements of high-sensitive C-reactive protein and risk of prostate cancer: The PROCA-life study

E. Stikbakke[1], H.S. Haugnes[2], I. Thune[1], T. Wilsgaard[3], T. Knutsen[4], E.H. Richardsen[5]

[1]Department of Clinical Medicine, University of Tromso The Arctic University of Norway, Tromso, Norway, [2]Department of Oncology, University Hospital of North Norway, Tromso, Norway, [3]Department of Community Medicine, University of Tromso The Arctic University of Norway, Tromso, Norway, [4]Department of Urology, University Hospital of North Norway, Tromso, Norway, [5]Department of Pathology, University Hospital of North Norway, Tromso, Norway

Background: Inflammation may promote prostate cancer development, which can be characterized by elevated circulating levels of inflammation markers, such as high-sensitivity C-reactive protein (hs-CRP). Whether pre-diagnostic measurements of hs-CRP are associated with prostate cancer remains unknown.

Methods: In the Prostate Cancer Study throughout life (PROCA-life), a total of 11 064 initially healthy men, who participated in the Tromsø Study between 1994 and 2008,

were included. Pre-diagnostic hs-CRP was assessed and height and weight were measured at study entry. During a mean follow-up time of 14.2 years, a total of 459 men developed histological verified prostate cancer and detailed medical and histological records were obtained.

Results: At study entry, the cohort participants had a mean age of 60.5, mean level of hs-CRP of 2.18 mg/l and a mean body mass index (BMI) of 25.8 kg/m^2. The 459 prostate cancer cases identified had a mean age at diagnosis of 72.0 years. Among normal weighted men (BMI<25kg/m^2), we observed a positive linear relationship between pre-diagnostic hs-CRP levels and prostate cancer risk after adjustments, both when using single and repeated measurements of hs-CRP, with hazard ratio 1.09 (95% CI 1.03-1.14) and 1.08 (95% CI 1.01-1.16), respectively. This relationship was not present in the overweight (BMI 25-30 kg/m^2) or obese (BMI>30kg/m^2) group.

Conclusions: Our study supports the hypothesis that inflammation may play a role in prostate cancer development, but this association may vary by body composition.

Legal entity responsible for the study: University of Tromsø.

Funding: University of Tromsø.

Disclosure: All authors have declared no conflicts of interest.

130P Training and validation of a gene expression signature for microsatellite instability

S.E. Warren[1], P. Danaher[2], S. Ong[3], N. Elliott[4], A. Cesano[5]

[1]Research, NanoString Technologies, Seattle, WA, USA, [2]Bioinformatics, NanoString Technologies, Seattle, WA, USA, [3]Bioinformatics, NanoString Technologies, Inc., Seattle, WA, USA, [4]Research, NanoString Technologies, Inc., Seattle, WA, USA, [5]Clinical, NanoString Technologies, Inc., Seattle, WA, USA

Background: Clinical response to cancer immunotherapy can be predicted from two biologically distinct variables: tumor foreignness, manifested in some tumors as deficient DNA mismatch repair (dMMR)/microsatellite instability (MSI), typically measured by qPCR or IHC, and anti-tumor immunity, typically measured by gene expression signatures or IHC. Clinical benefit should be more accurately predicted by the combination of the two variables than by either alone, but measuring both variables requires multiple clinical assays. Here, we investigate the ability of gene expression alone to provide a surrogate measure of both tumor foreignness and immunogenicity, empowering a single assay to measure both axes of predictive biology. In addition, we explore the relationships between tumor foreignness and immunogenicity in both dMMR and MMR-proficient (pMMR) tumors.

Methods: Using TCGA datasets from colon, esophageal, stomach and uterine cancers, we trained two algorithms predicting hypermutation: the first detecting loss of expression of mismatch repair genes (MLH1, MSH2, MSH6 and PMS2) and the second identifying expression patterns shared by hypermutated tumors across these four cancer types. A final algorithm synthesizes the two above algorithms into a single score. For independent validation, we evaluated 60 colorectal cancer (CRC) FFPE samples, 30 dMMR and 30 pMMR as previously identified by IHC, and a cohort of 10 MSI and 5 MSS endometrial and neuroendocrine tumors with the NanoString nCounter® platform.

Results: We show that our algorithms successfully predicted hypermutation phenotypes and MMR status in TCGA training data and in the independent CRC and endometrial datasets analyzed with NanoString; with an AUROC of 0.94. Additionally, we demonstrate that higher mutational burden is linked to a heightened tumor immune environment as shown by adaptive immune gene signatures.

Conclusions: Gene expression proves to be a powerful predictor of microsatellite instability and hypermutation in cancers where dMMR subtypes are known to exist. This discovery raises the possibility that a gene expression algorithm measuring both hypermutation and immune activity may be advantaged in predicting response to checkpoint inhibition in these cancer types.

Legal entity responsible for the study: NanoString Technologies.

Funding: NanoString Technologies.

Disclosure: S.E. Warren, S. Ong, N. Elliott, A. Cesano: Employee and stockholder: NanoString Technologies. P. Danaher: Stockholder: NanoString Technologies.

131P Development and analytical validation of a plasma-based tumor mutational burden (TMB) score from next-generation sequencing panels

K. Quinn[1], E. Helman[1], T. Nance[1], C. Artieri[1], J. Yen[1], J. Zhao[1], S. Fairclough[1], M. Sikora[1], D. Chudova[1], R.B. Lanman[2], A. Talasaz[3]

[1]Bioinformatics, Guardant Health, Redwood City, CA, USA, [2]Medical Affairs, Guardant Health, Redwood City, CA, USA, [3]Guardant Health, Redwood City, CA, USA

Background: The advantages of plasma-based tumor mutational burden (TMB) include non-invasive, real-time assessment of mutational load, without the limitations of insufficient tissue. However, at low levels of tumor DNA shedding, TMB may be underestimated if a fraction of the genomic alterations is below assay limit of detection. Currently available blood TMB panels report a 1% tumor content limit of detection, which would result in about half of all clinical plasma samples (based on > 30,000 patients) with unevaluable TMB. Hence, clinically effective blood-based diagnostics must be highly sensitive and account for tumor shedding. Here, we present a comprehensive cfDNA-based TMB using a 500-gene (GuardantOMNI) and a 73-gene (Guardant360) panel.

Methods: We developed a statistical model to calculate TMB on plasma samples with low cell-free circulating tumor DNA (ctDNA) content. Theoretical panel performance was assessed in silico by subsetting mutations from whole exome sequencing (WES) to the Guardant panel space (2Mb for GuardantOMNI and 200Kb for Guardant360) from 9,104 TCGA samples and 30 lung cancer samples with published immunotherapy outcomes. Sensitivity was evaluated using 50 serially diluted cfDNA specimens. Analytical validation was performed against tissue-based WES TMB using matched plasma and tissue samples across multiple tumor types.

Results: High correlation was observed between TMB called on the Guardant panel and WES mutations from the TCGA dataset ($r = 0.99$ with GuardantOMNI; $r = 0.92$ with Guardant360). Subsetting WES from clinical outcome cohorts to each panel recapitulated the association with PFS on immunotherapy (HR = 0.41 with GuardantOMNI; HR = 0.27 with Guardant360). The sensitivity of detection was assessed down to 0.3% tumor content and 5ng cfDNA input. Lastly, we show high quantitative concordance between matched plasma and tissue WES samples for both GuardantOMNI and Guardant360.

Conclusions: We describe a plasma-based TMB score that correlates with tissue-derived TMB at tumor fractions down to 0.3%, enabling TMB calculation on > 70% of all clinical samples. Accurate reporting of TMB from a plasma sample has the potential to accelerate clinical trial enrollment and improve outcomes.

Legal entity responsible for the study: Guardant Health, Inc.

Funding: Guardant Health, Inc.

Disclosure: K. Quinn, E. Helman, T. Nance, C. Artieri, J. Yen, J. Zhao, S. Fairclough, M. Sikora, D. Chudova, R.B. Lanman, A. Talasaz: Employee and ownership (stock): Guardant Health, Inc.

132P Carbohydrate antigen 19-9 and apolipoprotein A2 isoform as early detection biomarkers for pancreatic cancer: A prospective evaluation by the EPIC study

K. Honda[1], V. Katzke[2], A. Hüsing[2], S. Okaya[1], H. Shoji[3], K. Onidani[1], F. Canzian[4], R. Kaaks[2]

[1]Department of Biomarkers for Early Detection of Cancer, National Cancer Center Research Institute, Tokyo, Japan, [2]Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany, [3]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [4]Genomic Epidemiology, German Cancer Research Center, Heidelberg, Germany

Background: This study prospectively evaluated the performance of an apolipoprotein A2 isoform (ApoA2-ATQ/AT) in combination with carbohydrate antigen 19-9 (CA19-9) as early detection biomarkers for pancreatic cancer.

Methods: Using ELISA, we measured CA19-9 and ApoA2-ATQ/AT in plasma samples collected ≤60 months before diagnosis from 159 pancreatic cancer patients and 217 matched controls within the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. The diagnostic sensitivity, specificity, and C-statistics were calculated for risk scores by strata of the time before diagnosis.

Results: The C-statistics of CA19-9 and CA19-9+ApoA2-ATQ/AT for distinguishing pancreatic cancer patients from cancer-free individuals were 0.87 and 0.68, respectively, for samples taken ≤6 months before diagnosis, and 0.74 and 0.72, respectively, for samples taken <6 to 18 months before diagnosis. The joint diagnostic model using CA19-9+ApoA2-ATQ/AT showed significantly improved diagnostic discrimination in samples taken ≤18 months before diagnosis. Before diagnosis, the specificity of CA19-9+ApoA2-ATQ/AT was 98%, while the sensitivities of CA19-9+ApoA2-ATQ/AT were 57%, 36%, and 43%, respectively, and those of CA19-9 alone were 50%, 29%, and 36%, respectively. This joint model also showed significantly improved C-statistics for the diagnostic discrimination of samples taken >6 to 18 months (0.80 for CA19-9+ApoA2-ATQ/AT, 0.74 for CA19-9; $p = 0.004$) and ≤18 months (0.8 for CA19-9+ApoA2-ATQ/AT, 0.78 for CA19-9; $p = 0.003$) before diagnosis.

Conclusions: Compared to CA19-9 alone, CA19-9+ApoA2-ATQ/AT showed improved diagnostic discrimination for early detection ≤18 months before diagnosis. This plasma biomarker panel may provide a useful first measure for detecting pancreatic cancer prior to imaging. We have reported those results on behalf of the EPIC Europe.

Legal entity responsible for the study: National Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

133P Sarcopenia and inflammation predicts survival in advanced stage cancer patients (pts) treated with immunotherapy (IO)

M.A. Bilen[1], D.J. Martini[2], J.M. Shabto[2], Y. Liu[3], A.I. Khan[2], M.A. Williams[2], C. Lewis[1], H.H. Collins[1], H. Kissick[4], B.C. Carthon[1], M. Akce[1], W.L. Shaib[1], O.B. Alese[1], D.H. Lawson[1], R. Kudchadkar[1], B. El-Rayes[1], S.S. Ramalingam[5], T.K. Owonikoko[1], R.D. Harvey[1], V.A. Master[4]

[1]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA, [2]Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA, [3]Departments of Biostatistics and Bioinformatics, Emory University, Atlanta, GA, USA, [4]Department of Urology, Emory University, Atlanta, GA, USA, [5]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA

Background: Sarcopenia is associated with poor prognosis in cancer pts and inflammation has been recognized as a hallmark of cancer. In this study, we investigated the synergistic effect of sarcopenia and inflammation on survival in advanced stage cancer pts treated with IO.

Methods: We performed a retrospective analysis of 90 pts treated on IO-based phase 1 clinical trials at Winship Cancer Institute of Emory University from 2009-2017. CT images at mid-L3 were obtained at baseline. Skeletal muscle density was obtained using SliceOmatic v5.0 by TomoVision and converted to skeletal muscle index (SMI) by dividing by height^2. We defined sarcopenia as SMI<39. Neutrophil-to-lymphocyte ratio (NLR) was obtained at baseline and used as a surrogate of inflammation. Pts were categorized based on recursive partitioning methods into three groups: (1) low NLR, (2) high NLR without sarcopenia, (3) high NLR with sarcopenia. Overall survival (OS) and progression-free survival (PFS) were measured from date of first dose of IO to date of death or clinical or radiographic progression, respectively. Multivariable analysis (MVA) was carried out using Cox proportional hazard model.

Results: The majority of pts (n = 53) were males and most (68.9%) had at least 2 prior lines of therapy. Melanoma (33%) and GI (22.2%) tumors were the most common histologies. Low NLR was associated with longer OS and PFS (Table). Sarcopenic pts with high NLR had shorter survival than pts with high NLR who were not sarcopenic (Table).

Conclusions: Sarcopenia may have a synergistic effect with inflammation on decreasing survival in pts treated with IO. Prospective validation of the impact of body composition parameters on survival and whether adipose tissue plays a role in the relationship may be warranted. Equal contribution: MAB, DJM, JMS.

Legal entity responsible for the study: Emory University IRB.

Funding: Research reported in this publication was supported in part by the Biostatistics and Bioinformatics Shared Resource of the Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure: M.A. Bilen: Consulting/advisory role: Exelixis, Sanofi; Research funding: Bayer, Bristol-Myers Squibb, Genentech/Roche, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Peleton, Pfizer. B.C. Carthon: Consulting/advisory role: Astellas Medivation, Pfizer, Blue Earth Diagnostics; Travel accommodations: Bristol-Myers Squibb. W.L. Shaib: Research funding: ArQule and Lilly. R. Kudchadkar: Consulting/advisory role: Bristol-Myers Squibb, Novartis, Array BioPharma; Honorarium: Bristol-Myers Squibb; Research funding: Merck. B. El-Rayes: Consulting/advisory role: Merrimack, BTG, Bayer, Loxo, RTI Health Solutions; Speakers' bureau: Lexicon, Bristol-Myers Squibb; Honorarium: Lexicon, RTI Health Solutions, and Bayer; Research funding: Taiho Pharmaceutical, Bristol-Myers Squibb, Boston Biomedical, Cleave Biosciences, Genentech, AVeo, Pfizer, Novartis, Hoosier Cancer Research Network, Five Prime Therapeutics, PPD Inc., Merck, ICON Clinical Research. S.S. Ramalingam: Consulting/advisory role: Amgen, Boehringer Ingelheim, Celgene, Genetech/Roche, Lilly/ImClone, Bristol-Myers Squibb, AstraZeneca, Abbvie, Merck, and Takeda; Travel, accommodations: EMD Serono, Pfizer, and AstraZeneca. T.K. Owonikoko: Consulting/advisory role: Novartis, Celgene, Lilly, Sandoz, Abbvie, Eisai, G1 Therapeutics, Takeda, Seattle Genetics, Bristol-Myers Squibb, and MedImmune; Intellectual property of the following: "Overcoming acquired resistance to chemotherapy treatments through suppression of STAT3" and "Selective chemotherapy treatments and diagnostic methods related thereto"; Research funding: Novartis, Astellas Pharma, Celgene, Bayer, Stem CentRx, Regeneron, AstraZeneca/MedImmune, Abbvie, G1 Therapeutics, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

134P Prediction of irAEs in ipilimumab-treated melanoma patients based on serum autoantibodies

J.C. Hassel[1], J. Mangana[2], R. Dummer[3], C. Pföhler[4], K. Wistuba-Hamprecht[5], B. Weide[6], L. Hakim-Meibodi[1], F. Meier[7], J. Roth[1], H-D. Zucht[8], P. Budde[8], M. Tuschen[8], P. Schulz-Knappe[8]

[1]Section of Dermato-Oncology, Department of Dermatology and NCT, University Hospital Heidelberg, Heidelberg, Germany, [2]Department of Dermatology, University Hospital Zürich, Zurich, Switzerland, [3]Dermatology, Universitätsspital Zürich, Zurich, Switzerland, [4]Department of Dermatology, University Hospital Homburg/Saar, Homburg/Saar, Germany, [5]Department of Dermatology, University Hospital Tübingen, Tübingen, Germany, [6]Dermatologische Onkologie, Universitäts-Hautklinik, Tübingen, Germany, [7]Skin Cancer Center at the University Cancer Center and NCT, University Hospital Carl Gustav Carus Dresden, Dresden, Germany, [8]Science, Protagen AG, Dortmund, Germany

Background: Checkpoint inhibition is an effective treatment in patients with metastatic melanoma (MM). T cell activation can induce tumor rejection but also possibly severe autoimmune side effects (irAE). Autoantibody biomarkers from serum have potential to predict irAEs such as an ipilimumab-induced colitis.

Methods: We use a cancer immunotherapy array consisting of 850 human protein antigens from 4 classes: 1. Tumor-associated antigens (TAA), 2. cancer pathway proteins, 3. autoimmune antigens, 4. cytokines/interleukins. Protein antigens were covalently coupled to magnetic beads and serum AABs were analyzed by Luminex FlexMap 3D. First, we screened pre-immunotherapy sera from 142 patients with MM (Heidelberg Cohort: 82 Ipilimumab (Ipi) treated; 11 Ipi/Nivolumab (Nivo); 40 Pembrolizumab (Pembro), 119 healthy controls (HC)). In this cohort, 41.5% (n = 59) experienced irAEs of any grade and 7% (n = 10) had colitis of grade 3 or 4. In a second study, 200 MM patients from 5 European sites (53 Ipi/Nivo; 111 Pembro, 100 HC) were analyzed. 25.6% (n = 42) had grade 3 or 4 irAEs, 12.8% (n = 21) had diarrhea or colitis of any grade and 9.8% (n = 16) had grade 3 or 4 colitis.

Results: 40 different AABs were significantly more prevalent in MM compared to HC including NY-ESO1, NY-ESO 2 and other TAAs, cytokines, and nuclear proteins. Significant correlations of AABs were seen in Ipi-treated patients who experienced irAEs, both in mono- but also in combination therapy, allowing to dichotomize MM in risk groups. Also different sets of AABs were seen in Pembro-treated patients with irAEs. The protein antigens represent a variety of biological processes: they are involved in melanoma progression including transcription factors or components of the E3 ubiquitin ligase complex, cytokeratins, and proteins involved in cell adhesion.

Conclusions: In MM, screening of AABs prior to start of Checkpoint inhibition holds potential to predict risk for irAEs such as colitis. As irAEs are especially frequent in Ipi-based treatment regimes, AABs presented here may serve as useful biomarkers for a risk-based treatment decision.

Legal entity responsible for the study: Jessica C. Hassel and Protagen AG.

Funding: Protagen AG.

Table: 133P Univariable analysis (UVA) and MVA[†] of inflammation and sarcopenia with survival

		UVA			MVA		
	Median Survival in Months (95% CI)	N	HR (CI)	p-value	N	HR (CI)	p-value
OS							
Group 1: NLR <2.9	24.3 (10.3, 44.8)	36	–	–	36	–	–
Group 2: NLR ≥2.9, SMI ≥ 39	9.4 (5.5, NA)	33	2.65 (1.22-5.72)	0.013*	33	2.08 (0.90-4.77)	0.085
Group 3: NLR ≥ 2.9, SMI < 39	3.8 (2.8, 5.9)	21	8.40 (3.47-20.31)	<0.001*	21	7.93 (3.19-19.73)	<0.001*
PFS							
Group 1: NLR <2.9	4 (2.5, 5.4)	36	–	–	34	–	–
Group 2: NLR ≥ 2.9, SMI ≥ 39	2.8 (1.6, 4.1)	33	1.62 (0.95-2.79)	0.078	33	1.35 (0.77-2.39)	0.298
Group 3: NLR ≥ 2.9, SMI < 39	1.6 (1.2, 1.8)	21	4.16 (2.26-7.67)	<0.001*	21	4.37 (2.26-8.48)	<0.001*

[†]The multivariable model was built by controlling for gender, checkpoint indication, # of previous treatment lines, royal marsden hospital (RMH) risk group, age, ECOG PS, race, # of metastatic sites, and histology. *statistical significance at alpha < 0.05.

Disclosure: J.C. Hassel: Consulting role: Merck, Amgen; Honoraria: Bristol-Myers Squibb, Merck, Novartis, Roche and Pfizer; Science projects support: BMS. J. Mangana: Temporary advisory relationship and receives travel support: MSD, Merck. C. Pföhler: Consulting role: Merck Serono, Novartis, Roche, Amgen, BMS; Honoraria: Merck Serono, Novartis, Roche, Amgen, BMS. B. Weide: Consulting role: Curevac, Philogen, BMS; Honoraria: MSD, BMS, Roche, Amgen, Philogen; Science projects support: BMS, Philogen. L. Hakim-Meibodi: Travel grants: BMS. F. Meier: Honoraria: Roche, BMS, GSK, Novartis, MSD; Travel support: Roche, BMS; Research funding: Wyeth/Pfizer, Merck-Serono, Novartis. H.-D. Zucht, P. Budde; M. Tuschen: Employee: Protagen AG. P. Schulz-Knappe: Board member and chair holder: Protagen AG. All other authors have declared no conflicts of interest.

135P Combined tumor-based BRCA/TP53 mutation testing in ovarian cancer

B. Edith[1], A. Leary[2], P. Pautier[2], E. Santana[3], L. Lacroix[4], O. Cabaret[3], M. Guillaud-Bataille[3], J. Michels[5], A. Auguste[6], C. Genestie[7], E. Rouleau[7]

[1]Gynecology Unit, Gustave Roussy, Villejuif, France, [2]Gynecological Unit, Gustave Roussy Cancer Center, INSERM U981, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), Villejuif, France, [3]Cancer Center, Gustave Roussy, Villejuif, France, [4]Department of Medical Biology and Pathology, Laboratory of Translational Research and Biological Resource Center, AMMICA, INSERM US23/CNRS UMS3655, Gustave Roussy, University Paris-Saclay, Villejuif, France, [5]Gynecological Unit, Gustave Roussy Cancer Center, Villejuif, France, [6]INSERM U981, Gustave Roussy Cancer Center, Gustave Roussy - Cancer Campus, Villejuif, France, [7]Department of Medical Biology and Pathology, Gustave Roussy, University Paris-Saclay, Villejuif, France

Background: Somatic or germline BRCA mutations remain the best predictive biomarker for PARP inhibitor benefit and > 95% of high grade serous ovarian cancers (HGSOC) have a clonal somatic TP53 mutation. Combined tBRCA/TP53 testing might provide the advantages of i) rapid results, ii) identification of somatic BRCAm, and iii) indirect evidence of the '2nd hit' event, ie loss of heterozygosity (LOH).

Methods: Between 1/1/2016 and 1/2/2018 182 pts with HGOC underwent tBRCA/TP53 testing with a capture NGS panel and were oriented to a germline BRCA (gBRCA) testing via a dedicated genetics consultation. The ratio of allelic fractions (AF) for BRCAm/TP53m was calculated to estimate the proportion of cells carrying the BRCAm and derive LOH.

Results: At the time of data cut-off, gBRCA results were available for 125/182, and still pending for 61 pts. 15/125 (12%) demonstrated a deleterious (DEL) gBRCA1m (N = 12) or gBRCA2m (N = 3). Tumor testing was performed on 182 with a median testing turn-around time of 16 days (range 7-539 days). Twenty-seven (15%) were non-contributive. Among 155 contributive tumor samples, 31 DEL tBRCAm (21%) were identified. All gBRCAm (15/15) were identified on tumor testing including one large re-arrangement. 16 additional DEL BRCA1m or BRCA2m were detected: 10 somatic BRCAm in pts with confirmed wild-type (WT) germline status, and 6 among pts with pending germline results. Median TP53m AF was 0.48 (range 0.012-0.92) confirming a huge variability in tumor cellularity among samples. Among gBRCAm cases, ratio AF BRCAm/TP53m was always>1 confirming germline origin and suggesting LOH. AF BRCAm/TP53m was lower among known sBRCAm tumors (median AF BRCAm/TP53m=1.1) but always>0.8 suggesting acquired BRCA mutation was clonal and associated with LOH. For 3 gBRCA WT samples with <10% tumor cellularity and very low DEL BRCAm AF (0.04, 0.04 and 0.05), TP53m AF were also <0.05, thus validating the somatic BRCAm.

Conclusions: Combined BRCA/TP53 tBRCA testing is fast, sensitive and identifies somatic BRCA mutations. In addition, information on TP53 AF is useful to validate % neoplastic cells, identify somatic BRCAm in low cellularity samples and provides indirect evidence for LOH as the '2nd hit'.

Legal entity responsible for the study: Alexandra Leary.

Funding: Has not received any funding.

Disclosure: A. Leary: Honoraria: AstraZeneca; Consulting: AstraZeneca, GamaMabs Pharma, Clovis Oncology, Gritstone Oncology; Research funding (institution): AstraZeneca, GamaMabs Pharma, Clovis Oncology, AstraZeneca, Pfizer, MSD; Accommodation: AstraZeneca. P. Pautier: Honoraria: AstraZeneca; Consulting: AstraZeneca, Roche, Tesaro; Research funding (institution): AstraZeneca, Roche, ImmunoGen; Accommodation: AstraZeneca, PharmaMar. L. Lacroix, C. Genestie: Honoraria: AstraZeneca. J. Michels: Research funding (institution): Roche, MSD. E. Rouleau: Honoraria: AstraZeneca; Consulting: AstraZeneca, Roche, BMS UK; Research funding (institution): AstraZeneca. All other authors have declared no conflicts of interest.

136P EML4-ALK fusion variants associate with gender and age in Chinese NSCLC patients

W. Zhao[1], G. Liang[2], L. Wang[3], L. Dai[2], D. Wu[4], K. Wang[4], A. Wang[5], H. Chen[6], Y-A. Dong[7], M. Wang[4]

[1]Department of Thoracic Surgery, The First Affiliated Hospital of Kunming Medical University, Kunming, China, [2]Department of Thoracic Surgery, First Affiliated Hospital of Guangxi Medical University, Nanning, China, [3]Department of Thoracic Surgery, Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [4]Department of Thoracic Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [5]Department of Clinical Analysis, OrigiMed, Shanghai, China, [6]Department of Bioinformatics, OrigiMed, Shanghai, China, [7]OrigiMed, OrigiMed, Shanghai, China

Background: EML4-ALK fusion is one of the major activating kinase mutations in NSCLC. It occurs with varying frequency in different populations and is known to associate with clinical features such as smoking history and age. Based on different breakpoints in EML4 and ALK genes, there exist several fusion subtypes (variants), which have been reported to respond differently to ALK inhibitors. In this study, we investigated the landscape of EML4-ALK in Chinese NSCLC patients and correlated fusion variants with clinical factors.

Methods: FFPE tumor and matched blood samples of over 1000 Chinese NSCLC patients were collected for NGS-based 450 cancer genes panel assay. Genomic alterations including single nucleotide variations (SNV), short and long insertions/deletions (Indel), copy number variations (CNV) and gene rearrangements in selected genes were assessed.

Results: A total of 73 EML4-ALK fusion samples were identified. In our cohort, younger patients were more likely to harbor ALK fusions, consistent with previous reports. In terms of EML4-ALK fusion variants, we observed three major subtypes: 30 E6:E20 (variant 3) cases, 20 E13:E20 (variant 1), and 11 E20:E20 (variant 2). Interestingly, E6-E20 was enriched in male patients (18 vs 12), while E13-E20 was enriched in female patients (13 vs 7); furthermore, for the E13-E20 variant all 13 female patients were younger than 60, while 4 out of 7 male patients were older than 60 ($p = 0.007$). To complete the picture, other subtypes of EML4-ALK fusion in our cohort included: 4 E18:E20, 4 E14:E20, 3 E2:E20, and 1 E21:E20.

Conclusions: EML4-ALK fusion is known to associate with clinical features including race, age, and smoking history. Our profiling of EML4-ALK alteration in Chinese NSCLC patients not only revealed the composition of fusion subtypes, but also connected variants with demographic factors such as gender and age. Our initial results need to be validated in larger cohorts and/or different populations. Given that different fusion variants respond differently to ALK inhibitors, our findings could have important implications.

Legal entity responsible for the study: OrigiMed.

Funding: Has not received any funding.

Disclosure: A. Wang, H. Chen, Y-A. Dong: Employee: OrigiMed. All other authors have declared no conflicts of interest.

137P Multi-dimensional immuno-oncology assays for understanding the immune system and tumor microenvironment

F. Hyland[1], T. Looney[2], R. Chaudhury[1], A. Kamat[1], A. Pankov[1]

[1]CSD, Thermo Fisher Scientific, South San Francisco, CA, USA, [2]Clinical Next-Generation Sequencing Division, Thermo Fisher Scientific, South San Francisco, CA, USA

Background: The promise of immuno-oncology (IO) is the potential for activating the immune system of an individual with cancer to destroy the tumor and metastases, and cause a complete and persistent response. A percentage of patients treated with checkpoint inhibitors or Car-T cell therapies exhibit complete response. However understanding all the determinants of response, and what combination of therapies can maximize efficacy and minimize adverse events, is still poorly understood. Further understanding the properties of the tumor micro-environment, the immune system, and driver mutations in the tumor provides the most comprehensive picture, enabling personalized oncology research.

Methods: We describe a suite of Oncomine assays that use a single chemistry and instrument with 20ng of input material each. The first measures patterns of gene expression of 395 genes that capture interferon and chemokine signaling, T and B cell activation, checkpoint pathway, antigen presentation, and tumor proliferation, measuring the expression of markers specific to different effector cell types. We demonstrate highly sensitive detection of low expressing genes including Interferon-Gamma. The second is the T-cell Repertoire sequencing assay. This assay uses total RNA from blood for long-amplicon TCRB chain sequencing, covering CDR1, 2 & 3. This assay provides an estimate of T cell diversity and other properties. The third is the Tumor Mutation Load assay. This 400-gene panel measures somatic mutations/Mb on FFPE samples, without requiring a matched normal. We demonstrated high reproducibility on FFPE, concordance with matched normal, correlation with exome mutation load, and accuracy on control cell lines.

Results: Together, these IO panels provide sensitive, accurate, complementary information to further elucidate biological factors underlying response, resistance, and adverse events. A single software for these diverse assays supports joint interpretation of this data.

Conclusions: These IO assays enable deep, broad, multidimensional characterization of biomarkers to explore predictors of response, optimal combination therapy, and avoidance of adverse events, accelerating research into immunotherapy for personalized oncology.

Legal entity responsible for the study: Thermo Fisher Scientific.

Funding: Thermo Fisher Scientific.

Disclosure: F. Hyland, T. Looney, R. Chaudhury, A. Kamat, A. Pankov: Employee of Thermo Fisher Scientific.

138P Monitoring the effect of PI3K inhibition on HER2 therapy resistant breast cancer using serial analysis of PIK3CA mutant tumour DNA in plasma

N. Keegan[1], S. Toomey[2], A. Farrelly[2], A. Carr[2], G. Calzaferri[3], J. Walshe[4], G. Gullo[4], J.P. Crown[4], K. Egan[5], A. Hernando[6], A. Teiserskiene[6], L. Grogan[7], O.S. Breathnach[7], P.G. Morris[5], B. Hennessy[8]

[1]Department of Molecular Oncology, RCSI Beaumont Hospital, Dublin, Ireland, [2]Oncology Molecular Medicine, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland, [3]Department of Medical Oncology, Cancer Clinical Research Trust, Dublin, Ireland, [4]Medical Oncology, St Vincent's University Hospital, Dublin, Ireland, [5]Cancer Clinical Trials and Research Unit, Beaumont Hospital, Dublin, Ireland, [6]Breast DSSG, Cancer Trials Ireland, Dublin, Ireland, [7]Medical Oncology, Beaumont Hospital, Dublin, Ireland, [8]Cancer Clinical Trials and Research Unit and Cancer Trials Ireland, RCSI Beaumont Hospital, Dublin, Ireland

Background: PIK3CA is mutated in up to 20% of HER2 positive breast cancers, contributes to HER-2 therapy resistance and may be predictive of response to PI3K inhibitor therapy. PIK3CA mutations in breast cancer occur primarily at hotspots E545K at exon 9 and H1047R at exon 20. Copanlisib (C) is a pan-class I PI3K inhibitor that shows particular activity against PI3Kα, the isoform encoded by the PIK3CA gene. The aim of this study was to assess PIK3CA mutation status in matched tumour and plasma samples pre copanlisib treatment and to monitor PIK3CA mutation concentration changes in plasma over the course of PI3K inhibition therapy.

Methods: For 12 patients with advanced HER2 positive, breast cancer treated on a clinical trial of copanlisib and trastuzumab, we prospectively examined serial plasma samples to quantify the PIK3CA hotspot mutations in circulating tumour DNA by droplet digital PCR (ddPCR). Samples were taken pre-treatment, then every two weeks on treatment and immediately after radiological disease progression. Archival formalin fixed paraffin embedded (FFPE) primary tumour tissue were examined using MassArray® to detect PIK3CA mutation.

Results: PIK3CA mutations were detected in 6/12 (50%) archival FFPE primary tumours ; either an exon 9 (n = 2) or exon 20 (n = 4), all of which were also oestrogen receptor positive and had at least one prior line of anti Her2 therapy in the advanced cancer setting. There were 106 plasma samples included in the mutation analysis. PIK3CA mutation (H1047R or E545K) >500copies/mL were detected in 66% (70/106) of the samples. Of the six tumour samples that had no PIK3CA mutation detected, three had >500copies/mL (range: 0-25,500copies/mL) of mutated PIK3CA detected in serial plasma samples. Variations in plasma DNA mutation levels over time were found in all 12 patients.

Conclusions: Our data demonstrate that PIK3CA mutation is detectable in the plasma of a large proportion of a cohort of patients with HER2 therapy resistant advanced breast cancer, is potentially a more meaningful representation of current mutation status than archival primary tumour tissue given discordance and levels of mutation fluctuate with PI3K inhibition combined with trastuzumab.

Legal entity responsible for the study: Cancer Trials Ireland.

Funding: Bayer Pharmaceuticals.

Disclosure: B. Hennessy: Research funding: Bayer Pharmaceuticals. All other authors have declared no conflicts of interest.

139P Analysis of circulating biomarkers in a randomized phase II trial of maintenance oral metronomic vinorelbine in advanced NSCLC following platinum-based chemotherapy: A correlative MA.NI.LA. trial study

M. Boeri[1], F. Nichetti[2], L. Porcu[3], V. Torri[4], A. Del Conte[5], A. Martinetti[2], E. Sottotetti[2], E. Vattemi[6], F. Verderame[7], M.C. Garassino[8], L. Cavanna[9], A. Tuzi[10], L. Irtelli[11], F.G.M. de Braud[12], M. Platania[2]

[1]Research Department, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [2]Medical Oncology 1, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Oncology, ASUIUD Azienda Ospedaliero-Universitaria di Udine, Udine, Italy, [4]Oncology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy, [5]Oncology, Azienda Ospedaliera Sta Maria degli Angeli, Pordenone, Italy, [6]Medical Oncology, Ospedale Centrale di Bolzano ASDAA/SABES, Bolzano, Italy, [7]Oncology, Presidio Ospedaliero Cervello, Palermo, Italy, [8]Thoracic Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [9]Oncology Department, Azienda Ospedaliera Piacenza, Piacenza, Italy, [10]Oncology, Ospedale di Circolo Fondazione Macchi, Varese, Italy, [11]Oncology, P.O. Clinicizzato Ss. Annunziata Universita' Degli Studi, Chieti, Italy, [12]Medical Oncology & Haematology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy

Background: The efficacy of maintenance chemotherapy (CT) in advanced NSCLC is still under investigation. The multicenter, open label, randomized, phase II MA.NI.LA trial aimed to assess the activity of metronomic oral vinorelbine versus close observation as maintenance treatment following platinum-based CT in patients with advanced NSCLC. Serum angiogenesis biomarkers and the plasma microRNA signature classifier (MSC) associated with tumor aggressiveness in NSCLC patients were here investigated as prognostic and predictive factors.

Methods: 119 advanced NSCLC patients with stable disease after platinum-based CT received maintenance metronomic oral vinorelbine (ARM A) or close observation (ARM B). The primary endpoint of the trial was progression free survival (PFS). Plasma samples for biomarkers evaluation were collected at the baseline from all patients. Concentrations of VEGFA and THBS1 were determined using EIA kit (Chemicon International). To determine MSC risk level, custom made microfluidic cards (Thermo Fisher) were adopted to analyze 8 samples simultaneously by RT-qPCR. Cox regression model was used to evaluate the association of biomarkers to PFS and OS.

Results: In the whole cohort, median age was 68.8; M/F: 79/40; stage IIIb/IV:14/105; adeno/other:73/46; PS 0-1/2:113/7. In front of a median follow up of 23.9 months, median PFS was 4.3 and 2.8 months for ARM A and ARM B, respectively (HR = 0.73; 90%CI 0.53-0.999; p = 0.0493). Considering all 119 patients, high VEGFA and THBS1 plasma levels and positive MSC expression were associated with shorter both PFS and OS. HR for 1000 unit, VEGF: 1.56 (90%CI 0.99-2.46; p = 0.054); HR for 10000 unit, THBS1: 1.16 (90%CI 0.97-1.38; p = 0.114); HR for MSC pos vs neg: 1.61 (90%CI 1.05-2.47; p = 0.028). Similar results were obtained considering OS. No interaction between treatment effect and biomarker values were detected.

Conclusions: In advanced NSCLC following platinum-based induction CT, metronomic oral vinorelbine showed a modest, but significant improvement in PFS. In addition, VEGF and MSC could be considered as prognostic but not predictive factors

Clinical trial identification: NCT02176369.

Legal entity responsible for the study: Clips srl.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

140P Oral cavity immune response in pancreatic ductal adenocarcinoma (PDAC)

J.P. Marquez, P.A. Lucero-Diaz, J.A. Matute-Briseno, M.O. Rosas-Delgado, A. Camacho-Hernandez, Y. Cortez-Vargas, I. Nava-Sanchez, G.T. Montano, L.N. Montijo-Fernandez, M.A. Perez-Astorga

Clinical ImmunoOncology and Relapse Prevention Clinic, Centro de Investigacion de Cancer en Sonora-CICS, Ciudad Obregon, Mexico

Background: We studied the humoral immune response in patients with pancreatic ductal adenocarcinoma (PDAC) using mouthwashes from the oral cavity. We found lower immune response against recall antigens, fusobacterium nucleatum and tumor associated antigens before immunotherapy treatment. We also found better prognosis when the antibodies against tested antigens got higher. Finally, we found significant differences in the humoral immune response in the oral cavity against serum.

Methods: Antigens from fusobacterium nucleatum, recall and tumor associated antigens were tested by IgG + IgM + IgA ELISA in both oral cavity and serum of PDAC patients n = 50. We provided 5 ml of saline solution to all the patients and controls to rinse the oral cavity hardly for 5 minutes and deposit the content in 15 ml tube. Sera were obtained. All was done after the approval of the local IRB committee.

Results: All the evaluated antigens were lower in the oral cavity of PDAC patients compared with controls (p = 0.001). Serum responses for all antigens were significantly different than oral cavity (p = 0.03). At the end of the immunotherapy treatment consisting in a combination of immunomodulation, multi peptide antigen specific active immunotherapy and immunogenic chemotherapy with doxorubicin and oxaliplatin the levels of antibodies were increased significantly. For example, FAP (p = 0.0001), EGFR (p = 0.005), Fascin-1 (p = 0001), VCP (P = 001). Also, the immunotherapy combination significantly increased antibody immune response against fusobaterium lysate (p = 0001).

Conclusions: PDAC is a challenge disease especially in late stages. PDAC patients had low antibody titters against several antigens in comparison with controls and before treatment the oral cavity. Serum antibodies were lower than oral cavity even after treatment. Oral cavity antibodies may be a useful early biomarker in patients in high risk of PDAC. This data also suggest that antibodies get low when the cancer or premalignant lesions of PDAC are present.

Legal entity responsible for the study: Centro de Investigacion de Cancer en Sonora (CICS).

Funding: CICS USA.

Disclosure: All authors have declared no conflicts of interest.

141P Tumor mutational burden (TMB) standardization initiative: Establishing a consistent methodology for TMB measurement in clinical samples

A. Stenzinger[1], J. Allen[2], J. Maas[3], M. Stewart[4], D. Merino[4], M. Dietel[5]

[1](On behalf of QuIP® GmbH, Berlin, Germany) Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany, [2]Leadership Department, Friends of Cancer Research, Washington, DC, USA, [3]Management Department, QuIP® GmbH, Berlin, Germany, [4]Science Policy Analysis, Friends of Cancer Research, Washington, DC, USA, [5](On behalf of QuIP® GmbH, Berlin, Germany) Pathology, Charité Berlin, Berlin, Germany

Background: Clinical studies have established TMB, a measurement of mutations in the tumor genome, as a predictive biomarker for clinical efficacy of immune checkpoint inhibitors (ICIs). There is a lack of standardization for TMB estimation and reporting, which is critical for ensuring consistency for clinical implementation. An international collaboration organized by Friends of Cancer Research (Friends) and Qualitätssicherungs-Initiative Pathologie GmbH (QuIP) is establishing recommendations for achieving consistency in TMB estimation and reporting.

Methods: Friends and QuIP are using complementary TMB harmonization approaches. Friends will conduct in silico analyses where TCGA data will be compared between TMB estimates derived from whole exome sequencing (WES) and commercial targeted gene panels, followed by the use of patient-derived tumor cell lines to establish a universal reference standard for the alignment of panel-derived estimates. QuIP will compare TMB estimates from selected tissue (NSCLC and other solid tumors) using a WES-derived reference standard with commercial next-generation sequencing panels and lab-developed tests at several German academic institutions. These data will inform consistency of TMB estimation, assay comparability, and TMB cutoff values for potential clinical use.

Results: Preliminary data indicate several components influence TMB estimation: pre-analytical factors (eg, input material quality/quantity), sequencing parameters (eg, enrichment technologies), library preparation, bioinformatics (eg, filtering of germline variants), FFPE-induced deamination artifacts, mutation types, and clonal vs subclonal events. Analyses of panel size and composition suggest that larger panels may yield more reliable TMB estimation and that the panel should include actionable targets, genes associated with mutagenesis (eg, microsatellite instability), and potential negative predictors of response (eg, mutated β2M, JAK1/2, PTEN).

Conclusions: The Friends and QuIP collaboration will establish recommendations for reliable and reproducible TMB measurement to ensure consistent identification of patients who are likely to respond to ICIs.

Editorial acknowledgement: Medical writing assistance was provided by Amrita Dervan, MSc, of Spark Medica Inc. (US), funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: A. Stenzinger: Advisory board and honoraria for talks: AstraZeneca, Novartis, BMS, Roche, Illumina, Thermo Fisher. All other authors have declared no conflicts of interest.

142P DNA damaging agents and immunotherapy in NSCLC: Is there a STING in the tale?

C.M. Della Corte[1], K. Ramkumar[1], T. Sen[1], P. Tong[2], D.L. Gibbons[1], J.V. Heymach[1], J. Wang[2], Y-H. Fan[1], R. Cardnell[1], L. Byers[1]

[1]Thoracic Head and Neck, MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Bioinformatics & Computational Biology, MD Anderson Cancer Center, Houston, TX, USA

Background: In NSCLC patients, several clinical trials are testing the efficacy of DNA damage response inhibitors (DDRi) and chemotherapy in combination with anti-PDL1 drugs. DDRi activate antitumor immune responses in cancer through release of cytosolic DNA leading to STING activation, stimulation of neo-antigens and release of pro-inflammatory cytokines. Our group has previously demonstrated a strong correlation between EMT and immune activation, showing that tumors with high EMT score have the highest levels of targetable immune markers.

Methods: We analyzed mRNA and protein expression of immune and EMT genes in the lung adenocarcinoma (LUAD) and lung squamous carcinoma (LUSC) TCGA NSCLC and in a panel of NSCLC cells, correlating them with the presence of somatic mutations in DDR genes. Contemporary, we treated NSCLC cell lines in vitro with cisplatin and various DDRi combinations, including PARP/ATR/ATM/WEE-inhibitors, to determine the effect on DNA damage and immune markers expression (by western blot and RPPA analysis).

Results: In both TCGA cohorts, immune markers mRNA expression clustered together and were positively correlated with EMT genes. In the LUAD cohort, high expression of CD274 (PDL1) was associated with high levels of other immune suppressive markers (LAG3, IDO1, PDCD1LG2, HAVCR2, CTLA4, ICOS, CD4, and CD40) and chemokines (CXCL10, CCL5, CCL2). Notably, expression of STING pathway mediators (TBK1 and TMEM173) and mesenchymal markers (TWIST1/2, SNAI1, SMO, and TGFB1) were positively related with CD274. Moreover, we found that mutations in DDR related genes TP53, RB1, POLE, FANCM and BRCA1 were allied with higher levels of targetable immune suppressive markers (LAG3, IDO1, and CD274) and the mesenchymal marker, TWIST1, but lower levels of TMEM173. Finally, in vitro treatments with DDRi and cisplatin increased DNA damage, as demonstrated by increased p-H2AX, and proportionally upregulated PDL1 and STING in some cell lines.

Conclusions: Our findings provide rationale to combine DNA damaging agents with immunotherapy drugs targeting immune suppressive markers in NSCLC. From our data, expression of EMT genes and deleterious mutations in DDR genes represent the best candidates to select patients that can benefit from these combinations.

Legal entity responsible for the study: MD Anderson Cancer Center.

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.

143P Tumor infiltrating lymphocytes (TILs) and PDL1 expression as prescreening enrichment biomarkers of clinical benefit to immune checkpoint inhibitors (CI) in early clinical trials (ECT)

J. Martin-Liberal[1], F. Pagliuca[2], C. Hierro[1], C. Viaplana[3], E. Muñoz Couselo[4], J. Capdevila[5], I. Matos[4], L. Fariñas Madrid[4], E. Zamora[4], I. Braña Garcia[4], E. Elez Fernandez[4], M. Ochoa De Olza Amat[4], A. Azaro[4], M. Alsina[4], M. Vieito Villar[1], R. Fasani[1], J. Tabernero[4], E. Garralda[6], R. Dienstmann[3], P.G. Nuciforo[7]

[1]Oncology, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [2]Department of Advanced Biomedical Sciences, Pathology Section, Naples University Federico II, Naples, Italy, [3]Oncology Data Science (ODysSey) Group, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron University Hospital, Barcelona, Spain, [6]Early Drug Development Unit, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [7]Molecular Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Patients (pts) enrolled in ECT with CI are mainly selected based on tumor type. Genomic markers are informative in few cases. We assessed microenvironment markers as prescreening tool to identify pts with higher chances of clinical benefit from CI.

Methods: Pts treated with anti PD1/PDL1 drugs in monotherapy or in combination with other CI in ECT at our centre were evaluated for TILs on hematoxylin-eosin stained sections and PDL1 expression in tumor (tumcells) and immune cells (immcells) by immunohistochemistry (SP263 antibody). Results were correlated with clinical outcomes.

Results: From June 16 to June 17, 64 pts were recruited. TILs and PDL1 expression were available for all and 39 pts, respectively. Tumor types were melanoma (16 pts), neuroendocrine (9), gyne (8), breast (5), H&N (4), others (22). In total, 38 pts received anti PD1/PDL1 in monotherapy, the rest received anti PD1/PDL1 based combinations (12 pts had prior CI treatment). Response rate (RR) was 22%; median PFS was 4 months (m) (CI95% 3.30-5.57). We found no differences in PDL1 expression in tumcells according to tumor type (Kruskal test $p = 0.33$) and a weak correlation between TILs and PDL1 in tumcells (Pearson 0.44; $p = 0.004$) or immcells (Pearson 0.57; $p = 0.0001$). Median TILs was 7% (range 1-90), with no difference according to tumor type (Kruskal test $p = 0.45$). Median TILs was higher in pts with response to CI (17.5% v 5%, Kruskal test $p = 0.06$). RR in pts with TILs $\geq$7% was 32% v 9% if TILs <7% (Fisher test $p = 0.06$). In a multivariable logistic model adjusting for tumor type and CI regimen, RR was significantly higher in pts with TILs $\geq$7% (odds ratio 8.2; $p = 0.05$). Median PFS in pts with TILs $\geq$7% was 5 m v 3.7 m if TILs <7% (HR = 0.57 in a multivariable Cox model, $p = 0.06$). In univariate models, there was a trend for higher RR if PDL1 $\geq$1% in tumcells (35% v 12%, fisher test $p = 0.28$) or if PDL1 $\geq$1% in immcells (35% v 16%, fisher test $p = 0.27$). PFS was not correlated with PDL1 expression.

Conclusions: Quantifying TILs is a simple prescreening strategy that may help select pts for CI therapy in ECT from otherwise unselected population. The value of adding PDL1 expression needs further investigation.

Legal entity responsible for the study: VHIO.

Funding: Has not received any funding.

Disclosure: J. Tabernero: Advisory boards: Bayer, Boehringer Ingelheim, Genentech/Roche, Lilly, MSD, Merck Serono, Merrimack, Novartis, Peptomyc, Roche, Sanofi, Symphogen, Taiho. All other authors have declared no conflicts of interest.

144P Cyclin D1 differential activation and its prognostic impact among advanced breast cancer patients treated with trastuzumab

G. Mountzios, V. Kotoula, G-A. Koliou, K. Papadopoulou, G. Lazaridis, C. Christodoulou, G. Pentheroudakis, M. Skondra, A. Koutras, H. Linardou, E. Razis, P. Papakostas, S. Chrisafi, G. Aravantinos, I. Nicolaou, A. Goussia, K.T. Kalogeras, D.G. Pectasides, G. Fountzilas

Data Office, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece

Background: The cyclin D1-mediated molecular pathway depicts significant cross-talk with the ER/PR and HER2 pathways in patients with advanced breast cancer and these correlations may have clinical implications. We sought to determine the level of activation of the critical components of the cyclin D1-mediated pathway and to evaluate their

prognostic significance across the different molecular subtypes of advanced breast cancer.

Methods: The study population included 219 trastuzumab-treated women with advanced breast cancer who had been found to have HER2-positive disease by local testing. For all tumors, central testing for HER2 was performed and cyclin D1 (CCND1) gene amplification and mRNA and protein expression were assessed by FISH, qRT-PCR and IHC, respectively.

Results: Only 134 of the 219 patients (61.2%) were HER2-positive (HER2 gene amplification and/or 3+ HER2 protein expression). After a median follow-up of 136.0 months, 105 HER2-positive patients (78.4%) and 76 HER2-negative patients (89.4%) had died, while 80.0% of the former and 87.1% of the latter had disease progression. Median PFS was 14.0 months for HER2-positive and 8.9 months for HER2-negative patients, while median survival was 48.1 months and 35.0 months, respectively. Cyclin D1 mRNA expression was higher in patients with positive ER/PgR. Cyclin D1 (as assessed by FISH, qRT-PCR and IHC) did not reach significance in terms of PFS or survival either in the entire study population or in HER2-positive patients. In the HER2-negative subgroup, negative cyclin D1 protein expression was associated with higher risk of progression (HR = 1.66, 95% CI 1.01-2.72, Wald's p = 0.045), while in de novo metastatic patients, the risk of progression was higher for patients with non-amplified CCND1 tumors (HR = 2.00 95% CI 1.03-3.90, p = 0.041).

Conclusions: Aberrant activation of the cyclin D1-mediated pathway appears to reduce the risk of progression in HER2-negative tumors, but not in HER2-positive ones. If our results are validated by larger prospective trials, further evaluation of the cyclin D1-mediated pathway might identify prognostic and therapeutic implications in patients with advanced breast cancer.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group (HeCOG).

Funding: Roche, Hellenic Cooperative Oncoogy Group.

Disclosure: G. Mountzios, C. Christodoulou, P. Papakostas: Honoraria: Roche; Advisory role: Roche. G. Lazaridis: Honoraria: Roche. A. Koutras, G. Fountzilas: Advisory role: Roche. E. Razis: Advisory role, travel, honoraria: Roche; Research funding: Roche/Genentech. All other authors have declared no conflicts of interest.

145P Expression of TK1 and CDK9 in plasma-derived exosomes is associated with clinical response to CDK4/6 inhibitors in breast cancer

S. Crucitta[1], M. Del Re[1], A. Fontana[2], I. Bertolini[2], E. Rofi[1], C. De Angelis[2], L. Diodati[2], D. Cavallero[2], B. Salvadori[2], A. Falcone[2], R. Morganti[3], R. Danesi[1]

[1]Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [2]Medical Oncology Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, [3]Section of Statistics, University of Pisa, Pisa, Italy

Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) improve PFS in patients with hormone receptor-positive (HR+) advanced breast cancer (Finn et al., 2016). In order to better characterize the response to these agents and increase our knowledge on the pharmacogenetic profile of CDK4/6i, the aim of this study was to analyse the expression of targets relevant to the activity of CDK4/6i in plasma-derived exosomes.

Methods: Blood samples were collected from patients affected by HR+, HER2- advanced breast cancer receiving palbociclib/ribociclib in association with hormonal therapy. Three ml of plasma were taken at the beginning of treatment (baseline) and at the first clinical evaluation (after 3 months). Objective responses were defined following the RECIST criteria v.1.1. RNA from plasma-derived exosomes was extracted by the ExoRNeasy kit (Qiagen) and analysed for the expression of thymidine kinase 1 (TK1), CDK 4, 6 and 9 by digital droplet PCR (BioRad). Mann-Whitney test was applied.

Results: Thirty-four metastatic breast cancer patients were prospectively enrolled in this study. The comparison of mRNA levels of TK1, CDK4, 6 and 9 between baseline and the first clinical evaluation was available in 22 patients treated with letrozole/anastrozole + palbociclib and 22 patients given fulvestrant + palbociclib. 18 patients had newly diagnosed advanced breast cancer while 16 patients received ≥1 line of treatment. Objective responses were: 1 (2,9%) CR, 4 (11,8%) PR, 16 (47,1%) SD and 13 (38,2%) PD. The comparison of changes in the expression between TK1, CDK 4, 6 and 9 at baseline compared to first evaluation was statistically significant for TK1 (PR+SD vs. PD p = 0.009), CDK4 (PR+SD vs. PD p = 0.020), CDK6 (PR+SD vs. PD p = 0.047) and CDK9 (PR+SD vs. PD p = 0.008). The univariate analysis didn't find any significant correlation between patients clinical variable and PFS (i.e. type of hormonal treatment, the line of treatment, performance and menopausal status, visceral metastasis, bone only metastasis, number of metastasis, previous hormonal or lines of chemotherapy received).

Conclusions: Exosomal expression of CDK4, CDK6 and in particular of TK1 and CDK9 may be useful to early identify patients who are likely to respond to CDK4/6i.

Legal entity responsible for the study: Romano Danesi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

146P HER2 amplification is associated with higher tumor mutation burden in breast cancer

Y. Yin[1], W. Li[1], X. Huang[1], H. Wu[1], Y. Zhang[2], S. Cai[2], S. Zhou[3]

[1]Department of Oncology, Jiangsu Province Hospital, Nanjing, China, [2]The Medical Department, 3D Medicines Inc., Shanghai, China, [3]Department of Breast Surgery, The Third Affiliated Hospital of Kunming Medical University, Yunnan Cancer Hospital, Kunming, China

Background: ErbB family consists of four transmembrane proteins (ErbB1/EGFR/HER1, ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4) and plays a prominent role in the process of cell growth. Previous studies suggested that EGFR gene driven non-small-cell-cancer exhibited a suppressive immunity with lower tumor mutation burden (TMB) level. HER2 gene amplification ($HER2^+$) is a well-known poor prognosis predictor in breast cancer and anti-HER2 target therapy has significantly improved the clinical prognosis of $HER2^+$ patients. However, the association between HER2 gene alteration and TMB in breast cancer is still unclear.

Methods: Whole-exome sequencing data and clinical data of 366 breast tumors from The Cancer Genome Altas (TCGA) and next generation sequencing (NGS) data of 335 breast tumors from clinical dataset were analyzed to explore the association between HER2 gene alteration and TMB. TMB was defined as total number of somatic non-synonymous mutations in coding region.

Results: 20.5% (75/366) of breast tumors in TCGA cohort and 20.3% (68/335) in clinical cohort harbored HER2 amplification. HER2 amplification was significantly associated with higher TMB in both TCGA cohort (P = 0.010) and clinical cohort (P = 0.008). HER2 somatic alteration occurred in 3.7% (12/366) of breast tumors in TCGA cohort and 7.2% (24/335) in clinical cohort. HER2 somatic alteration was also associated with higher TMB level in TCGA cohort (P = 0.016), but no association was observed in clinical cohort (P = 0.339). In addition, hormonal receptor (HR) + HER2- breast tumors exhibited the lowest TMB level compared with HR+ HER2 + (P = 0.001), HR-HER2 + (P = 0.052) and triple negative breast cancer (P = 0.000). Patients with low TMB level also tended to have a better overall survival than patients with higher TMB level (median, 216.6 vs. 112.0 months; HR, 0.572; 95% CI 0.31-3.05; P = 0.067).

Conclusions: HER2 amplification is associated with higher TMB in breast cancer. These findings may assist the selection of breast cancer patients likely to benefit from immunotherapy.

Legal entity responsible for the study: Yongmei Yin and Shaoqiang Zhou.

Funding: National Natural Science Foundation of China.

Disclosure: All authors have declared no conflicts of interest.

147P Application of CRISPR/Cas9 system for identification of genes involved in the regulation of pancreatic cancer cells platinum sensitivity

V. Skripova[1], I. Serebriiskii[1], R. Kiyamova[1], I. Astsaturov[2]

[1]Biochemistry and Biotechnology, Kazan Federal University, Kazan, Russian Federation, [2]Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA, USA

Background: Pancreatic cancer (PC) is an aggressive disease with high lethality rate due to multiple resistance mechanisms. We used in vitro CRISPR/Cas9 genetic drop-out screening to identify genes involved in the regulation of PC cell line sensitivity to platinum chemotherapy drugs.

Methods: We used two sgRNA libraries: 1) enriched for genes regulating cell cycle and nuclear proteins genes (CC, 50 000 sgRNA targeting 4 716 genes); 2) genome-wide (GW, 90 000 sgRNA targeting 18 164 genes). We performed screens in MIA PaCa-2 cells expressing doxycycline-inducible Cas9. Cells were treated with established IC30 of oxaliplatin (1 uM) or cisplatin (3 uM) for 9 cell divisions (12 days). Genomic DNA was extracted and sgRNA-containing regions were amplified and barcoded by PCR for further analysis by NGS. Statistical analysis for sgRNA enrichment or depletion was performed using R package comparing cells treated with the drugs vs. vehicle in the presence of Cas9/doxycycline.

Results: We identified 755 genes which significantly changed in cisplatin or oxaliplatin-treated cells (FDR 5%, p < 0.05). Candidate genes (n = 130) were further selected if at least 2 sgRNA per gene showed more than 2-fold change vs. vehicle. Among the 130 genes, 16 were known platinum sensitivity regulators involved in the double stranded break DNA repair pathway; 11 genes were positive platinum sensitivity regulators as their inactivation reduced sensitivity; 119 genes were negative platinum sensitivity regulators as their inactivation increased sensitivity. Gene Ontology analysis of the 130 candidate genes allowed us to identify regulators of cell cycle (n = 46), DNA replication and repair (n = 43), cellular compromise (n = 15), cellular assembly and organization (n = 35) and cell morphology (n = 48). Analysis of protein-protein interaction network showed that the majority of the hits (n = 74) are directly involved into cell cycle regulation and DNA repair processes.

Conclusions: We identified 130 candidate genes potentially involved in the modulation of platinum resistance most of which are regulating the cell cycle and DNA repair which is in keeping with the known DNA damaging mechanisms of action of platinum chemotherapy.

Legal entity responsible for the study: Kazan Federal University.

Funding: The work is performed according to the Russian Government Program of Competitive Growth of Kazan Federal University.

Disclosure: All authors have declared no conflicts of interest.

148P Elevated 70kDa heat shock protein (hsp70) and autophagy levels in peripheral blood mononuclear cells (PBMCs) in women with a malignant breast mass

A.I. Athanasiou[1], T. Orfanelli[2], D. Lapolla[3], E. Andreopoulou[3], T.A. Moo[4], J. Marti[4], T. Cigler[3], A.M. Bongiovanni[1], S.S. Witkin[1]

[1]Department of OBGYN, Weill Cornell Medical College, New York, NY, USA, [2]Department of OBGYN, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, USA, [3]Department of Medical Oncology, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY, USA, [4]Department of Surgical Oncology, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY, USA

Background: PBMCs respond to adverse physiological conditions to maximize survival and to alleviate the threat. Hsp70 is produced to maintain protein function and activates an immune response. Autophagy is induced to provide sufficient nutrients in response to accelerated gene activation. We tested the hypothesis that PBMCS respond to the presence of a malignant breast mass by increasing production of hp70 and manifesting a higher level of autophagy.

Methods: In this pilot study seventy women had their breast mass evaluated by mammogram and/or breast ultrasound. A core biopsy and surgery was performed as indicated. PBMCs were isolated from peripheral blood, lysed and intracellular levels of hsp70 and p62 (a measure of autophagy) were quantitated by ELISA. Extracellular hsp70 in plasma was also measured. Differences in lab measurements between women with a diagnosis of a benign or malignant breast mass were determined. All assays were performed by personnel blinded to the clinical data.

Results: A breast malignancy was diagnosed in 42 women while 28 had a benign lesion. Plasma hsp70 levels were higher in women with a malignant lesion ($p = 0.03$). PBMCs from 46 women were available for analysis. Mean hsp70 levels were higher in PBMCs from 38 women with a malignant lesion than in 8 women with a benign breast mass ($p = 0.04$). The PBMC p62 levels were higher in women with a benign breast lesion than in those with a malignant breast mass ($p < 0.0001$). Since p62 is inversely related to the level of autophagy this indicates that autophagy is higher in PBMCs from women with a malignant breast lesion. There was no difference in the concentration of hsp70 or p62 between women with different histological types or stage of breast cancer.

Conclusions: Detection of elevated levels of hsp70 and autophagy in PBMCs, and higher plasma hsp70 levels, may differentiate between women with a malignant or benign breast lesion. Further studies on a larger sample are needed to confirm if the extent of autophagy and hsp70 induction in PBMCs may be of value in the preoperative triage of women with a breast mass.

Legal entity responsible for the study: Weill Cornell Medicine.

Funding: Weill Cornell Medicine.

Disclosure: All authors have declared no conflicts of interest.

149P Only estrogen receptor "positive" is not enough to predict the prognosis of breast cancer running head: Revisiting estrogen positive tumors in 8th AJCC staging era

J.M. Ryu[1], S.K. Lee[1], J.E. Lee[1], S.J. Nam[2], J. Yu[1], H.J. Choi[2], I. Kim[2], S.W. Kim[1]

[1]Department of Surgery, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Breast Surgery, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: Beginning in 2018, biomarkers including estrogen receptor (ER) status were incorporated in the 8th AJCC staging system. ER expression levels were not considered in these changes. We hypothesized that the levels of ER expression could affect the prognosis of breast cancer.

Methods: A retrospective review was conducted to identify all female patients with invasive breast cancer between 2003 and 2012. ER negative (group I), weakly ER-positive (group II), and strongly ER-positive (group III) were defined as Allred total scores of 0-2, 3-5, and 6-8, respectively. We examined a multigene panel, designated the BCT score, which is a newly developed prognostic model for predicting the risk of a distant metastasis.

Results: Among the 4,949 patients enrolled in this study, 1,310 (26.5%), 361 (7.3%), and 3,277 (66.2%) were categorized as group I, II, and III, respectively. Median F/U duration was 57.8 months. Compared to group III, patients in group II were younger, had larger tumors, and were also more likely to have PR-negative tumors, HER-2 amplification, high Ki-67, and high nuclear grade. Between group II and III, there was a significant difference in OS ($P = 0.0764$, .909, and 0.010, respectively). After adjusting for additional factors that may affect OS, the HR for OS showed higher in group II than in group III. The baseline median BCT score indicated that lower ER expression was associated with significantly higher BCT score ($P < 0.0001$) and significantly more likely to have high risk group ($P < 0.0001$) relative to higher levels of ER expression group.

Conclusions: ER expression levels affect the prognosis of breast cancer. The risk for patients with weakly ER-positive breast cancer should not be underestimated.

Legal entity responsible for the study: Institutional Review Board (IRB) of Samsung Medical Center in Seoul, Korea (IRB number: 2017-06-130).

Funding: This research was supported by Samsung Medical Center grant (SMO1170021) and by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI17C1142).

Disclosure: All authors have declared no conflicts of interest.

150P Adjuvant radiation therapy leads to an up-regulation of programmed death ligand 1 (PD-L1) on circulating epithelial tumor cells (CETCs) which might contribute to radioresistance in primary breast cancer patients

D. Schott[1], M. Pizon[1], U. Pachmann[1], K. Pachmann[1], M. Mäurer[2]

[1]Transfusion Center Bayreuth, Bayreuth, Germany, [2]Radio-Oncology, University Hospital of Jena, Jena, Germany

Background: Radiation therapy (RT) is an integral part of the treatment of breast carcinoma but unfortunately many patients experience local recurrence. During the inflammatory response that accompanies radiation tumor cells may develop multiple resistance mechanisms for example the up-regulation of PD-L1 on tumor cells which leads to immune evasion. Since CETCs arise from the tumor it is conceivable that under evolutionary pressure they might share some of the immune escape mechanism inherent to tumor cells. In this study we demonstrate that RT leads to a transitory adaptive up-regulation of PD-L1 expression on CETCs.

Methods: CETCs and the expression of PD-L1 and Ki-67 were analyzed from 25 patients with primary non-metastatic breast cancer using the maintrac method. The fraction of PD-L1 and Ki-67 positive CETCs were assessed at baseline, 3 and 6 weeks after start of RT and 6 weeks after end of therapy. Additionally, copy number status of PD-L1 was determined using FISH.

Results: Fractionated-dose RT leads to a significant increase in PD-L1 expression on CETCs with the highest expression level midterm of irradiation as compared to baseline (49% vs. 74%, $p < 0.01$). 6 weeks after end of RT the number of PD-L1 positive CETCs returned to baseline value. The up-regulation of PD-L1 was dose dependent. Patients who received higher total dose had significantly more PD-L1 positive CETCs as compared to patients treated with lower total dose midterm of RT (64% vs. 43, $p < 0.05$). Before start of therapy there was a correlation between the fraction of PD-L1 and Ki-67 positive CETCs ($r = 0.6$, $p < 0.01$). PD-L1 copy number gains were significantly associated with PD-L1 expression ($r = 0.6$, $P < 0.05$).

Conclusions: RT leads to an up-regulation of PD-L1 expression on CETCs, which could be a possible mechanism of acquired radioresistance. Combining immunomodulatory agents with radiation might have the potential to overcome this resistance and could improve clinical outcome in breast cancer.

Legal entity responsible for the study: Katharina Pachmann.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

151P Recurrent and metastatic carcinomas of the lacrimal gland: High frequency of ERBB2 driven disease

N. Girard[1], R.J. Corona[2], J. Chung[3], S.Z. Millis[3], L.M. Gay[4], J.A. Elvin[3], J-A. Vergilio[3], S. Ramkissoon[3], E. Severson[3], S. Daniel[3], J.K. Killian[3], S.M. Ali[3], A.B. Schrock[3], V.A. Miller[3], J.S. Ross[5]

[1]Institut du Thorax Curie Montsouris, Institut Curie, Paris, France, [2]Medical Oncology, Upstate Medical University, Syracuse, NY, USA, [3]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA, [4]Pathology, Foundation Medicine, Inc., Cambridge, MA, USA, [5]Medicine, SUNY Upstate Medical University, Syracuse, NY, USA

Background: Lacrimal gland carcinomas (LGC) are uncommon primary malignancies that have a propensity to recur locally but rarely undergo metastasis. We performed comprehensive genomic profiling (CGP) on a series of 12 LGC to uncover genomic alterations (GA) that could possibly be used to design novel routes to targeted and immunotherapies for these rare neoplasms.

Methods: From a series of 158,360 clinically advanced cancer cases, FFPE tissue samples from 12 cases of LGC underwent CGP to find base substitutions, short indels, copy number changes and gene fusions. Microsatellite instability (MSI) was determined on 114 loci andtumormutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and reported as mutations (mut) per megabase (Mb).

Results: The 12 LGC patients ranged in age from 34 to 76 years (median 61 years) and 67% of the patients were male. The LGC included 7 (58%) adenocarcinomas, 2 (17%) squamous cell carcinomas, 2 (17%) adenoid cystic carcinomas and 1 (8%) undifferentiated carcinomas. There were 1 (8%) grade 1, 8 (67%) grade 2 and 3 (25%) grade 3 tumors. 2 (17%) of LGC were stage III and 10 (83%) were stage IV at the time of sequencing. There were an average number of 4.25 GA per tumor. Three (25%) of the LGC featured ERBB2(HER2) gene amplification. One (33%) of the 3 ERBB2amplified

LGC also featured TOP2A amplification. ERBB2copy numbers in the amplified LGC ranged from 5 to 35 copies. Additional potentially targetable GA included PTENand PIK3CAboth at 25%, NF1 at 17% and RET, BRCA2, FGFR3and NTRK3all at 8% of cases. No (0%) LGC were MSI-High and the median TMB was 4.3 mut/Mb (range 0 to 12 mut/Mb) with no (0%) of LGC having >20 mut/Mb.

Conclusions: The high frequency ofERBB2amplification in clinically advanced LGC is similar to that seen in the approved indications for breast and upper gastrointestinal carcinomas raising opportunities for anti-HER2 therapies for these patients. In addition, a smaller cohort of LGC patients have opportunities for other targeted therapies with TKIs directed at RET, FGFR3 and NTRK. Given the lack of MSI-high and high TMB in LGC, the opportunities for immunotherapies for these patients appears limited.

Legal entity responsible for the study: Foundation Medicine, Inc, Cambridge, MA, USA.

Funding: Foundation Medicine Inc, Cambridge, MA, USA.

Disclosure: J. Chung, S.Z. Millis, L.M. Gay, J.A. Elvin, J-A. Vergilio, S. Ramkissoon, E. Severson, S. Daniel, J.K. Killian, S.M. Ali, A.B. Schrock, V.A. Miller: Employment: Foundation Medicine, Inc. All other authors have declared no conflicts of interest.

152P Circulating tumour DNA experience in patients with cancer of unknown primary

H. Winter[1], I. Faull[2], P. Bains[1], C. Murias[1], M. Kushnir[1], M.D. Forster[3], A. Kulkarni[4], D. Moore[3], C. Swanton[5], K. Shiu[3], H-T. Arkenau[6]

[1]Early Phase Trials, Sarah Cannon Research Institute, London, UK, [2]Business Development & Medical Affairs, Guardant Health, Barcelona, Spain, [3]Medical Oncology, University College London Cancer Institute, London, UK, [4]Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, London, UK, [5]Translational Cancer Therapeutics, The Francis Crick Institute, London, UK, [6]SCRI, Sarah Cannon Research Institute UK, London, UK

Background: Improving the outcome for patients diagnosed with Cancer of Unknown Primary (CUP) is an unmet clinical need where survival is usually less than 1 year. Molecular characterisation of the disease may have diagnostic and therapeutic implications. The circulating tumour DNA test - Guardant 360™ is designed to detect gene alterations with a range of clinical utility.

Methods: Twenty-five patients were referred to Sarah Cannon Research Institute for the Guardant 360™ test. Panel version 2.10 reports single nucleotide variants in 73 genes, gene copy number amplifications in 18 genes, fusions/rearrangements in 6 genes as well as indels in 23 genes. The panel covers all NCCN somatic mutations. Digital Sequencing™ technology essentially eliminates false positives allowing sequencing of targeted regions at very low DNA concentrations. Variants of unknown significance (VUS) were also measured. All patients were discussed at our institutional Genomics Review Board.

Results: Twenty-five patients (14 female; 11 male) were recruited from 24 August 2017 to 17 April 2018. Median age was 67 years (range 27-76). Main sites of disease were: lymph nodes (8); pelvis (8); liver (6); bone (3) and adrenal glands (2). The median turnaround time (TAT) from sample collection to report was 10 days (range 6-15). Seventeen patients (68%) had potentially actionable mutations; 4 patients had no mutations detected: 1 post resection; 2 were responding to chemotherapy; 1 was sampled prior to commencing chemotherapy. Genetic alterations detected included: BRAF V600E; KRAS; FGFR; MYC; KIT; PIK3CA and HER2. Twelve patients had ≥ 3 somatic mutations (including variants of uncertain significance (VUS)); ≥ 6 mutations were found in six of these patients.

Conclusions: ctDNA is feasible with an acceptable TAT and the identification of significant potentially actionable targets. Targetable mutations were detected including BRAF, V600E, HER2 and FGFR. Two patients now have access to BRAF and MEK inhibitors. Twelve patients had ≥ 3 mutations that is emerging as potential biomarker of response to immunotherapy. The burden of VUS and presence of actionable targets supports more research on personalised medicine in patients with CUP.

Legal entity responsible for the study: Sarah Cannon Research Institute.

Funding: Has not received any funding.

Disclosure: I. Faull: Employee: Guardant Health. All other authors have declared no conflicts of interest.

153P Reproducibility of the mRECIST criteria for the assessment of HCC treated by anti-VEGFR therapy: Impact of readers' expertise

H. Beaumont[1], S. Egels[2], N. Faye[1], C. Klifa[1], A. Iannessi[3], E. Bonnard[4], O. Lucidarme[2]

[1]R&D, Median Technologies, Valbonne, France, [2]Radiology, Groupe Hospitalier Pitié Salpetriere, Paris, France, [3]Radiology, Hopital Antoine Lacassagne, Nice, France, [4]Radiology, Hopital Pasteur, Nice, France

Background: The imaging criteria mRECIST, which was initially introduced to assess the efficacy of HCC vascular bed destruction induced by TACE, is now often used to assess subtler vascular effects induced by anti-VEGFR therapy. However, variability of mRECIST assessment has been only partially investigated. In this study, we evaluated the inter-reader variability and its sources in the mRECIST assessment of treatment response for HCC treated by anti-VEGFR drugs.

Methods: A subset of 41 advanced HCC tumors in 24 patients treated by anti-VEGFR drugs were selected from a phase I/II nalysedre study (the original study). These data were retrospectively reviewed according to mRECIST criteria by 3 mRECIST non-expert radiologists each having different levels of experience. Each liver lesion measurement was hand drawn using an electronic caliper. Results from these 3 radiologists were then compared to those extracted by an mRECIST expert at the time of the original study. The precision of measurements among the 3 non-experts and between the expert and the 3 non-experts were nalysed by assessing bias and standard deviation (SD) using the Bland-Altman method. The agreement of readers' responses was assessed using the Kappa coefficient statistic. The causes of discrepancies were nalysed.

Results: Among the 3 non-experts, SD of measurements ranged [24.9%; 36.3%] and the Kappa coefficients were moderate 0.41 [0.28; 0.55]. SD in measurements of expert versus non-experts ranged [33.2%; 41.1%] and Kappa coefficients were poor 0.20 [0.06; 0.35]. Pooling the four readers together, the rate of discrepancy at declaring either Progressive Disease (PD) or Partial Response (PR) per patient was identical at 41.7% (10/24). The main cause of discrepancy at declaring PD came from the complexity of HCC enhancement patterns and the poor definition of tumors boundaries. Discrepancies at detecting PR came from the reader variability at selecting only the viable part or the entire liver tumor.

Conclusions: When used by mRECIST non-experts to assess the subtle vascular effect induced on HCC by anti-VEGFR therapy, mRECIST appears to lack reproducibility. It is therefore important when using mRECIST to require specific training to reduce readers variability.

Legal entity responsible for the study: Median Technologies.

Funding: Has not received any funding.

Disclosure: H. Beaumont, N. Faye, C. Klifa: Employee: Median Technologies. All other authors have declared no conflicts of interest.

154P PD-L1 expression pattern in large cell neuroendocrine carcinoma of the lung

D. Damotte[1], M.C. Charpentier[2], M. Bernardi[3], E. Watkin[4], I. Goubin Versini[5], R. Lamy[6], N. Piton[7], L. Geriniere[8], F. Forest[9], R. Gervais[10], I. Monnet[11], A. Madrosyk[12], F. Guisier[13], C. Serrand[14], C. Locher Genty[15], C. Decroisette[16], J.B. Auliac[17], T. Jeanfaivre[18], H. Doubre[19], D. Arpin[20]

[1]Pathology, Université Paris Descartes, Paris, France, [2]Pathology, APHP, Paris, France, [3]Pneumology, CH d'Aix, Aix en Provence, France, [4]Pathology, Selas Cypath, Villeurbane, France, [5]Pathology, CH Rene Dubos, Pontoise, France, [6]Pneumology, CH Sud Bretagne, Lorient, France, [7]Pathology, CHU Charles Nicolle, Rouen, France, [8]Pneumology, CHLS, Lyon, France, [9]Pathology, CHU St Etienne, St Etienne, France, [10]Pneumology, Centre Francois Baclesse, Caen, France, [11]Pneumology, CH Intercommunal de Créteil, Créteil, France, [12]Medical Oncology, Institut Paoli Calmette, Marseille, France, [13]Medical Oncology, CHU Hôpitaux de Rouen-Charles Nicolle, Rouen, France, [14]Pneumology, Hôpital Nord Ouest, Villefranche Sur Saone, France, [15]Medical Oncology, Centre Hospitalier Général Meaux, Meaux, France, [16]Pneumology, Le Centre Hospitalier Annecy Genevois, Metz-Tessy, France, [17]Pneumology, CH François Quesnay, Mantes La Jolie, France, [18]Pneumology, CHU Angers, Angers, France, [19]Pneumology, Hopital Foch, Suresnes, France, [20]Pneumology, CH Nord Ouest, Villefranche Sur Saone, France

Background: Large cell neuroendocrine carcinomas of the lung (LCNECs) are rare neoplasms with limited therapeutics options. Pathological diagnostic of LCNECs is morphologically based, may be difficult and need immunohistochemical (IHC) analysis. Immune checkpoint inhibitors targeting tumoral and immune cells interaction have changed the NSCLC treatment but few data are available on LCNECs immune environment and particularly the expression of PD-L1 on both tumors (TC) and immune infiltrating (IC) cells. The objective of the present study is to determine the expression and pattern of PD-L1 staining in a cohort of LCNECs patients.

Methods: Clinical files and tumors biopsies of patients (pts) with a LCNEC diagnosed between 01.01.2014 and 31.12.2016 were retrospectively collected (GFPC 03-2017). All histological samples were centrally reviewed by six pathologists, according to the latest WHO 2015 classification. LCNEC was confirmed and PD-L1 expression was determined both in TC and IC, using the anti-PD-L1 antibody 22C3 (kit and automat Dako). PD-L1 expression was scored on TC as the percentage of PD-L1 positive cells (0 to 100%). PD-L1 expression on IC was determined as follows: IC0: positive IC representing $<$ 1% of the tumor surface; IC1 : positive IC representing $\geq$1% but $<$5 % of the tumor surface ; IC2 : positive IC representing $\geq$ 5% but $<$10% of the tumor surface ; and IC3 : positive IC representing $>$10% of the tumor surface.

Results: 86pts were initially included in the study, 28 (32%) were excluded for non-LCNEC diagnosis. Among the 58 pts with LCNEC, five (8%) had a composite LCNEC with a NSCLC component. The mean age of the population was 65 years, mainly mens (86%) and former or current heavy smokers (93%). PD-L1 was positive on TC for only 12% of the samples, while 76 % of the samples shows IC PD-L1 positive, with respectively 18 (35%) IC3, 8(14%) IC2, and 13(25%) IC1.

Conclusions: LCNEC display a particular PDL1 expression pattern, different from NSCLC and from SCLC and may suggest a potential effectiveness of therapeutic anti PD-L1 antibodies, this hypothesis have to be addressed in clinical trial.

Legal entity responsible for the study: GFPC.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

155P Inter-rater reliability of programmed death ligand 1 (PD-L1) scoring using the VENTANA PD-L1 (SP263) assay in non-small cell lung cancer (NSCLC)

G.H. Williams[1], A.G. Nicholson[2], D.R.J. Snead[3], E. Thunnissen[4], S. Lantuejoul[5], P. Cane[6], K.M. Kerr[7], M. Loddo[1], M. Scott[8], P.W. Scorer[8], C. Barker[8]

[1]Oncologica UK Ltd., Cambridge, UK, [2]Department of Histopathology, Royal Brompton and Harefield NHS Foundation Trust, National Heart and Lung Institute, Imperial College, London, UK, [3]Department of Pathology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK, [4]Department of Pathology, VU University Medical Center, Amsterdam, Netherlands, [5]Department of Biopathology, Centre Léon Bérard UNICANCER, Grenoble Alpes University, Lyon, France, [6]Department of Histopathology, Guy's and St Thomas' NHS Foundation Trust, London, UK, [7]Department of Pathology, Aberdeen University Medical School and Aberdeen Royal Infirmary, Aberdeen, UK, [8]Precision Medicine Laboratories, Precision Medicine and Genomics, IMED Biotech Unit, AstraZeneca, Cambridge, UK

Background: The VENTANA PD-L1 (SP263) assay has been developed as a companion diagnostic for anti-PD-L1 immune checkpoint inhibitors. Here we investigate assay inter-rater reliability, applied to PD-L1 scoring of tumour cells (TCs) and immune cell (IC) infiltrates in NSCLC.

Methods: Six expert European pulmonary pathologists independently scored 200 NSCLC samples stained using the VENTANA PD-L1 (SP263) assay. Archival, commercially-sourced formalin-fixed paraffin-embedded resections were selected to represent the dynamic range of PD-L1 expression. Each pathologist scored the proportion of TCs expressing PD-L1 (TM score), tumour-associated IC population as a percentage of total tumour area (PIC value), and percentage of ICs expressing PD-L1 (IC score). Scores were analysed using intra-class correlation coefficient (ICC) and patient classification using Fleiss' Kappa.

Results: Interim results were available for 3 pathologists and 180 cases. TM scoring between pathologists showed strong pair-wise correlations between individuals (R^2>0.90) with an ICC >0.95. Pair-wise and overall agreement was ≥85% for TC ≥ 1% and >93% for TC ≥ 20%, TC ≥ 25%, and TC ≥ 50%. Fleiss' Kappa showed substantial agreement for TC ≥ 1% and excellent agreement for TC ≥ 20%, TC ≥ 25%, and TC ≥ 50%. There were systematic and substantial differences in PIC values and IC scores between pathologists with poor pair-wise correlations. ICC indicated poor reliability for both IC score (0.36) and PIC values (0.044). Fleiss' Kappa showed poor agreement for IC ≥ 25% (0.183).

Conclusions: Assessment of TM score in NSCLC was highly reproducible using VENTANA PD-L1 (SP263) assay, building confidence in the accuracy of this assay in patient selection for anti-PD-L1 therapy. However, expert pathologists were unable to reproducibly assess IC score in NSCLC suggesting assessment methodology is unreliable for this tumour type and assay. This contrasts with urothelial cancer (UC) in which pathologist agreement for PIC values and IC scores was generated as part of UC VENTANA PD-L1 (SP263) IHC assay CE marking and FDA approval. This difference in pathology of the different tumour types requires further investigation.

Editorial acknowledgement: Editorial assistance, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Kaveri Sidhu, PhD, of Cactus Communications (Mumbai, India).

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: A.G. Nicholson: Consultant: Abbvie and Oncologica; Educational grant: Pfizer. E. Thunnissen: Corporate sponsored research: Oncologica; Honorarium: Roche Ventana, Histogenex; Advisory boards: Roche. P. Cane: Speaker fees: Pfizer, Roche; Fees for interview: AstraZeneca. K.M. Kerr: Advisory boards: Roche, AstraZeneca, BMS, MSD, Pfizer, Merck Serono, Roche Diagnostics. M. Scott, P.W. Scorer, C. Barker: Employment: AstraZeneca; Stockholder: AstraZeneca. All other authors have declared no conflicts of interest.

156P Relationship between ring-type dedicated breast PET and tumor-infiltrating lymphocytes in early breast cancer

S. Sasada[1], N. Shiroma[2], E. Suzuki[1], S. Sueoka[1], N. Goda[1], K. Kajitani[1], A. Emi[1], N. Masumoto[1], T. Kadoya[1], R. Haruta[1], T. Kataoka[1], K. Arihiro[2], M. Okada[1]

[1]Breast Surgery, Hiroshima University Hospital, Hiroshima, Japan, [2]Pathology, Hiroshima University Hospital, Hiroshima, Japan

Background: FDG uptake on PET is related to biological parameters and prognosis in breast cancer. The predominance of stromal tumor-infiltrating lymphocytes (TILs) in breast cancer is a biomarker for prognosis and pathological complete response after neoadjuvant chemotherapy. However, whether whole-body PET (WBPET) and dedicated breast PET (DbPET) can reflect the amount of TILs is unclear. This study investigated the relationship between TILs and maximum standardized uptake value (SUVmax) in WBPET and ring-type DbPET.

Methods: A total of 125 invasive breast cancers underwent WBPET and ring-type DbPET and resected specimens were pathologically assessed. The impact on SUVmax on the tumor biological parameters and TILs was retrospectively evaluated. SUVmax was classified as high and low relative to the median values (WBPET-SUVmax: 2.2 and DbPET-SUVmax: 6.0).

Results: SUVmax correlated with tumor size, nuclear grade, Ki-67 labeling index, and TILs in both WBPET and DbPET (all $P < 0.001$). The cut-off values of tumor size, Ki-67 labeling index, and TILs predicting high SUVmax were 20 mm, 20%, and 20%, respectively. In multivariate analysis, the predictive factors for high SUVmax were tumor size and Ki-67 labeling index for WBPET and tumor size and TILs for DbPET. A high SUVmax in DbPET was related to high numbers of TIL tumors after propensity score matching analysis; however, WBPET was not ($P = 0.007$ and $P = 0.624$, respectively).

Table: 156P Logistic regression analysis for predicting high SUVmax tumor on WBPET and DbPET

Factors	Univariate analysis		Multivariate analysis	
	Odds ratio	P	Odds ratio	P
<WBPET>				
Histology_IC-NST	6.71	0.003	1.35	0.655
T2–3	6.18	< 0.001	13.0	< 0.001
Nuclear grade 3	6.48	< 0.001	2.70	0.071
ER positive	0.39	0.285	0.32	0.404
HER2 positive	1.62	0.486	0.31	0.211
Ki-67 labeling index ≥ 20%	3.03	0.005	3.68	0.020
TILs ≥ 20%	1.99	0.084	2.29	0.144
<DbPET>				
Histology_IC-NST	3.18	0.003	1.68	0.393
T2–3	4.38	< 0.001	4.81	< 0.001
Nuclear grade 3	4.43	< 0.001	1.82	0.238
ER positive	0.98	0.929	0.70	0.758
HER2 positive	0.97	0.857	0.53	0.450
Ki-67 labeling index ≥ 20%	3.54	0.001	1.39	0.513
TILs ≥ 20%	7.50	< 0.001	6.98	< 0.001

Conclusions: Unlike WBPET, the SUVmax in ring-type DbPET can represent the immune microenvironment after adjusting for tumor biological factors. DbPET might be a biomarker of pathological response to neoadjuvant chemotherapy and prognosis.

Legal entity responsible for the study: Shinsuke Sasada.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

157P Short-term responders of non-small cell lung cancer patients to EGFR tyrosine kinase inhibitors display high prevalence of TP53 mutations and primary resistance mechanisms

Y. Fan[1], Y. Xu[1], X. Tong[2], J. Yan[3], X. Wu[2], Y.W. Shao[2]

[1]Key Laboratory on Diagnosis and Treatment Technology on Thoracic Cancer, Zhejiang Cancer Hospital, Hangzhou, China, [2]Geneseeq Technology Inc, Translational Medicine Research Institute, Ontario, ON, Canada, [3]Medical Department, Nanjing Geneseeq Technology Inc, Nanjing, China

Background: Non-small cell lung cancer (NSCLC) with activating EGFR mutations in exon 19 and 21 usually responds to EGFR tyrosine kinase inhibitors (TKI), but sometimes the responses can only be maintained for a few months. The underlying mechanisms of such short responses have not been fully elucidated.

Methods: The genomic profiles of sixteen short-term responders (SR) that had progression free survival (PFS) of less than 6 months on the first-generation EGFR TKI were interrogated, in comparison to twelve long-term responders (LR) that had more than 24 months of PFS. All patients were diagnosed with advanced lung adenocarcinoma and harbored EGFR 19del or L855R mutation before treatment. Paired tumor samples collected before treatment and after relapse (or at the last follow-up) were subjected to next-generation sequencing of 416 cancer-relevant genes.

Results: SR patients were significantly younger than LR patients ($p < 0.001$). 88% of SR patients have TP53 variations compared to 13% in LR patients ($p < 0.001$), and 37.5% SR patients carry EGFR amplification, which is much higher than LR patients (8%). In

addition, 12 SR patients (75%) were identified with other potential primary resistance mechanisms in pre-treatment samples, including PTEN loss, BIM deletion polymorphism, amplifications of EGFR, ERBB2, MET, HRAS and AKT2. Comparatively, only 3 LR patients (25%) were detected with EGFR or AKT1 amplification that could possibly exert resistance.

Conclusions: The diversified pre-existing resistance mechanisms in SR patients revealed the complexity of defining treatment strategies even for EGFR sensitive mutations.

Legal entity responsible for the study: Fan Yun.

Funding: Has not received any funding.

Disclosure: X. Tong, X. Wu, Y.W. Shao: Employee: Geneseeq Technology Inc. J. Yan: Employee: Nanjing Geneseeq Technology Inc. All other authors have declared no conflicts of interest.

158P Assessment of cfDNA in patients with metastatic colorectal cancer treated with cetuximab monotherapy

L. Angus[1], E.J. van Helden[2], S.C. van Es[3], E. Boon[4], C.M.L. van Herpen[4], D.J. de Groot[3], E.G.E. de Vries[3], C.W. Menke-van der Houven van Oordt[2], S. Sleijfer[1], H.M. Verheul[2], M.P.H.M. Jansen[1]

[1]Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [2]Medical Oncology, Cancer Center Amsterdam, VU University Medical Center, Amsterdam, Netherlands, [3]Medical Oncology, University Medical Center Groningen, Groningen, Netherlands, [4]Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands

Background: Third line systemic treatment for patients with RAS wild-type metastatic colorectal cancer (mCRC) includes anti-EGFR monoclonal antibodies such as cetuximab. Here, we examined cell-free DNA (cfDNA) to gain insight into mechanisms underlying primary and acquired resistance in patients with mCRC receiving cetuximab.

Methods: 34 patients with RAS wild-type mCRC (KRAS and NRAS exon 2-4) received biweekly cetuximab monotherapy (500mg/m^2). cfDNA was isolated from plasma obtained at baseline, after 2 weeks of treatment and at disease progression (PD). ± 20 ng DNA was used for targeted next generation sequencing using the Oncomine™ Colon cfDNA Assay (14 genes, 242 hotspots). Mutation analysis of tumor tissue was performed according standard of care, at least including KRAS and NRAS. Outcome was defined as clinical benefit (CB; PD $>$ 8 weeks, n = 21) versus no CB (NCB; PD $\leq$ 8 weeks, n = 13).

Results: Baseline cfDNA concentration correlated with the sum of diameters on CT ($p = 0.043$) and metabolically active tumor volume on [^{18}F]FDG PET ($p < 0.001$). In 6/13 (46%) of patients with NCB, mutations in KRAS (n = 3) and BRAF (n = 3) were detected in baseline cfDNA. Two KRAS mutations were detected cfDNA, but not in tissue. All BRAF mutations in cfDNA were present in tissue, one BRAF mutation in tissue was not detected in cfDNA. In one patient (5%) with CB a polyclonal KRAS mutation was detected in cfDNA, which was not found in tumor tissue. In 9 patients with CB, cfDNA concentrations were measured and decreased from a median of 45 ng/mL plasma (range 13 – 784 ng/mL) at baseline to 19 ng/mL after 2 weeks of treatment (range 9 – 42 ng/mL) ($p = 0.008$). In patients with CB an enrichment of mutations in genes associated with resistance (KRAS, NRAS and BRAF) was found in 12/17 (70%) at PD compared to baseline. Moreover, in 8/17 (47%) of these patients EGFR mutations in codons coding for the epitope binding site of cetuximab emerged and in 9/17 patients (53%) multiple mutations in the same gene occurred suggesting the presence of multiple subclones.

Conclusions: A subset of mCRC patients with NCB could be identified based on baseline cfDNA mutations in genes associated with cetuximab resistance. By using cfDNA we can optimize patient selection for cetuximab therapy and elucidate mechanisms of resistance.

Clinical trial identification: NCT02117466.

Legal entity responsible for the study: Erasmus University Medical Center.

Funding: Dutch Cancer Society.

Disclosure: L. Angus: Advisory board: Merck B.V. All other authors have declared no conflicts of interest.

159P Quantifying circulating cell-free DNA as clinical biomarker

M. Romain[1], Z.A.A. Dache[1], A. Otandault[1], R. Tanos[1], B. Pastor[1], C. Sanchez[1], J. Azzi[1], G. Tousch[1], S. Azan[1], C. Mollevi[1], S. Thezenas[2], P. Blache[1], A.R. Thierry[1]

[1]Integrated Research for Personalized Medicine in Digestive Oncology, ICM Regional Cancer Institute of Montpellier, Montpellier, France, [2]Biostatistics, ICM Regional Cancer Institute of Montpellier, Montpellier, France

Background: This is the first comprehensive study on the effect of pre-analytical and demographic parameters that could be a source of variability in the quantification of nuclear and mitochondrial circulating DNA (NcirDNA and McirDNA, respectively).

Methods: We set an optimal calculation of the simultaneous quantification of circulating nuclear and mitochondrial genome copy number based on a clinically validated q-PCR method. We report data from a total of 217 subjects, 99 healthy individuals and 118 metastatic colorectal cancer (mCRC) patients. We also investigated the influence of blood storage and collection time on cirDNA concentration from healthy volunteers.

Results: Approximately 26,650 and 3,000-fold more mitochondrial than nuclear genome copies were found in healthy subjects and mCRC patients, respectively. Neither NcirDNA nor McirDNA plasma concentrations depended on age in the healthy and mCRC cohorts taken as a whole. Remarkably however NcirDNA levels were significantly higher in healthy men as compared to women (n = 99, P = 0.010). Men and women did not differ in McirDNA levels. NcirDNA levels increased slightly with age in healthy women, suggesting a potential influence of menopause. A highly significant statistical difference was found between mCRC patients and healthy individuals for NcirDNA ($P < 0.0001$) and McirDNA ($P = 0.019$). In healthy volunteers, there was a higher level of NcirDNA at 9:00 AM with no food intake.

Conclusions: Nuclear and mitochondrial cirDNA levels do not vary in the same way with regards to blood stability, collection time, and pathological status. Our observations, of pre-analytical, analytical and demographical factors, could serve to set standard operating procedures and to transpose cirDNA analysis into clinical practice in oncology. Guidelines on the preanalytical conditions will be also presented from data from this study and a complete review of the literature.

Legal entity responsible for the study: Alain R. Thierry.

Funding: SIRIC Montpellier Cancer Grant INCa_Inserm_DGOS_12553.

Disclosure: All authors have declared no conflicts of interest.

160P Gene expression profile (GEP) and survival among patients with advanced ovarian cancer

E. Høgdall[1], C.K. Høgdall[2], P-T. Vo[3], W. Zhou[3], L. Huang[3], M. Marton[3], S.M. Keefe[3], M. Busch-Sørensen[3], S.M. Sørensen[4], J. Georgsen[5], E. Mejlgaard[5], L. Nedergaard[6], T. Steiniche[5]

[1]Department of Pathology, Herlev Hospital, Copenhagen, Denmark, [2]Gynecology and Obstetrics, Rigshospitalet, Copenhagen, Denmark, [3]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [4]Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [5]Pathology, Aarhus University Hospital, Aarhus, Denmark, [6]Pathology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Background: The ability of T-cell–inflamed GEP (Ayers et al. J Clin Inv. 2017) to predict clinical outcome in ovarian cancer is not fully understood. A retrospective observational study was conducted to evaluate the prognostic value of GEP and its association with programmed death ligand 1 (PD-L1) expression in patients with advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer (OvCa).

Methods: Patients diagnosed as FIGO stages II-IV OvCa from 2004 to 2012 at Aarhus University Hospital and Rigshospitalet, Copenhagen, Denmark, were included. Patients were considered platinum sensitive if treatment-free interval [TFI] was $\geq$6 months. PD-L1 was assayed using the 22C3 antibody, and positivity was defined as $\geq$ 1 stained tumor or immune cells per 100 tumor cells. T-cell–inflamed GEP score was defined as low ($<$ –0.318), intermediate (–0.318 to $<$ –0.162), or high ($\geq$ –0.162). The log-rank test and Cox proportional hazards model were used for survival analyses, adjusting for age, stage, histology, residual tumor, surgery type, performance status, platinum sensitivity, and PD-L1 expression status.

Results: Median age of the 376 patients was 63 years (range, 26-86); 9%, 70%, and 20% were FIGO stages II, III, and IV disease, respectively. Of these patients, 80% had type II histologic type, and 76% were platinum sensitive; 49% had a GEP score of low, 16% had intermediate, and 35% had high. Baseline characteristics between GEP groups were similar; PD-L1 and GEP scores were correlated (Spearman r, 0.71; Kendall tau r, 0.57). Median overall survival (OS) was 43 months (95% CI, 38-49) in all patients and was similar for patients with low GEP (41 months) and intermediate GEP (40 months), compared with patients with high GEP (52 months). There was no significant association between GEP status (intermediate/low vs high) and OS among all patients (adjusted hazard ratio, 1.00 [95% CI, 0.72-1.38]), by platinum sensitivity or by PD-L1 expression status.

Conclusions: GEP correlated with PD-L1 expression in patients with advanced OvCa, but OS was not significantly different between GEP categories.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Matthew Grzywacz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: P-T. Vo, W. Zhou: Employee and stockholder: Merck. L. Huang: Employee: Merck. M. Marton: Employee and stockholder: Merck; Stockholder of Biogen, CVS Health, Gilead Sciences, Intuitive Surgical, Johnson and Johnson, Pfizer and United Health Group. S.M. Keefe: Employment: Merck. M. Busch-Sørensen: Employment and stockholder: Merck. T. Steiniche: Research funding: Merck; Travel expenses: Merck. All other authors have declared no conflicts of interest.

161P Predicting survival benefit of capecitabine plus cisplatin in patients with metastatic gastric cancer patients using quantitative proteomics

D. Yan[1], M-H. Ryu[2], E. An[1], Y.S. Park[3], H. Na[2], J. Ma[2], Y. Tian[1], F. Cecchi[1], T. Hembrough[1], Y-K. Kang[2]

[1]R&D, NantOmics, LLC, Rockville, MD, USA, [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Capecitabine plus cisplatin (XP) is a standard treatment for metastatic gastric cancer (mGC). Capecitabine activation requires the enzymes uridine-cytidine kinase 2 (UCK2) and orotate phosphoribosyl transferase (OPRT). We previously used mass spectrometry to quantitate UCK2 in tumor samples from 5-FU-treated patients with stage II/III colorectal cancer; UCK2 protein expression > 319 amol/ug of tumor protein was associated with improved survival. Here, we assessed whether these biomarkers would predict survival among mGC patients treated with XP.

Methods: Archived tumor samples from patients with mGC were microdissected and solubilized for mass spectrometric quantitation of 16 protein biomarkers. Kaplan-Meier survival curves were compared using a log-rank test. Multivariate Cox models of survival included clinical covariates and protein biomarkers.

Results: mGC tumor samples from 116 XP-treated patients were analyzed (males: 64%; median age: 55 years). All samples expressed OPRT protein (range: 202 – 1719 amol/ug), and 114 of 116 expressed UCK2 (range: 119 – 933 amol/ug). Patients with UCK2 expression above the pre-defined cutoff of 319 amol/μg (n = 30) had longer time to progression (TTP) (HR: 0.60; p = 0.020) than patients below the cutoff. Results for overall survival (OS) were similar (HR: 0.59; p = 0.015). OPRT protein expression > 790 amol/ug (n = 24) was associated with longer TTP (HR: 0.58; p = 0.019) and longer OS (HR: 0.60; p = 0.029). In multivariate analysis, UCK2 and OPRT remained independent predictors of survival after adjustment for age, gender, ECOG performance status, metastatic sites, and other clinical covariates.

Conclusions: We validated a pre-defined UCK2 expression cutoff and discovered an OPRT cutoff in an XP-treated mGC patient cohort. Patients with tumor expression of UCK2 and OPRT proteins above quantified thresholds survived longer than patients with lower expression. Mass spectrometric quantitation of these common tumor proteins at diagnosis may improve patient selection for XP. Studies to validate these and other chemopredictive biomarkers are ongoing.

Legal entity responsible for the study: NantOmics.

Funding: NantOmics.

Disclosure: D. Yan, E. An, Y. Tian, F. Cecchi, T. Hembrough: Employment: NantOmics. All other authors have declared no conflicts of interest.

162P Detection of microsatellite instability (MSI) with a novel set of 7 Idylla biomarkers on colorectal cancer samples in a multi-center study

B. De Craene[1], J. Van de Velde[1], E. Bellon[1], M. Gazin[1], E. Rondelez[1], L. Vandenbroeck[1], T. Vanhoey[1], N. Elsen[1], L.C. Melchior[2], G.L. Willemoe[2], E. Watkin[3], N. Arens[4], C. Altmann[4], K. Decanniere[1], E. Sablon[1], G.G. Maertens[1]

[1]Create, Biocartis NV, Mechelen, Belgium, [2]Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [3]Pathology, Selas Cypath, Villeurbane, France, [4]Pathology, Molekularpathologie Trier (MPT), Trier, Germany

Background: Detection of microsatellite instability (MSI) is recommended for all patients with colorectal cancer (CRC). Current clinical reference methods are immunohistochemical (IHC) staining of mismatch repair (MMR) proteins and/or PCR analysis of frequently mutated repetitive regions of DNA. The prototype Idylla™ MSI Test has been developed using a new set of short homopolymers located in the ACVR2A, BTBD7, DIDO1, MRE11, RYR3, SEC31A & SULF2 genes. This marker set allows probe-based detection with great specificity in a simplified workflow compared to current methods.

Methods: Repeat length with this set of biomarkers was determined on 333 formalin-fixed and paraffin-embedded (FFPE) CRC samples using Idylla™ MSI Test prototype cartridges, which allow a fully automated workflow including sample preparation, DNA amplification and automated repeat length calling. A neural network based algorithm was built on a large cohort of reference/patients samples (n > 3000) obtained from different clinical sites (n > 10) and different ethnic groups (n = 5). Three-hundred fourteen samples were characterized by means of the Promega MSI analysis system and 272 samples by means of MMR protein IHC staining. Approximately 30% of the samples included in the study were previously characterized to be MSI-H by either one of these methods.

Results: Concordance analysis revealed an overall agreement of 98.7% (96.7%-99.5% 95% CI) with Promega and 97.6% (94.8%-98.9% 95% CI) with IHC analysis. Analysis of consecutive sections of 182 samples with the three methodologies revealed a higher number of invalid results for Promega (3.8%) and IHC (13.2%) compared to the prototype Idylla™ MSI Test (2.2%).

Conclusions: This study verified the robustness of the prototype Idylla™ MSI Test including novel MSI biomarkers to discriminate MSI-H from MSS status on a large and diverse set of CRC samples. The study was conducted in multiple centers demonstrating the possibility of a rapid and fully automated analysis for MSI testing close to the point of need. The prototype Idylla™ MSI Test provided accurate and reliable results within 150 minutes from just one FFPE tumor section (no normal reference sample required).

Legal entity responsible for the study: Biocartis NV.

Funding: Biocartis NV.

Disclosure: B. De Craene, J. Van de Velde, E. Bellon, M. Gazin, E. Rondelez, L. Vandenbroeck, T. Vanhoey, N. Elsen, K. Decanniere, E. Sablon, G.G. Maertens: Employee: Biocartis NV. E. Watkin: Advisory board, speaker's fees: MSD. All other authors have declared no conflicts of interest.

163P Accurate measurement of tumor mutation burden in liquid biopsy (bTMB) using a 500 gene panel

T. Jiang, S. Zhang, A. Jager, S. Katz, J. Lococo, P. Le, B. Andrian, C. Zhao, D. Baker, T. Pawlowski, S. Bilke

Clinical Genomics, Illumina, Inc, San Diego, CA, USA

Background: Tumor mutation burden (TMB) has been shown as a new predictive biomarker for immune checkpoint inhibitor in various cancer types. It is typically measured by processing tumor tissue with substantial input which limits its clinical utility in patients with metastatic or unresectable disease. Meanwhile, there is increasing interest in circulating tumor DNA (ctDNA) that act as a noninvasive real-time biomarker for cancer patients. Therefore, here we develop a new next generation sequencing assay that can identify patients with sufficient tumor fraction in plasma and accurately measures the TMB from blood (bTMB).

Methods: Cell free DNA (cfDNA) was extracted from plasma across four original tissue types by different tumor stages. CfDNA Assay was performed with unique molecular identifier (UMI) , sequenced on the Illumina® platforms and analyzed using an internal pipeline for variants down to 0.4%. By integrating the fragment size distribution and the clonal mutation frequency, we were able to estimate the tumor fraction per plasma sample. A bTMB score was also derived using all the coding variants on a 1.3M panel across 500+ genes. The matched TMB score is derived by the same assay using FFPE tissue.

Results: Our assay has generated sufficient results from 1-4ml plasma for variant detection down to 0.4%. Across four tissue types by various cancer stages, our assay and pipeline yield a variant concordance of 70% between cfDNA and FFPE. Majority of mutations only found in plasma may be associated with clonal hematopoiesis in genes such as TET2, DMBT3A and etc. By combining fragment size distribution and driver mutation frequency, we were able to estimate tumor fraction in plasma. Tumor fraction in plasma is significantly associated with tumor stage that >50% of metastatic cancers and > 25% early stage lung cancers contain high tumor fraction. In patients with at least 1% tumor content, there is high correlation between bTMB measured by plasma and TMB measured by FFPE (R^2=0.92).

Conclusions: We have developed a ctDNA assay to detect somatic variants and determine bTMB with high accuracy and precision with input as low as 10 ng of cfDNA. Our assay yield accurate measurement of TMB compared to tissue biopsy.

Legal entity responsible for the study: Illumina, Inc.

Funding: Has not received any funding.

Disclosure: T. Jiang, S. Zhang, A. Jager, S. Katz, J. Lococo, P. Le, B. Andrian, C. Zhao, D. Baker, T. Pawlowski, S. Bilke: Employee and shareholder: Illumina, Inc.

164P Circulating tumor DNA and RNA as an exploratory biomarker to evaluate GT0918 in a phase I/II clinical trial in mCRPC patients

M. Tan[1], S. Zhang[1], Z. Zhao[2], A. Wang[3], D. Cheung[3], P. Du[4], J. Yu[3], S. Jia[3], C. Guo[5], Y. Tong[6], K. Zhou[7]

[1]Translational Medicine, Predicine, Inc, Hayward, CA, USA, [2]Research & Development, Predicine, Inc, Hayward, CA, USA, [3]Clinical Research, Predicine, Inc, Hayward, CA, USA, [4]Bioinformatics, Predicine, Inc, Hayward, CA, USA, [5]Research & Development, Suzhou Kintor Pharmaceuticals, Inc., Suzhou, China, [6]Business Development, Suzhou Kintor Pharmaceuticals, Inc., Suzhou, China, [7]Medical Oncology, Suzhou Kintor Pharmaceuticals, Inc., Suzhou, China

Background: Metastatic castration resistant prostate cancer (mCRPC) is a complex disease with distinct molecular features in relation to genomic instability and selective treatment pressure. Circulating tumor DNA and RNA fragments (ctDNA & ctRNA) found in blood offers the potential of disease diagnosis, monitoring and resistance mechanism interrogation by detecting genomic alterations from tumor. We explored ctDNA & ctRNA-based biomarkers from patient blood to assess their associations with clinical response of GT0918, a potent AR antagonist, in a Phase 1/2 clincal study in mCRPC who progressed after abiraterone or enzalutamide and docetaxol, or cannot tolerate either or both therapies.

Methods: We performed a retrospective analysis of blood samples from mCRPC patients collected at baseline, on- and after study during the trial. A highly sensitive ctDNA- & ctRNA-based NGS assay was developed to detect mutation, copy number gain, fusion and splicing variants. Statistical analyses were performed in R.

Results: 20 blood samples were collected at multiple time points from 8 patients. CtDNA-based variants are detected in all of patients. The most frequent mutations are TP53 (55.0%) and AR (30.0%). Combined mutation rates in PTEN-PI3K-AKT and DNA damage repair pathways (BRCA1/BRCA2/ATM) are both 35.0%. Importantly, AR hotspot mutations (W742C, T878A, and S889G) and amplifications are detected in 4 subjects. AR splicing variants (AR-V3, AR-V7) were found in 3 patients by ctRNA assay. Interestingly, one AR-V3+ patient became negative during the treatment accompanied by a decrease of other molecular biomarkers including prostate-specific SPOP mutation and cfDNA yield. In contrast, another patient who was AR-V3+ at C4D1, had constantly high AR amplification and increasing cfDNA yields over treatment. Last, as a hallmark of prostate cancer, TMPRSS2-ERG fusion was also detected in 2 patients.

Conclusions: This is a preliminary study to explore genomic alterations in mCRPC in response to GT0918 treatment. As a non-invasive assay, the ctDNA & ctRNA-based assay was highly sensitive and provided useful molecular insights for monitoring treatment effect and deciphering drug sensitivity & resistance mechanisms.

Clinical trial identification: NCT02826772.

Legal entity responsible for the study: Suzhou Kintor Pharmaceuticals, Inc.

Funding: Suzhou Kintor Pharmaceuticals, Inc.

Disclosure: M. Tan, S. Zhang, Z. Zhao, A. Wang, D. Cheung, P. Du, J. Yu: Sockholder: Predicine, Inc. S. Jia: CEO and stockholder: Predicine, Inc. C. Guo, Y. Tong, K. Zhou: Stockholder: Suzhou Kintor Pharmaceutials, Inc.

165P The frequency of primary cilia, CD8+ tumor infiltrating lymphocytes and PD-1 expression in renal cell carcinoma of clear-cell type

J. Dvorak[1], B. Rosova[2], A. Filipova[3], D. Hadzi Nikolov[4], L. Dusek[5], A. Rozsypalova[1], J. Proks[1], I. Richter[6], B. Melichar[7], T. Buchler[1], R. Zachoval[8], R. Matej[2]

[1]Oncology, Thomayer University Hospital, Prague, Czech Republic, [2]Pathology, Thomayer University Hospital, Prague, Czech Republic, [3]Radiobiology, Faculty of Military Health Sciences in Hradec Kralove, University of Defense in Brno, Hradec Kralove, Czech Republic, [4]Pathology, Regional Hospital, Kolin, Czech Republic, [5]Institute of Biostatistic and Analyses, Masaryk University Brno, Brno, Czech Republic, [6]Oncology, Regional Hospital, Liberec, Czech Republic, [7]Oncology, University Hospital Olomouc, Olomouc, Czech Republic, [8]Urology, Thomayer University Hospital, Prague, Czech Republic

Background: Primary cilium (PC) is considered to represent a functional homologue of the immune synapse due to morphological and functional similarities in architecture. Both microtubule structures, i.e. primary cilia of cancer-associated fibroblasts and immune synapses between cytotoxic CD8+ tumor infiltrating lymphocytes (TILs) and antigen-presenting or cancer cells, are regularly found in varying amounts in the microenvironment of solid tumors. These could, in fact, represent two sides of the same coin. However, so far both parameters have not been evaluated simultaneously within the same group of patients.

Methods: The presence of PC in cells, programmed cell death protein-1 receptor (PD-1) expression and the frequency of intraepithelial CD8+ TILs was retrospectively evaluated in tumor tissue blocks of the resected specimens of the kidney in 104 patients with renal cell carcinoma of clear-cell type, 71 males and 33 females, with a median age of 64 years (range 38-82 years). Twenty-eight patients had stage I, 15 stage II, 31 stage III and 30 patients had stage IV tumor. Grade was as follows: grade 1 in 27 patients, grade 2 in 15 patients, grade 3 in 31 patient and grade IV in 30 patients.

Results: The median frequency of PC was 0.0028% (0-0,0465%). The frequency of intraepithelial CD8+ TILs was negative in 1 patient, <25% in 63, 26-50% in 29 and 26-50% in 11, respectively. The expression of PD-1 was <5% in 52 patients, 5-25% in 34 patients, 26-50% in 13 patients, 51-75% in 4 patients and 75% in 1 patient. During the follow-up, recurrence occurred in 42 patients and 43 patients died. Median PFS was 44% (95% CI: 34-67%) and median OS was 98% (95% CI: 84-117%).

Conclusions: The present study provides the first data on the potential association frequency of PC, PD-1 and CD8+ TILs in patients with renal cancer.

Legal entity responsible for the study: MH CZ-DRO (TH, 0064190).

Funding: MH CZ-DRO (TH, 0064190) and Ministry of Defense of the Czech Republic - long-term organization development plan Medical Aspects of Weapons of Mass Destruction of the Faculty of Military Health Sciences, University of Defense.

Disclosure: All authors have declared no conflicts of interest.

166P Association of MMR protein expression and MMR gene mutations in Chinese colorectal cancer patients

S. Wang[1], S. Zhang[2], Z. Zeng[3], Y. Ou[4], M. Han[5], J. Guo[6], D. Chen[7], X. Dong[7], J. Hu[8], G. Chirn[9], W. Shi[9], M. Yao[8]

[1]Department of Pathology, School of Basic Medical Sciences, Southern Medical University, Guangzhou, China, [2]Colorectal-Anal Surgery Department, First Affiliated Hospital of Guangxi Medical University, Nanning, China, [3]Medical Oncology, First Affiliated Hospital of Guangxi Medical University, Nanning, China, [4]Department of General Surgery, The First Affiliated Hospital of Clinical Medicine of Guangdong Pharmaceutical University, Guangzhou, China, [5]Chest Surgery, Jincheng General Hospital, Jincheng, China, [6]Medical Oncology, Xingtai People's Hospital, Xingtai, China, [7]Department of Pathology, OrigiMed, Shanghai, China, [8]Medical Department, OrigiMed, Shanghai, China, [9]Department of Bioinformatics, OrigiMed, Shanghai, China

Background: DNA mismatch repair (MMR) deficiency is a genetic abnormality that has important clinical implications related to therapeutic option, familial cancer risk assessment, and checkpoint inhibitor response. It occurs in approximately 15% of colorectal cancers (CRC). Associations between MMR protein expression, microsatellite instability (MSI), and gene mutations remain under investigation.

Methods: Thirty-one FFPE samples from primary CRC patients (pts) were collected for immunohistochemistry (IHC) assay of MMR proteins, PCR-based MSI assay if available and NGS-based panel assay. Genomic alterations including single base substitutions, short and long insertions/deletions, copy number variations, and gene rearrangement were assessed. MSI status were predicted based from NGS data.

Results: Out of 31 sample, 12 CRC were identified as MMR deficiency (dMMR) by IHC including 5 males and 7 females (median age: 66 years), and 19 samples as MMR proficiency (pMMR) including 13 males and 6 females (Median age: 53 years). Eight of the 12 dMMR samples (67%) harbored at least one MMR gene mutations predicted as loss of functions,[u1] including nonsense mutations or truncations in MSH2, MSH6 or MLH1. No MMR gene mutation was detected in any of the 19 pMMR samples (p value<0.001). In addition, 2 BRAF and 6 KRAS hotspot mutations were detected in dMMR samples, and 8 KRAS, 1 BRAF and 1 NRAS mutations in pMMR samples. NGS panel based MSI algorithm successfully predicted the MSI status of all the 31 samples with 100% concordance with the MMR results. Neither copy number variation nor rearrangement was detected. Five pMMR samples were identified as microsatellite stability (MSS) by PCR, 6 dMMR were high level of microsatellite instability (MSI-H), and the rest were failed due to DNA contents.

Table: 166P

	n	MMR gene mutations (n, %)	KRAS mutations (n, %)	NRAS mutations (n, %)	BRAF mutations (n, %)	NGS MSI-H status (n, %)
dMMR (IHC)	12	8 (66.7%)	6 (50%)	0 (0%)	2 (16.7%)	12 (100%)
pMMR (IHC)	19	0 (0%)	8 (42.1%)	1 (5.2%)	1 (5.2%)	0 (0%)

Conclusions: We observed a significant association between MMR deficiency and MMR gene mutations from deep DNA sequencing. The results suggested that CRC pts with MMR gene mutations could be more likely to have dMMR status.

Legal entity responsible for the study: OrigiMed.

Funding: Has not received any funding.

Disclosure: D. Chen, X. Dong, J. Hu, G. Chirn, W. Shi, M. Yao: Employee: OrigiMed. All other authors have declared no conflicts of interest.

167P Somatic and germline mutations of Chinese gastric cancer patients

Y. Wang[1], W. Gu[2], Y. Zhang[3], K. Li[4], Z. Niu[5], Y. Zheng[6], Q. Cui[6], A. Wang[7], H. Chen[8], W. Shi[8], K. Wang[9], M. Yao[6]

[1]Digestion Department, Shanxi Provincial Cancer Hospital, Taiyuan, China, [2]Medical Oncology, The People's Hospital of Nan Hai, Nanhai, China, [3]Department of Chemotherapy, Chaozhou People's Hospital, Chaozhou, China, [4]Oncology Department, Guangdong Second Provixcial General Hospital, Guangzhou, China, [5]Gastrointestinal Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China, [6]Medical Department, OrigiMed, Shanghai, China, [7]Department of Clinical Analysis, OrigiMed, Shanghai, China, [8]Department of Bioinformatics, OrigiMed, Shanghai, China, [9]OrigiMed, Shulan (Hangzhou) Hospital, Shanghai, China

Background: Gastric cancer is a high incidence malignancy in China, but the disease is often diagnosed at an advanced stage with limited therapeutic options and poor prognosis. Unfortunately, limited progress of target and immune therapy has achieved in gastric cancer due to tumor heterogeneity and the lack of effective biomarkers in the clinical. Thus the precise understanding of gastric cancer genomic profiling is urgent for exploring clinical strategy of this malignancy.

Methods: Formalin Fixed Paraffin Embedded (FFPE) samples of 110 Chinese gastric cancer patients were collected for next-generation sequencing (NGS)-based 450 genes

panel assay. Genomic alterations including single base substitution, short and long insertions/deletions, copy number variations, gene fusions and rearrangement were assessed. Microsatellite instability (MSI) status and tumor mutational burden (TMB) were also acquired by NGS algorithm.

Results: There were 71 males (64.6%) and 39 females (35.4%) diagnosed as gastric cancer with a median age of 62 years old. The most frequent genomic alterations in Chinese gastric cancer patients were revealed as TP53 (66.4%), ARID1A (18.2%), LRP1B (17.3%), CDH1 (15.5%), CCNE1 (14.5%), FAT4 (13.6%), ERBB2 (11.8%), SMAD4 (10.9%), KMT2D (10.9%), RNF43 (10.9%), TGFBR2 (10.0%), KRAS (10.0%), APC (10.0%). Some actionable aberrantly activated mutations were identified in genes such as FGFR1/2/3 (10.0%), BRCA1/2 (6.4%) and PI3K/mTOR pathway including FBXW7, MTOR, PIK3CA, PTEN, STK11, TSC1 and TSC2 (20.0%). In total, 39.1% of patients carried one or more actionable genomic alterations, which indicated the potential clinical benefits of targeted therapies for them. The percentage of patients with germline mutations was 9.1% in current cohort. These germline mutation genes were mainly in homologous recombination (HR) pathways such as BRCA1/2, ATM and BARD1.

Conclusions: In this study, 39.1% of Chinese gastric cancer patients carried actionable genomic alterations which could potentially guide and influence personalized treatments. About 9.1% patients harbored germline mutations mainly in HR pathway. All these genomic identifications in Chinese gastric cancer cohort may provide useful information on drug discovery and biomarker exploration.

Legal entity responsible for the study: OrigiMed.

Funding: Has not received any funding.

Disclosure: Y. Zheng, Q. Cui, A. Wang, H. Chen, W. Shi, K. Wang, M. Yao: Employee: OrigiMed. All other authors have declared no conflicts of interest.

168P Validation of the MammaTyper® pathological complete response (pCR)-score as a predictor for response after neoadjuvant chemotherapy (NACT) in patients with early breast cancer (BC)

P.A. Fasching[1], M. Laible[2], K.E. Weber[3], R.M. Wirtz[4], C. Denkert[5], K. Schlombs[6], S. Schmatloch[7], O. Camara[8], H.J. Lück[9], J. Huober[10], T. Karn[11], M.T. van Mackelenbergh[12], F. Marme[13], V. Müller[14], C. Schem[15], E. Stickeler[16], U. Sahin[17], S. Loibl[18], M. Untch[19]

[1]Department of Gynecology and Obstetrics, Universitätsklinik Erlangen, Erlangen, Germany, [2]Gynäkologie, BioNTech Diagnostics GmbH, Mainz, Germany, [3]Statistic, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [4]STRATIFYER Molecular Pathology GmbH, Cologne, Germany, [5]Institute of Pathology, Charite Berlin Mitte, Berlin, Germany, [6]BioNTech Diagnostics GmbH, Mainz, Germany, [7]Brustzentrum, Elisabeth Krankenhaus, Kassel, Germany, [8]Brustzentrum, Hufeland Klinikum, Bad Langensalza, Germany, [9]Gynäkologie, Gynäkologisch-Onkologische Praxis, Hannover, Germany, [10]Gynecol. & Obstetrics, Universitaetsfrauenklinik Ulm, Ulm, Germany, [11]Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Frankfurt(Johannes-Wolfgang Goethe Institute), Frankfurt am Main, Germany, [12]Clinic for Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Kiel, Germany, [13]Gynecologic Oncology, Nationales Zentrum für Tumorerkrankungen (NCT), Heidelberg, Germany, [14]Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany, [15]Mammazentrum Hamburg, Hospital Jerusalem, Hamburg, Germany, [16]Gynäkologie und Geburtsmedizin, Uniklinik RWTH, Aachen, Germany, [17]Management, BioNTech AG, Mainz, Germany, [18]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [19]Gynäkologie und Geburtshilfe, Helios Klinikum Berlin-Buch, Berlin, Germany

Background: Prediction of the response to NACT in early BC patients (pts) can lead to improved treatment decisions. The MammaTyper® test can be used to predict the probability of pCR after NACT by integrating accurate and reproducible assessment of ERBB2, ESR1, PGR and MKI67 mRNA into a standardized prediction model (Varga et al. Breast Cancer Research 2017).

Methods: Total RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor samples of pts with cT1-2 BC enrolled in in the single arm phase II TECHNO trial (Untch et al. JCO 2011) and the randomised phase III PREPARE trial (Untch et al. Ann Oncol. 2011). MammaTyper®, a molecular in vitro diagnostic RT-qPCR test, was used to assess the expression of ERBB2 (HER2), ESR1 (ER), PGR (PR) and MKI67 (Ki67) genes from which a predefined continuous score was calculated. The study aimed to validate the MammaTyper® pCR-score for predicting pCR (ypT0 ypN0) after NACT in BC. Pts were classifed into a low or high score group according to a predefined cutoff: score $\leq$41 predicts a low probability of pCR; score $\geq$42 predicts a high pCR rate.

Results: A total of 324 pts with available FFPE samples and MammaTyper® measurements were analyzed. The MammaTyper® score was significantly associated with an increased pCR rate (AUC=0.805, $p < 0.001$). Similarly, pts with high MammaTyper® score (N = 159) had more frequently pCR compared to pts with low score (N = 165) (30.2% vs 3.0%, respectively; OR = 13.84 [95%CI 5.34-35.86], $p < 0.001$). In addition, the MammaTyper® pCR-score remained significantly predicitve when adjusted for age, nodal status, tumor grade and treatment (OR = 10.90 [95%CI 3.38-35.16], $p < 0.001$). Within the non-pCR subgroup, pts with low score had a significantly longer disease-free (DFS) and overall (OS) survival compared to pts with high score (DFS HR = 1.59, 95%-CI 1.04-2.44, $p = 0.032$; OS HR = 2.85, 95%-CI 1.62-5.00, $p < 0.001$).

Conclusions: The MammaTyper® pCR-score predicts pCR after NACT and seems to improve prognosis additionally to clinical predictors in pts with early BC. Its utility with regard to conventional ER, PR, Ki67 and HER2 has to be analyzed in future studies.

Legal entity responsible for the study: GBG Forschungs GmbH and BioNTech Diagnostics GmbH, Mainz.

Funding: BioNTech Diagnostics GmbH, Mainz, Germany.

Disclosure: P.A. Fasching: Personal fees: Celgene, during the conduct of the study; Grants and personal fees: Novartis; Personal fees: Pfizer, Roche, Teva, outside the submitted work. M. Laible: Personal fees: BioNTech Diagnostics GmbH, outside the submitted work; Employee: BioNTech Diagnostics GmbH); Patent WO 2015/024942 pending, new patent application pending. K.E. Weber: Grants and non-financial support: BioNTech Diagnostics GmbH, Mainz, Germany, during the conduct of the study; Patent EndoPredict issued. C. Denkert: Personal fees: Teva, Novartis, Pfizer, Roche, Amgen, MSD Oncology; Other: Sividon Diagnostics, outside the submitted work. K. Schlombs: Personal fees: BioNTech Diagnostics GmbH, outside the submitted work; Patent WO 2015/024942 pending; New patent application pending. F. Marme: Personal fees; Roche, AstraZeneca, Pfizer, Tesaro, Novartis, Amgen, PharmaMar, GenomicHealth, CureVac, Eisai, outside the submitted work. S. Loibl: Grants: AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, Teva, Vifor during the conduct of the study and outside the submitted work. All other authors have declared no conflicts of interest.

169P Selective induction of PD-L1 expression in plasma-derived exosomes by gemcitabine-nab-paclitaxel vs. FOLFIRINOX in pancreas cancer

E. Rofi[1], M. Del Re[2], C. Vivaldi[3], S. Crucitta[4], E. Arrigoni[1], G. Pasquini[5], S. Catanese[5], I. Pecora[5], G. Musettini[6], E. Vasile[7], A. Falcone[8], R. Danesi[9]

[1]Department of Clinical and Experimental Medicine, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy, [2]Clinical and Experimental Medicine, Università degli Studi di Pisa, Pisa, Italy, [3]Oncology, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy, [4]Clinical and Experimental Medicine, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy, [5]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, [6]Department of Translational Research and New Technologies in Medicine and Surgery, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy, [7]Medical Oncology Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, [8]Oncology, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy, [9]Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Background: Pancreatic ductal adenocarcinoma (PDAC) is considered a poorly immunogenic tumor and treatment with immune checkpoint inhibitors lacks efficacy in this disease. Recently, the use of immune checkpoint inhibitors with radiation therapy in PDAC has demonstrated synergistic activity. The aim of this study was to evaluate the effect of FOLFIRINOX and GEMnPAC on PD-L1 expression in plasma-derived exosomes of PDAC patients.

Methods: Four ml of plasma were obtained at baseline (before initiation of chemotherapy) and at the time of first radiological evaluation (3 months) from patients undergoing first-line FOLFIRINOX or GEMnPAC chemotherapy. Exosomes and RNA extraction from plasma were performed using the exoRNeasy kit (Qiagen®, Valencia, CA, USA); PD-L1 expression was evaluated by digital droplet PCR (Bio-Rad®, Hercules, CA, USA).

Results: A total of 22 pancreatic cancer patients were enrolled in this study; 15 (68.2%) were treated with GEMnPAC and 7 (31.9%) with FOLFIRINOX. In the GEMnPAC group one patient had a partial response (RP), 11 patients had stabilization of disease (SD) and 3 progressed (PD). In the FOLFIRINOX group there were 1 RP, 5 SD and 1 PD. Eleven patients treated with GEMnPAC had a significant increase of PD-L1 expression at 3 months vs. baseline. Indeed, the mean PD-L1 copies/ml was 90 at baseline and 170 at 3 months ($p = 0.02$). On the contrary, in the FOLFIRINOX group, PD-L1 levels were increased in 3 patients and remained stable/decreased in 4 subjects; the mean baseline copies/ml were 70 vs. 80 at 3 months ($p = 0.4$). The selective induction of PD-L1 expression was independent from tumor response.

Conclusions: These pilot data suggest that, due to its ability to increase PD-L1 expression, GEMnPAC regimen may be used as induction-treatment for immunotherapy in pancreatic cancer, either sequentially or concomitantly.

Legal entity responsible for the study: Romano Danesi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

170P Ecological diversity indices as measurements of tumor heterogeneity correlates with clinical outcomes in late stage small cell lung cancer (SCLC)

S. Yaung[1], L. Xi[1], C. Woestmann[2], S. McNamara[2], B. Hinzmann[3], S. Froehler[2], N. Tikoo[4], C. Ju[4], A. Balasubramanyam[4], H-P. Adams[5], M. Thomas[6], F. Lasitschka[6], M. Meister[6], M. Schneider[6], F.J.F. Herth[6], T. Muley[6], B. Wehnl[7], J. Palma[8], X.M. Ma[8]

[1]Bioinformatics, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [2]Bioinformatics, Roche Sequencing Solutions, Inc., Potsdam, Germany, [3]Assay Development, Roche Sequencing Solutions, Inc., Potsdam, Germany, [4]Biostatistics, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [5]Biostatistics, Roche Sequencing Solutions, Inc., Potsdam, Germany, [6]Translational Research Unit, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [7]Clinical Operations, Roche Diagnostics GmbH, Penzberg, Germany, [8]Medical Scientific Affairs, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA

Background: Tumor heterogeneity is difficult to characterize with tissue biopsies in late stage cancers, in which primary and metastatic tumors may have diverged in their mutational profiles. Assessing the diversity of mutations detected by sequencing circulating tumor DNA (ctDNA) from liquid biopsies can quantify the genetic complexity of tumors shedding DNA into the blood.

Methods: In a prospective, observational study, we obtained pre-treatment plasma samples from 56 subjects with Stage IV small cell lung cancer (SCLC) treated with first-line chemo or chemoradiation therapies. Plasma samples were analyzed with the AVENIO ctDNA Surveillance Kit, a targeted next-generation sequencing panel of 198 kilobases. We applied the Shannon and Simpson diversity indices by considering each somatic variant as a species and the number of detected duplex molecules with that mutation as the abundance of that species. Samples were ranked as low tumor heterogeneity if their plasma variant diversity score was below the first tertile of the cohort.

Results: Stage IV SCLC subjects with low tumor heterogeneity evaluated by the Shannon diversity had shorter overall survival (hazard ratio = 1.8; 95% CI 1-3.3; log-rank p = 0.034; median survival difference = 4.5 months). Furthermore, subjects with low tumor heterogeneity evaluated by the Gini-Simpson or inverse Simpson diversity index had shorter overall survival (hazard ratio = 1.8; 95% CI 1-3.3; log-rank p = 0.033; median survival difference = 4.5 months).

Conclusions: The molecular barcoding scheme in the AVENIO kit allows for each strand of the original double-stranded ctDNA molecule to be tracked. From this reconstructed profile of circulating duplex molecules harboring tumor variants, we derived a tumor heterogeneity measure based on the Shannon and Simpson diversity indices commonly used in ecology. We found that late stage SCLC subjects with low tumor heterogeneity had shorter overall survival, suggesting that highly heterogeneous SCLC tumors may respond better to chemotherapy or radiation. Studies to further validate these findings are ongoing.

Legal entity responsible for the study: Roche Sequencing Solutions, Inc.

Funding: Roche Sequencing Solutions, Inc.

Disclosure: S. Yaung, L. Xi, C. Woestmann, S. McNamara, B. Hinzmann, S. Froehler, C. Ju, A. Balasubramanyam, H-P. Adams, B. Wehnl, X.M. Ma: Employment: Roche. N. Tikoo: Employment: Roche; Stock ownership: BeiGene, Celgene, Denali Therapeutics, Exelixis, Gilead Sciences. F. Lasitschka: Consulting role: Roche; Research funding: Boehringer Ingelheim International GmbH. M. Meister, M. Schneider: Research funding: Roche. F.J.F. Herth: Stock ownership: Roche, Lilly, Novartis; Consulting role: Novartis. T. Muley: Royalty sharing agreement: Roche; Research funding: Roche. J. Palma: Employment: Roche; Stock ownership: Exact Sciences, Clovis Oncology, Johnson & Johnson, Roche. All other authors have declared no conflicts of interest.

171P MET exon 14 splicing mutation and its correlation with clinocopathological features in subjects with non-small cell lung cancer

D. Katalinic[1], I. Aleric[2], A. Vcev[1]

[1]Department of Clinical Medicine, Faculty of Medicine and Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia, [2]Department of Internal Medicine, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Background: Driver mutations are genomic alterations important for tumor initiation and growth. They are found in genes that control cellular proliferation and long-term survival. Mesenchymal-to-epithelial transition (MET) exon 14 splicing mutation occurs in about 3% of cases of non-small cell lung cancer (NSCLC). It has been recognized as an important biomarker to predict response to MET tyrosine-kinase inhibitor therapy. The aim of this study was to investigate possible connection among the MET exon 14 mutations and genomic as well as clinicopathological features in patients with NSCLC.

Methods: The study was performed among 270 patients (58% males and 42% females; mean age of 57.14 ± 16.48 years) with histologically confirmed diagnosis of NSCLC. The distribution of MET exon 14 splicing mutation was detected using the quantitative real-time polymerase chain reaction restriction fragment length polymorphism assay. RNA was extracted from formalin-fixed paraffin-embedded samples. The study was conducted according to the Declaration of Helsinki, the protocol was reviewed and approved by the institutional Ethics committee and all patients provided written informed consent.

Results: MET exon 14 splicing mutation was detected in 9 patients (3.4%). It was found in 7 adenocarcinomas (18.9%) and in 2 squamous cell carcinomas (5.4%). Most adenocarcinomas occurred in females and non-smokers. Squamous cell carcinoma predominantly occurred in male smoking patients. All subjects with MET exon 14 splicing mutation had earlier pathology stage of disease (IA, IB, IIA, IIB) (31%) and older age (>75 years) (43%). Overall survival (OS) of these patients were statistically longer than in patients with KRAS and EGFR mutations (2.2 vs. 1.3 months and 2.4 vs. 1.8 months).

Conclusions: We found that MET exon 14 splicing mutation occurs at a frequency of 3.4%, in older age, and mostly in early stage of NSCLC. OS of patients harboring MET exon 14 splicing mutation has lasted longer than in patients harboring KRAS and EGFR mutations. Patients with MET exon 14 splicing mutation may respond well to MET tyrosine-kinase inhibitor therapy. Further studies are needed to confirm our results.

Legal entity responsible for the study: Cancer Genomic Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

172P Cancer stem cell markers in pancreatic ductal adenocarcinoma

F. Aksoy[1], E. Kaya[1], U. Egeli[2], H.Z. Dundar[1], P. Tasar[1], S.A. Aksoy[2], Y. Ozen[1], B. Tunca[2], G. Cecener[2], O. Yerci[3]

[1]General Surgery, Uludag University Medical Faculty, Bursa, Turkey, [2]Medical Biology, Uludag University Medical Faculty, Bursa, Turkey, [3]Pathology, Uludag University Medical Faculty, Bursa, Turkey

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer deaths in both men and women world-wide. Despite development of scientific, PC remains lethal disease. Recently, cancer stem cells (CSC) of pancreatic cancer that often are resistant to treatment have been identified. Present study aims to investigate the existence and prognostic value of CSC markers in PDAC patients.

Methods: 52 hematoxylin and eosin-stained slides cut from formalin-fixed, paraffin-embedded (FFPE) PDAC tissues were evaluated by a pathologist, and the areas of the slide representing tumor and normal were identified. The samples were analyzed for the presence and differential expression of LGR5, CD44 and CD133 using RT2 Profiler PCR Array Data Analysis (http://www.sabiosciences.com/pcr/arrayanalysis.php) to compare the PCR array analysis results and the characteristics of the tumors and cases.

Results: Of the 52 patients, 29 were men and 23 were women, with an average age of 63 years (range, 26-91 years). All patients underwent pancreaticoduodenectomy (Whipple prosedure). The median size of tumors was 2.3 cm (range, 0.5-6.0 cm). Lymphatic, vascular, and perineural invasions were observed in the tumors of 23 (44.2%), 9 (17.3%), and 5 (9.6%) patients, with 2 patients showing concurrent lymphatic, vascular, and perineural invasions. Tumors were classified as stage IA (n = 4), stage IB (n = 11), stage IIA (n = 7), stage IIB (n = 10), and stage III (n = 22). All surgically resected specimens showed negative (R0) resection margin status. The CD44 was not significantly expressed in eCC tumors compared to normal tissue. LGR5 and CD133 expression level was significantly higher in tumors than in corresponding normal tissues (4.5 fold, P = 0.034; 3.7 fold P = 0.045, respectively). Increased CD133 expression was associated with ampulla vateri tumor localization (P < 0.001). Over expression of LGR5 and CD133 were associated with short overall survival.

Conclusions: Here, we report that CD133 and LGR5 may acts as a functional CSC in the aggressivite of PDAC. Our results suggest that these molecules may serve as a candidate prognostic biomarker and target for new therapies in PDAC.

Legal entity responsible for the study: Ekrem Kaya.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

173P Tumor mutation burden assessment on FFPE samples using a targeted next-generation sequencing assay

R. Chaudhary[1], D. Cyanam[2], V. Mittal[3], W. Tom[1], J. Au-Young[1], C. Allen[4], S. Sadis[3], F. Hyland[1]

[1]Clinical Next-Generation Sequencing, Thermo Fisher Scientific, South San Francisco, CA, USA, [2]Clinical Next-Generation Sequencing, Thermo Fisher Scientific, Santa Clara, MI, USA, [3]Clinical Next-Generation Sequencing, Thermo Fisher Scientific, Ann Arbor, MI, USA, [4]Clinical Next-Generation Sequencing, Thermo Fisher Scientific, Liverpool, UK

Background: Tumor mutation burden (TMB) predicts durable benefit from immune checkpoint blockade in several cancer types. We demonstrate the ability of a targeted panel with fast turn-around time and low input needs to estimate TMB from research samples.

Methods: We developed a single sample analysis workflow to estimate mutation burden (TMB; nonsynonymous mutations/Mb) from FFPE and fresh frozen tumor research samples. The assay utilizes a PCR-based targeted panel that covers 409 genes and 1.7 Mb of genomic regions. The workflow requires only 10 ng of input DNA and

enables a 2.5-day turn-around time from sample to the final report. Sequencing is performed on high throughput semiconductor sequencing platform to achieve sufficient depth (~500x coverage) and accuracy. The workflow is tumor sample only, with no matched normal sample required; germ-line variants, along with background noise, are removed through filters based on population databases. The assay is research use only, not for diagnostic procedures.

Results: A comparison with whole exome sequencing (WES) on 12 FFPE tumors, where WES was performed on tumors and their matched normal using Agilent's exome enrichment kit (~150x coverage for tumor; ~100x coverage for normal) on illumina platform and our assay ran on tumors only, showed high correlation (r2=0.83) between TMB estimates by our assay with that from WES. To assess reproducibility, we compared raw somatic mutations/Mb in library replicates for a cohort of 21 FFPE research samples (19 CRC, 2 Melanoma) and observed high correlation (r2=0.97). Our pipeline identifies mutation signatures consistent with specific mechanisms such as UV and tobacco damage, as well as substitutions from FFPE processing.

Conclusions: A simple workflow has been developed on the Ion Torrent sequencing platform with an AmpliSeq panel to estimate TMB from FFPE and fresh frozen tumor research samples. This solution will advance research in immuno-oncology.

Legal entity responsible for the study: Thermo Fisher Scientific.

Funding: Thermo Fisher Scientific.

Disclosure: R. Chaudhary, D. Cyanam, V. Mittal, W. Tom, J. Au-Young, C. Allen, S. Sadis, F. Hyland: Employment: Thermo Fisher Scientific.

174P Microsatellite instability-high (MSI-H) colorectal cancers with elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) signature represent a target population for immune checkpoint and DNA damaging therapies

K.T. Tan[1], P-N. Yu[1], S-J. Chen[1], Y-T. Liu[1], S-C. Chang[2], M-H. Chen[3]

[1]Medical Informatics, ACT Genomics, Co., Ltd, Taipei, Taiwan, [2]Department of Surgery, Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan, [3]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan

Background: Elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) is a different type of genomic instability in colon cancer (CRC) in contrast to mono-, and dinucleotide based instability microsatellite instability (MSI). In this study, we performed comprehensive genomic profiling (CGP) of CRC patients with different EMAST and MSI status to understand their genomic structure, which may help match them with relevant therapies.

Methods: 99 formalin-fixed, paraffin-embedded (FFPE) CRC tissues consisting of four subtypes based on their EMAST and MSI status, namely (1) EMAST+ and MSI-high (MSI-H), (2) EMAST+ and microsatellite-stable (MSS), (3) EMAST- and MSI-H, and (4) EMATS- and MSS, were subjected to next-generation sequencing (NGS) with a 440-gene panel to identify mutations and copy number variants (CNVs). Tumor mutational burden (TMB) was determined using mutations detected on exonic regions sequenced while CNV index was calculated to infer genome instability.

Results: In line with previous studies, the prevalence of TP53 (17.6%; n = 3) and APC (23.5%; n = 4) mutations was much lower whereas BRAF V600 mutation (41.2%; n = 7) was much higher in the subtype (1) CRCs which had both MSI-H and EMAST signatures. Interestingly, these dual positive tumors had a significant higher TMB and lower CNV index than other subtypes (TMB: (1) vs (2), (3) and (4); 54 vs 19, 25; and 16; $p < 0.0001$, CNV index: (1) vs (2), (3), and (4); 3.9 vs 13.7, 9.9, and 17.8; $p < 0.0114$, 0.006, and 0.0003), suggesting there are more likely to benefit from immune checkpoint inhibitors. Notably, ATM and ARID1A genes mutated in a mutually exclusive way in up to 13/17 (76.5%) of tumors with MSI-H and EMAST signatures, which may predict treatment benefit from the PARP inhibitors.

Conclusions: MSI-H and EMAST+ CRCs show distinctive genomic features that give them the potential opportunity for checkpoint inhibitors in combination with PARP inhibitors.

Legal entity responsible for the study: ACT Genomics.

Funding: Has not received any funding.

Disclosure: K.T. Tan, S-J. Chen: Shareholder: ACT Genomics. All other authors have declared no conflicts of interest.

175P Levels of circulating fibroblast growth factor (FGF) 23 and prognosis of cancer patients with bone metastasis

A.B. Mansinho[1], A.R. Ferreira[1], S. Casimiro[2], I. Alho[2], I. Vendrell[1], A.L. Costa[1], R.T.D. Sousa[1], C.D. Abreu[1], C. Pulido[3], D. Macedo[1], T. Pacheco[1], L. Correia[4], L. Costa[1]

[1]Medical Oncology, Centro Hospitalar Lisboa Norte - Hospital Sta Maria (HSM-CHLN), Lisbon, Portugal, [2]LCosta Lab, Instituto de Medicina Molecular, Lisbon, Portugal, [3]Oncology, Hospital da Luz, Lisbon, Portugal, [4]Pathology, Centro Hospitalar Lisboa Norte - Hospital Sta Maria (HSM-CHLN), Lisbon, Portugal

Background: The FGF signaling network plays a key role in tumorigenesis and is recognized as a potential therapeutic target. FGF23 is predominately expressed in bone osteocytes and can act as an autocrine, paracrine and/or endocrine growth factor in cancer. In this study, we aimed to assess the role of circulating FGF23 levels in the prognosis of cancer patients with bone metastases.

Methods: This study included a cohort of 112 patients with cancer (63% breast;16% prostate) and metastatic bone disease treated with bone targeting agents (BTA), in which serum baseline FGF23 was quantified by ELISA and further dichotomized in two groups ($FGF23^{high}$ and $FGF23^{low}$). Cut-off was defined by mean + one standard deviation. The association of FGF23 with overall survival (OS) and with time to skeletal related events (TTSRE) was investigated. Time to event outcomes was calculated using the Kaplan-Meier method and tested using univariate/multivariate Cox regression models controlling for established prognostic factors across patients with solid tumors and bone metastases: extra-bone involvement, urinary N-terminal telopeptide (uNTX), presence of bone fractures, and calcemia.

Results: Mean FGF23 was 38.16 ± 26.15 pg/mL (interquartile range [IQR] 19.77-50.72). 16.8% of patients were classified as $FGF23^{high}$ (n = 19). Baseline characteristics were balanced between groups, except for the median uNTX level, which was higher in the $FGF23^{high}$ group (824.30 vs 118.02 nmol BCE/mmol creatinine, $p = 0.040$). Median time from beginning of BTA was similar between groups (1.28 vs 1.10 months, $p = 0.161$). After a median follow-up of 26.0 months (IQR 13.0-47.0), median OS was 34.4 months in the $FGF23^{low}$ group and 12.2 months in the $FGF23^{high}$ group (multivariate HR 0.18, 95% CI 0.07 – 0.44, $p = 0.001$; univariate $p = 0.001$). As a continuous variable, FGF23 at baseline kept its prognostic association ($p = 0.001$). Patients with $FGF23^{low}$ status at baseline had a longer TTSRE (13.0 vs 2.0 months, $p = 0.04$).

Conclusions: In this exploratory cohort, patients in the $FGF23^{low}$ group had a longer OS and TTSRE. Further studies are warranted to define its role as a prognostic biomarker and as a potential predictor of response to drugs targeting the FGF axis.

Editorial acknowledgement: Joana Cavaco Silva - Medical Writer (Medical Oncology Department - Hospital de Santa Maria - Centro Hospitalar Lisboa Norte).

Legal entity responsible for the study: Instituto de Medicina Molecular.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

176P Clinical significance of RCAS1 and CD3 expression in non-small cell lung cancers in immunotherapy era

N.G. Tsoukalas[1], E. Aravantinou[1], K. Tsapakidis[1], C. Giaginis[2], M. Tolia[3], I. Binas[1], P. Baxevanos[1], M. Galanopoulos[1], M. Kiakou[1], M. Tsiatas, I. Kostakis[2], C. Nikolaou[1], I. Litos[1], M. Liontos[4], E. Tsiambas[1], I. Gioulbasanis[1], I. Sfiniadakis[2], A. Karameris[1], G. Kyrgias[3], S. Theocharis[2]

[1]Oncology, Veterans Hospital (NIMTS), Athens, Greece, [2]First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Athens, Greece, [3]Department of Radiotherapy-Radiation Oncology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece, [4]Oncology Unit, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece

Background: Lung cancer is the first cause of cancer related deaths. RCAS1 (Receptor-binding Cancer Antigen expressed on SiSo cells) is a protein that is expressed in different types of cancer and seems to be involved in the process of the tumour cells' escape from the immune system surveillance (immunoescape). CD3 (cluster of differentiation CD3), is an antigen that is part of the T cell receptor (TCR) complex on a mature T lymphocyte. Tumor infiltrating lymphocytes (TILs) have been correlated with patients' survival in several neoplasms.

Methods: The aim of this study was to evaluate the clinical importance of RCAS1 and CD3 expression in non-small cell lung cancer (NSCLC). Tissue microarrays of tumor specimens from 112 patients with newly diagnosed NSCLC were constructed. The sections were stained with monoclonal antibodies against RCAS1, Ki-67 and CD3 using immunohistochemistry and they were studied through classical pathological evaluation and computerized image analysis. Correlations among RCAS1, Ki-67 and CD3 expression, clinicopathological variables and survival were analyzed. In all cases p-value ≤ 0.05 was considered significant.

Results: 112 patients were included in this study with mean age 63.6 years old and 83% were males. RCAS1 expression was higher in grade III tumors comparing with grade I ($p = 0.004$) and grade II ($p = 0.005$) regardless of the histological type and in adenocarcinomas with lymphovascular invasion ($p = 0.014$). A positive correlation between RCAS1 and Ki-67 levels was observed ($p = 0.002$). There was an inverse correlation of overall survival with RCAS1 and Ki-67 levels and patients with higher expression of RCAS1 or Ki-67 had a significantly shorter survival. Also, an inverse correlation between RCAS1 expression and the percentage of CD3(+) TILs was found. Finally, a positive correlation between the percentage of CD3(+) TILs and the patients' overall survival ($p = 0.094$) was observed.

Conclusions: CD3 expression was negative correlated with RCAS1 and positive with overall survival in patients with NSCLC. RCAS1 could be a useful biomarker indicating tumor aggressiveness and immunoescape of cancer cells. Further studies needed to elucidate the possible role of RCAS1 as a biomarker in immunooncology era.

Editorial acknowledgement: Hellenic Society of Medical Oncology (HeSMO).

Legal entity responsible for the study: Medical School, National and Kapodistrian University of Athens.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

177P Comparative study of EGFR mutations detected in malignant pleural effusion, plasma and tumor tissue in patients with adenocarcinoma of the lung

S. Wang[1], H. Chen[1], J. Zhao[1], J. Zhong[1], J. Wang[2]

[1]Thoracic Medical Oncology, Peking University Cancer Hospital, Beijing, China, [2]Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: The utility of malignant pleural effusion (MPE) as a source of tissue for determining EGFRmutations to guide EGFR TKI therapy in advanced adenocarcinoma of the lung (LUAD) remains unclear. This study compared MPE, plasma and tumor as sources of tissue for EFGR mutational analysis in LUAD patients.

Methods: MPE samples were collected from 295 LUAD patients. Matched tissue and plasma samples were available for 92 patients, and 248 patients had plasma samples. EGFRexon 19-deletion and exon 21-L858R mutation were detected. The concordance of EGFR mutation status in MPE, tissue, and plasma were evaluated, and the predictive value of EGFRmutations in MPE with respect to efficacy of EGFR-TKI was investigated.

Results: The EGFRmutation rate in MPE samples was 39.3% (116/295). The concordance between MPEs and tissues was 87.1% (Kappa=0.712); the sensitivity and specificity of EGFRmutation in MPEs according to tissues was 71.4% and 96.5%,, respectively. 219 patients received EGFR-TKI, and the objective response rate of patients with EGFRmutations was similar for patients with EGFRmutation either in MPE, tissues or plasma (57.6 % vs 56.0 % vs 47.4%, $p = 0.51$). Similar results were found in progression free survival (8.9 months vs 9.0 months vs 7.7 months, $p = 0.077$ and overall survival (29.8 months vs 25.9 months vs 25.3 months, $p = 0.33$).

Conclusions: MPE is a reliable surrogate for tumor tissue for identifying EGFRmutations. MPE could offer reference of EGFRmutation to EGFR-TKIs treatment decision for advanced LUAD patients even when tissue and plasma were available.

Legal entity responsible for the study: Peking University Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

178P XmaI-RRBS DNA methylation screening resolves breast cancer epigenetic heterogeneity

A.S. Tanas[1], T. Kekeeva[1], V.O. Sigin[1], E.B. Kuznetsova[1], E. Poddubskaya[2], I. Trotsenko[3], D.V. Zaletaev[4], V.V. Strelnikov[1]

[1]Epigenetics, Research Centre for Medical Genetics, Moscow, Russian Federation, [2]Surgery, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [3]Oncology, Moscow Clinical Research Center, Moscow, Russian Federation, [4]Laboratory of Medical Genetics, Sechenov First Moscow State Medical University, Moscow, Russian Federation

Background: Breast cancer (BC) heterogeneity calls for molecular subtyping that would assist in personalized treatment. An advantage of DNA methylation markers is that their detection in tumors is not compromised by the presence of normal tissues. With a perspective to develop methylation-based BC diagnostic markers, we have performed a genome-wide DNA methylation profiling of a collection of breast tissues and cell lines.

Methods: XmaI-RRBS method was used to profile DNA methylation of 170 BC samples obtained before chemotherapy, six BC cell lines, and 10 normal breast autopsy specimens. Unsupervised hierarchical cluster analysis was used to discern intrinsic DNA methylation BC subtypes; clustering uncertainty was assessed with pvclust R package using bootstrap permutation approach.

Results: We have identified 10 epigenetic BC subtypes different in the DNA methylation profiles. Of these, BC cell lines constitute a separate extremely high methylated subtype clustering far from any tissues assessed. In turn, BC tissues are classified into two major epigenetic subtypes, high- and low-methylated at the promoter regions of genes. We identified 114 genes that distinguish between high- and low-methylated BC subtypes. Noteworthy are the genes of adenylate cyclases ADCY4, ADCY8 and adenylate cyclase stimulants ADORA2B, ADCYAP1; proteins of cell adhesion and extracellular matrix (CDH4, NRXN2, MXRA5, COMP, integrins A8 & A11, ADAM19; potassium channels (KCNH8, KCNJ2, KCNG1, KCNK10, KCNK17, ATP1A3). More than a third among differentially methylated are homeobox genes (VAX2, TLX3, GSX1, IRX1, FOXC2, FOXE3, NKX6-2, VSX1, SOX21, POU4F1) and genes encoding proteins involved in early development and morphogenesis (ZIC1, SPOCK2, DPYSL3, ATOH1, ITGA8). Expectedly, there is no statistically significant difference in methylation of the classical tumor suppressor genes between epigenetic subtypes of BC, as their abnormal methylation is ubiquitous in cancers and thus non-discriminative between tumor types.

Conclusions: Intrinsically epigenetically heterogeneous BC may be classified into a reasonable number of DNA methylation subtypes, promising the discovery of new diagnostic and prognostic markers, as well as of new therapeutic targets.

Legal entity responsible for the study: Research Centre for Medical Genetics.

Funding: Russian Science Foundation (project No.18-15-00430).

Disclosure: All authors have declared no conflicts of interest.

179P Prognostic value of change in neutrophil-lymphocyte ratio during treatment with first-line anti-PD1 therapy in metastatic melanoma

J.A. Soon, E. Blackley, M. Moore, L.E. Lim, H.L. Yeoh, M. Voskoboynik, A. Haydon

Medical Oncology, The Alfred Hospital, Melbourne, Australia

Background: With the advent of immunotherapy, the overall survival (OS) of patients (pts) with advanced melanoma has seen significant improvement. Multiple studies have demonstrated a negative correlation between elevated baseline serum neutrophil-lymphocyte ratio (NLR) and OS in melanoma and other solid tumours. This retrospective analysis aimed to identify a relationship between change in NLR during treatment and OS.

Methods: 83 consecutive pts with metastatic melanoma who received first-line anti-PD1 immunotherapy (mono or combination therapy) were identified at a single institution between May 2015 and August 2017. NLR was measured at baseline and following 4-6 weeks (4-6W) of therapy, with the result at each time point correlated with OS. An elevated NLR was defined as > 4.

Results: Median follow-up was 17 months. Median OS of pts with baseline NLR <4 was not reached (NR) compared with 17.1 months with NLR >4 (HR 0.29, 95% CI 0.13-0.65, $p = 0.003$). Pts whose NLR started and remained high after 4-6W of treatment performed significantly worse than pts whose NLR fell to < 4 at 4-6W (median OS 6.5 months vs NR, HR 0.18, $p = 0.028$). Survival in the latter group was comparable to those with a baseline NLR <4. NLR was more prognostic at 4-6W (HR 0.17, 95% CI 0.07-0.41, $p = 0.000091$) than at baseline (HR 0.29, 95% CI 0.18-0.65, $p = 0.003$). On Cox regression multivariate analysis including age, sex, M stage, lactate dehydrogenase level, presence of brain and/or liver metastases and NLR at the two time points, NLR >4 at 4-6W was the strongest prognostic factor (HR 0.14, 95% CI 0.06-0.37, $p = 0.00005$).

Conclusions: NLR is a simple and inexpensive prognostic biomarker in metastatic melanoma. NLR >4 at baseline is associated with a significantly poorer OS. In this cohort, NLR at 4-6W was the strongest predictor of outcome. Persistent elevation of NLR >4 at 4-6W after initiation of treatment was associated with a significantly poorer prognosis than those with a change in NLR to < 4 at this time point. Further analysis of a larger cohort may strengthen this association and potentially allow early identification of poor-risk pts and an opportunity to escalate treatment.

Legal entity responsible for the study: Andrew Haydon.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

180P A serum microRNA expression signature for radiosensitivity of non-small cell lung cancer

L. Fan[1], B. Li[2]

[1]Radiation Department, Shandong Provincial Western Hospital, Ji'nan, China, [2]Radiation Department, Shandong Cancer Hospital affiliated to Shandong University, Jinan, China

Background: Chemoradiotherapy represents the main treatment for non-small cell lung cancer (NSCLC), especially for the advanced lung cancer. However, the curative effect varies significantly. Many microRNAs are verified to be associated with it and microRNA signature may be a good biomarker to predict the radiosensitivity.

Methods: Genome-wide microRNA profiling was analyzed by microarray and validated by qRT-PCR in radio-resistant cell lines and their parent cell lines (A549 and PC9, the corresponding cell lines named A549-R and PC9-R). Then we used colony formation by transfecting miRNA-mimics into A549 and PC9 for functional verification. Finally, a potential microRNA signature was established by an independent set of non-small cell lung cancer (NSCLC) serum samples and validated by available corresponding formalin-fixed paraffin-embedded tissue (FFPE) samples.

Results: 73 up-regulated and 24 down-regulated miRNAs were found by microarray and 11 up-regulated, 3 down-regulated and 3 non-different miRNAs were rechecked by qRT-PCR. A miRNA signature, including miR-1290, miR-2861, miR-25-5p and miR-92a-1-5p was selected for further exploration. Overexpression of miR-1290 and miR-2861 increased the radio resistance of A549 and PC9 while overexpression of miR-25-5p and miR-92a-1-5p reversed the radio resistance of A549-R and PC9-R. The four-miRNAs signature could predict the chemotherapeutic response with high accuracy, 83.4% and 79.5% in both the test (serum samples) and validation (FFPE samples) cohorts respectively.

Conclusions: It is the first report of a miRNA signature for cell lines, serum and tissues. Serum and tissue miRNAs represent novel biomarkers to predict radiotherapy response clinically and may represent potential molecular targets to sensitize resistant cancers.

Legal entity responsible for the study: Shandong Cancer Hospital affiliated to Shandong University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

181P Anti-tNASP antibodies as a diagnostic marker for malignant tumors

O. Alekseev[1], K. Admire[2], J. Brogdon[2], B. Gorman[2], C. Davis[2], Z. Vaskalis[2]
[1]Physiology and Pathophysiology, Campbell University, Lillington, NC, USA, [2]School of Osteopathic Medicine, Campbell University, Lillington, NC, USA

Background: Nuclear Autoantigenic Sperm Protein (NASP), a facilitator of chromatin assembly, is expressed as two splice variants: tNASP, specific for testis and cancer cells, and sNASP, expressed in all somatic cells. Exposure of tNASP to the immune system induces a robust humoral immune response. We suggested that patients with malignancies have a higher level of serum anti-tNASP antibodies than those without malignancies. We hypothesized that detection of anti-tNASP antibodies in serum can be used as a cancer screening test.

Methods: Sera from cancer patients and healthy individuals (negative control) were tested for the presence of antibodies against tNASP using enzyme-linked immunosorbent assay (ELISA) with a recombinant tNASP fragment as bait. A total of 139 serum samples from patients with a known malignancy were tested. These included bladder (11), brain (12), breast (12), endometrial (10), gastrointestinal (10), lung (10), ovarian (10), prostatic (12), skin (10), soft tissue (12), thyroid (10), or urinary (10) malignancy, as well as sera from 10 control patients with no known cancers (negative control).

Results: The majority of samples (56.5%) demonstrated elevated levels of anti-tNASP antibodies compared to negative control: glioblastoma, astrocytoma, colorectal adenocarcinoma, pulmonary adenocarcinoma, large-cell and squamous cell lung carcinoma, ovarian serous carcinoma, ovarian adenocarcinoma, bladder urothelial and squamous cell carcinoma, adenocarcinoma of the urinary bladder, prostate adenocarcinoma, and endometrial adenocarcinoma. Samples from patients with melanoma, renal, thyroid, breast carcinomas, and different types of sarcomas demonstrated similar levels of anti-tNASP antibodies as control samples.

Conclusions: Serum anti-tNASP antibody levels are markedly elevated in the majority of cancer patients tested as compared to healthy controls. These data demonstrate that detection of anti-tNASP antibodies is a viable diagnostic approach and has the potential to be used as an early noninvasive screening method for detection of multiple cancers.

Legal entity responsible for the study: Oleg Alekseev.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

182TiP EXPRESS study: A multicenter, prospective trial in progress exploring the association between low level of genomic alteration and exceptional and unexpected response to targeted therapies in patients with solid tumors

A. Italiano[1], O. Le Saux[2], F. André[3], T. Filleron[4], D. Spaeth[5], P-E. Heudel[6], L. Albiges[7], T. Bachelot[8], A. Gonçalves[9], J-Y. Pierga[10], F. Barlesi[11], V. Boige[12], C. Lebbe[13], L. Mortier[14], J-S. Frenel[15], O. Tredan[8], M. Jimenez[16], F. Legrand[16], C. Ferté[17]
[1]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [2]Service d'Oncologie Médicale, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [3]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [4]Statistique, Centre Claudius-Regaud, Toulouse, France, [5]Service d'Oncologie, Centre d'Oncologie de Gentilly, Nancy, France, [6]Service d'Oncologie Médicale, Centre Léon Bérard, Lyon, France, [7]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [8]Service d'Oncologie Médicale, Centre Léon Bérard, Lyon, France, [9]Service d'Oncologie Médicale, Institute Paoli Calmettes, Marseille, France, [10]Service d'Oncologie Médicale, Institut Curie, Paris, France, [11]Service d'Oncologie Médicale, Aix-Marseille University - Faculté de Médecine Nord, Marseille, France, [12]Département de Médecine / Comité 040, Institut Gustave Roussy, Villejuif, France, [13]Hôpital St. Louis, Paris, France, [14]Department of Dermatology, Hôpital Huriez, Lille University Hospital, Lille, France, [15]Service d'Oncologie Médicale, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [16]R&D, UNICANCER, Paris, France, [17]Département de Médecine Oncologique, Institut Gustave Roussy, Villejuif, France

Background: Most anticancer drugs are approved by making marginal improvements in terms of tumor response or survival in non-selected populations, and are highly heterogeneous at the molecular level. Studying patients who present an exceptional and unexpected response (ER) to these drugs could enable the rapid identification of novel treatment response biomarkers, accelerate drug development and, more broadly, lead to a better understanding of the biology of cancer cells. Several studies are currently recruiting to build cohorts of patients, in order to subsequently analyze their tumors and reveal in detail the molecular anomalies associated with exceptional response.

Trial design: This is an exploratory, multicenter, multicohort, prospective trial conducted in 264 adult patients, with advanced breast, lung, colorectal, ovarian, kidney cancers and melanoma, having presented an ER to an approved antineoplastic targeted therapy. ER is defined using the definition chosen by the NCI which combines the three criteria: -complete or partial response -lasting >6 months -and not expected in $>10\%$ of the patients in this drug – organ situation. The primary objective is to assess whether ER can be associated with a low level of genomic instability in the tumor. Low genomic instability is defined by the presence of less than the 5th quantile of genomic alterations (mutations, amplifications, deletions) to be expected in the given tumor type as per TCGA database. For each tumor type, the null hypothesis H0: $\pi = 0.05$ will be tested, against the one-sided alternative hypothesis $\pi > 0.05$. For each of the 6 cohorts, a sample size of 44 patients is necessary to achieve 80% power at $\pi = 15$ with a one-sided level 5% test. Patients presenting an ER will be identified retrospectively, in a nationwide manner, then monthly reviewed and validated for inclusion by a panel of pathology experts. As of May 2018, 56 patients have been included. The identification of molecular traits associated with ER might serve the development of predictive classifiers for precision medicine. This study also represents a unique opportunity to better understand cancer biology.

Clinical trial identification: NCT02701907.
Legal entity responsible for the study: UNICANCER R&D.
Funding: Fondation ARC.
Disclosure: All authors have declared no conflicts of interest.

183TiP Neoadjuvant biomarker research study of palbociclib combined with endocrine therapy in estrogen receptor positive/HER2 negative breast cancer: The phase II NeoRHEA trial

M. Ignatiadis[1], M. Brandao[2], M. Maetens[3], N. Ponde[2], S. Martel[4], S. Drisis[5], I. Veys[6], S. Mazy[7], E. Bollue[8], P. Neven[9], F.P. Duhoux[10], J. Chapiro[11], A.H. Awada[12], T. Besse-Hammer[1], M. Paesmans[13], M. Piccart[1], P. Vuylsteke[14], C. Sotiriou[15]
[1]Oncologie Médicale, Institute Jules Bordet, Brussels, Belgium, [2]CTSU, Institute Jules Bordet, Brussels, Belgium, [3]BCTL, Institute Jules Bordet, Brussels, Belgium, [4]Oncologie Médicale, Hôpital Charles-Lemoyne, Greenfield Park, QC, Canada, [5]Radiology, Institute Jules Bordet, Brussels, Belgium, [6]Surgery, Institute Jules Bordet, Brussels, Belgium, [7]Senologie, Clinique Sainte-Elisabeth, Namur, Belgium, [8]Gynaecological Oncology, Clinique Sainte-Elisabeth, Namur, Belgium, [9]Gynaecological Oncology / Multidisciplinary Breast Center, University Hospitals Leuven - Campus Gasthuisberg, Leuven, Belgium, [10]Oncologie Médicale, Cliniques Universitaires St. Luc, Brussels, Belgium, [11]Oncologie Médicale, Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France, [12]Department of Medicine, Institute Jules Bordet, Brussels, Belgium, [13]Unité de Gestion de l'Information, Institute Jules Bordet, Brussels, Belgium, [14]Oncologie Médicale, CHU-UCL-Namur Clinique Ste Elisabeth, Namur, Belgium, [15]BCTL- Breast Cancer Translational Research Laboratory, Institute Jules Bordet, Brussels, Belgium

Background: Palbociclib (P) is a CDK4/6 inhibitor used in combination with endocrine therapy (ET) in metastatic estrogen receptor (ER)+/HER2- breast cancer (BC). The role of P in early BC treatment is currently being tested in phase III trials. Biomarkers that help us predict primary resistance to P may lead to better patient selection and thus avoid toxicity and reduce costs. In vitro studies suggest that CDK4 T172 phosphorylation is associated with sensitivity to P and an 11-gene expression signature has been developed that can predict the CDK4 modification profile in breast tumors. In order to identify biomarkers of resistance to P/ET and validate the 11-gene signature, we have launched the NeoRHEA study.

Trial design: Single arm, phase II trial, enrolling patients with ER+/HER2- breast tumors $\geq$ 15mm, N0-N1. Subjects will receive 4 months of neoadjuvant P/ET (tamoxifen$\pm$ goserelin or letrozole). Subjects' response to therapy will be evaluated before and after treatment by ultrasound, using WHO criteria. Biopsy samples will be collected at baseline and surgery. Primary objective is to identify biomarkers of resistance to P/ET (defined as stable or progressive disease by ultrasound) using RNA-sequencing of baseline samples. A key secondary objective is to validate the 11-gene signature as a biomarker of resistance to P/ET. Other secondary objectives include: to evaluate the safety of P/ET; to identify biomarkers of resistance to P/ET, defined as residual cancer burden of 3 or high tumor proliferation by the Genomic Grade Index; to understand mechanisms of resistance to P/ET by comparing tumors transcriptome at baseline and at surgery; to assess the role of plasma ctDNA in monitoring response to P/ET. Assuming a resistance rate of 20%-25% and a 10% dropout, 100 subjects are needed to develop a binary predictor. Any biomarker identified will be further validated in other studies e.g. NeoPAL (preliminary agreement in place). Accrual started in July 2017 and 38 patients have been enrolled thus far. The study is expected to be completed in 2019. Trial number is NCT03065621. Study sponsor is Institut Jules Bordet with a research grant from Pfizer.

Clinical trial identification: NCT03065621.
Legal entity responsible for the study: Institut Jules Bordet.
Funding: Pfizer.
Disclosure: M. Ignatiadis: Consulting or advisory role: Celgene, Roche, Pfizer, Seattle Genetics; Research funding: Roche; Patents: Université Libre de Bruxelles. S. Drisis: Travel, accomodation: Philips. M. Piccart: Honoraria: Pfizer. P. Vuylsteke: Honoraria: Roche, AstraZeneca, Pfizer; Travel, accommodation: Roche, Téva. C. Sotiriou: Consulting or advisory role: Pfizer; Research funding: Pfizer. All other authors have declared no conflicts of interest.

Annals of Oncology 29 (Supplement 8): viii58–viii86, 2018
doi:10.1093/annonc/mdy270

BREAST CANCER, EARLY STAGE

184O Distant disease-free survival (DDFS) according to response category in neoadjuvant endocrine therapy (NET): 6-year analysis in phase III NEOS trial

H. Iwata[1], N. Masuda[2], Y. Yamamoto[3], T. Fujisawa[4], T. Toyama[5], N. Taira[6], M. Kashiwaba[7], S. Ohtani[8], T. Sakai[9], Y. Hasegawa[10], R. Nakamura[11], H. Akabane[12], Y. Shibahara[13], H. Sasano[13], T. Yamaguchi[14], Y. Ohashi[15],

[1]Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [2]Surgery, NHO Osaka National Hospital, Osaka, Japan, [3]Breast Surgery, Kumamoto University, Kumamoto, Japan, [4]Breast Surgery, Gunma Prefectural Cancer Center, Gunma, Japan, [5]Breast Surgery, Nagoya City University, Aichi, Japan, [6]Breast Surgery, Okayama University Hospital, Okayama, Japan, [7]Breast Surgery, Sagara Hospital, Kagoshima, Japan, [8]Breast Surgery, Hiroshima City Hospital, Hiroshima, Japan, [9]Surgical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [10]Breast Surgery, Hirosaki Municipal Hospital, Hirosaki, Japan, [11]Breast Surgery, Chiba Cancer Center Hospital, Chiba, Japan, [12]Surgery, Hokkaido P.W.F.A.C. Asahikawa-Kosei General Hospital, Hokkaido, Japan, [13]Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan, [14]Statisticus, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan, [15]Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo, Japan

186O Tumor-infiltrating lymphocytes (TILs) as an independent prognostic factor for early HER2+ breast cancer patients treated with adjuvant chemotherapy and trastuzumab in the randomized shortHER trial

M.V. Dieci[1], P.F. Conte[1], G. Bisagni[2], A.A. Brandes[3], A. Frassoldati[4], L. Cavanna[5], A. Musolino[6], F. Giotta[7], A. Rimanti[8], O. Garrone[9], E. Bertone[10], K. Cagossi[11], S. Sarti[12], A. Ferro[13], C. Omarini[14], A. Maiorana[15], E. Orvieto[16], M. Sanders[17], R. D'Amico[18], V. Guarneri[1]

[1]Department of Surgery, Oncology and Gastroenterology, University of Padova, Istituto Oncologico Veneto IRCCS, Padua, Italy, [2]Medical Oncology, Azienda Ospedaliera Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Italy, [3]Medical Oncology, Ospedale Bellaria, Bologna, Italy, [4]Clinical Oncology, Azienda Ospedaliera di Ferrara St. Anna, Ferrara, Italy, [5]Oncology Department, Azienda Ospedaliera di Piacenza, Piacenza, Italy, [6]Medical Oncology, Azienda Ospedaliera di Parma, Parma, Italy, [7]Medical Oncology, Istituto Oncologico Bari, Bari, Italy, [8]Oncology, Azienda Ospedaliera di Mantova, Mantova, Italy, [9]Medical Oncology, Azienda Ospedaliera St. Croce e Carle, Cuneo, Italy, [10]Medical Oncology, S. Anna Hospital, Turin, Italy, [11]Medical Oncology, Ramazzini Hospital, Carpi, Italy, [12]Medical Oncology, Istituto Tumori della Romagna I.R.S.T., Meldola, Italy, [13]Medical Oncology, Ospedale Santa Chiara, Trento, Italy, [14]Medical and Surgical Sciences for Children & Adults, Università degli Studi di Modena e Reggio Emilia, Modena, Italy, [15]Diagnostic and Clinical Medicine and of Public Health, University of Modena and Reggio Emilia, Modena, Italy, [16]Pathology, ULSS 5 Polesana, Rovigo, Italy, [17]Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA, [18]Department of Diagnostic and Clinical Medicine and Public Health, University Hospital of Modena and Reggio Emilia, Modena, Italy

187O High-dose chemotherapy (HDCT) with hematopoietic stem cell transplantation (HSCT) in high-risk breast cancer (BC) patients with ≥4 involved axillary lymph nodes (ALN): 20-year follow-up of a randomized phase 3 study

T.G. Steenbruggen[1], L.C. Steggink[2], C.M. Seynaeve[3], J.J.M. van der Hoeven[4], M.J. Hooning[5], A. Jager[3], I.R. Konings[6], J.R. Kroep[7], W.M. Smit[8], V.C.G. Tjan-Heijnen[9], E. van der Wall[10], A.D. Bins[11], S.C. Linn[1], M. Schaapveld[12], F.E. van Leeuwen[12], C.P. Schroder[2], H. van Tinteren[13], E.G.E. de Vries[2], G.S. Sonke[1], J.A. Gietema[2]

[1]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [2]Medical Oncology, University Medical Center Groningen, Groningen, Netherlands, [3]Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, [4]Medical Oncology, Radboud University, Nijmegen, Netherlands, [5]Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [6]Medical Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [7]Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [8]Medical Oncology, Medisch Spectrum Twente (MST), Enschede, Netherlands, [9]Medical Oncology, Maastricht University Medical Center (MUMC), Maastricht, Netherlands, [10]Cancer Center, UMC - University Medical Center Utrecht, Utrecht, Netherlands, [11]Medical Oncology, Academic Medical Center (AMC), Amsterdam, Netherlands, [12]Epidemiology, Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital (NKI-AVL), Amsterdam, Netherlands, [13]Biostatistics, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands

193O An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients (EORTC QLQ-BC23) - EORTC QLQ-BR45

V. Bjelic-Radisic[1], A. Bottomley[2], F. Cardoso[3], D. Cameron[4], E. Brain[5], K. Kuljanic[6], R.A. de Costa[7], T. Conroy[8], E. Inwald[9], S. Serpentini[10], M. Pinto[11], J. Weis[12], O. Morag[13], G. Guro Lindviksmoen Astrup[14], K. Tomaszweksi[15], K. Pogoda[16], P. Sinai[17], M.A.G. Sprangers[18], N. Aaronson[19], E. Greimel[20]

[1]Senology, Helios University Hospital, Wuppertal, Germany, [2]QoL, EORTC - European Organisation for Research and Treatment of Cancer, Brussels, Belgium, [3]Breast Unit, Champalimaud Foundation Cancer Center, Lisbon, Portugal, [4]Oncology, Edinburgh Cancer Centre Western General Hospital, Edinburgh, Midlothian, UK, [5]Department of Medical Oncology, Institut Curie, Paris & Saint-Cloud, France, [6]Gynecology, Medical University Rijeka, Rijeka, Croatia, [7]Surgery, HC Barretas, Barretas, Brazil, [8]Medical Oncology, ICL Alexis Vautin, Lorraine, France, [9]Gynecology, Medical University Regensburg, Regensburg, Germany, [10]Oncology, IOV Oncologica Veneto Padova, Padova, Italy, [11]Oncology, Instituto Nazionale Tumori Fondazione Pascale Naples, Naples, Italy, [12]Oncology, Medical University Freiburg, Freiburg, Germany, [13]Medical Oncology, SHEBA_Israel, Tel Aviv, Israel, [14]Oncology, Oslo Univ. Hospital, Oslo, Norway, [15]Surgical oncology, Jagillonian University Medical College Krakow, Krakow, Poland, [16]Medical Oncology, The Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology (MCMCC), Warsaw, Poland, [17]Surgery, University of Bristol, Bristol, UK, [18]Department of Medical Psychology, Academic Medical Center (AMC), Amsterdam, Netherlands, [19]Psychology, NCI Amsterdam, Amsterdam, Netherlands, [20]Gynecology, Medical University Graz, Graz, Austria

188PD **Impact of nab-paclitaxel dose reduction on survival of the randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy of weekly nab-paclitaxel (nP) with solvent-based paclitaxel (P) followed by anthracycline/cyclophosphamide for patients with early breast cancer (BC)**

M. Untch[1], C. Jackisch[2], A. Schneeweiss[3], S. Schmatloch[4], B. Aktas[5], C. Denkert[6], C. Schem[7], H. Wiebringhaus[8], S. Kümmel[9], K. Rhiem[10], M. Warm[11], P.A. Fasching[12], M. Just[13], C. Hanusch[14], J. Hackmann[15], J-U. Blohmer[16], J. Furlanetto[17], V. Nekljudova[18], G. von Minckwitz[17], S. Loibl[17]

[1]Clinic for Gynecology, Gynecologic Oncology and Obstetrics, Helios Klinikum Berlin Buch, Berlin, Germany, [2]Geburtshilfe und Gynäkologie, Klinikum Offenbach GmbH, Offenbach, Germany, [3]National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany, [4]Brustzentrum, Elisabeth Krankenhaus, Kassel, Germany, [5]Women's Clinic, University Clinics, Leipzig, Germany, [6]Institute of Pathology, Charite Berlin Mitte, Berlin, Germany, [7]Mammazentrum Hamburg, Hospital Jerusalem, Hamburg, Germany, [8]Geburtshilfe und Gynäkologie, St. Barbara-Klinik, Hamm, Germany, [9]Breast Unit, Kliniken Essen Mitte Evang. Huyssens-Stiftung, Essen, Germany, [10]Center for Familial Breast and Ovarian Cancer, University Hospital Cologne, Cologne, Germany, [11]Breast Center, City Hospital Holweide, Cologne, Germany, [12]Department of Gynecology and Obstetrics, Universitätsklinik Erlangen, Erlangen, Germany, [13]Gynäkologie, Onkologische Schwerpunktpraxis, Bielefeld, Germany, [14]Frauenklinik, Rotkreuzklinikum, Munich, Germany, [15]Breast Center, Marien Hospital, Witten, Germany, [16]Gynäkologie, Klinik für Gynäkologie am Campus Charité Mitte, Berlin, Germany, [17]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [18]Statistics, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany

189PD **Tumor infiltrating lymphocytes predict benefit from TAC but not from ddAC in triple negative breast cancer in the randomized MATADOR trial (BOOG 2004-04)**

A.G.J. van Rossum[1], M. Hoogstraat[2], M. Opdam[1], H. Horlings[3], L. Wessels[2], R.M. Kerkhoven[4], A.E. van Leeuwen - Stok[5], H.M. Oosterkamp[6], M. Kok[7], S.C. Linn[7]

[1]Division of Molecular Pathology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [2]Division of Molecular Carcinogenesis, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [3]Department of Pathology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [4]Genomics Core Facility, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [5]BOOG Study Center, Amsterdam, Netherlands, [6]Department of Medical Oncology, Medisch Centrum Haaglanden Westeinde Hospital, The Hague, Netherlands, [7]Department of Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

190PD Research-based PAM50 predicts risk of relapse in residual disease after anti-HER2 therapies

G. Bianchini[1], J. Parker[2], L. Carey[3], C.M. Perou[2], L. Sica[1], A. Prat[4], T. Pieńkowski[5], Y-H. Im[6], G.V. Bianchi[7], T. Ling-Ming[8], M-C. Liu[9], A. Lluch[10], V. Semiglazov[11], J. de la Haba-Rodriguez[12], D-Y. Oh[13], B. Poirier[14], J.L. Pedrini[15], P. Valagussa[16], L. Gianni[1]

[1]Medical Oncology, IRCCS San Raffaele, Milan, Italy, [2]Cancer Genetics, University of North Carolina, Chapel Hill, NC, USA, [3]Hematology/Oncology, University of North Carolina, Chapel Hill, NC, USA, [4]Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [5]Onkologia Kliniczna, Radomskie Centrum Onkologii, Radom, Poland, [6]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea, [7]Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [8]Department of Surgery, Taipei Veterans Hospital, Taipei, Taiwan, [9]Medical Oncology, Koo Foundation Sun Yat-sen Cancer Center, Taipei, Taiwan, [10]Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain, [11]Medical Oncology, 14NN Petrov Research Institute of Oncology, St. Petersburg, Russian Federation, [12]Medical Oncology, Hospital Reina Sofia, Cordoba, Spain, [13]Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea, [14]Medical Oncology, Centre des Maladies du Sein, Hôpital du Saint-Sacrement, Quebec City, QC, Canada, [15]Department of Surgery, Hospital Ernesto Dornelles, Porto Alegre, Brazil, [16]Operative Office, Fondazione Michelangelo, Milan, Italy

192PD Randomized trial of lisinopril or carvedilol for the prevention of cardiotoxicity in patients with early stage HER2-positive breast cancer receiving trastuzumab

P.N. Munster[1], J. Krischer[2], R. Tamura[2], L. Bello-Matricaria[2], A. Fink[2], W. McCaskill-Stevens[3], M. Guglin[4]

[1]Medicine, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [2]Health Informatics Institute, University of South Florida, Tampa, FL, USA, [3]Prevention, National Cancer Institute Div. Cancer Treatment, Rockville, MD, USA, [4]Cardiology, University of Kentucky, Lexington, KY, USA

194P Real-life utilization of genomic testing for invasive breast cancer patients in Italy and France reduces chemotherapy recommendations

S. Barni[1], E. Curtit[2], F. Cognetti[3], D. Bourgeois[4], R. Masetti[5], S. Zilberman[6], G. Naso[7], J. Gligorov[8]

[1]Oncology, Azienda Ospedaliera Treviglio-Caravaggio, Treviglio, Italy, [2]Medical Oncology, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [3]Medical Oncology, Istituto Regina Elena, Rome, Italy, [4]Medical Oncology, ARETASC - Clinique Hartmann, Neuilly-sur-Seine, France, [5]Surgical Oncology, Policlinico Universitario Agostino Gemelli, Rome, Italy, [6]Surgical Gynecology, Hôpital Tenon, Paris, France, [7]Medical Oncology, Policlinico Umberto I, Rome, Italy, [8]Medical Oncology APHP, CancerEst, Tenon University Hospital, Paris, France

Background: Oncotype DX® (ODX) is a multigene assay allowing physicians to tailor treatment in HR+, HER2- early-stage breast cancer patients. Clinical validation and utility of ODX have been demonstrated across multiple studies in over 63,000 breast cancer patients worldwide. It provides level 1A evidence and has been incorporated in major international clinical guidelines. A market access program was initiated in 2015 in France and 2016 in Italy to assess real-life test utilization and its impact in current clinical practice.

Methods: The program allows for prospective data collection reflecting real life use of ODX by physicians in various clinical practice settings throughout France and Italy. Patient data were collected through an online dedicated platform including classical pathological and clinical parameters (e.g. histology, tumor grade and size, ER, PR, HER2 and Ki67), patient age, ODX Recurrence Score (RS) Results and recommended treatment both before and after the test results have been reported.

Results: A total of 53 and 19 qualified breast cancer centers, in France and Italy respectively, participated in the program and collected 2632 case reports. Study results demonstrated that ODX is used among a wide variety of patient profiles: 24% N1, 7% Nmic & 69% N0, 11% G1, 64% G2 and 25% of G3, 32% pre-, 8% peri- & 59% are post-menopausal, 34% are 35-50, 52% 51-70 and 13% are older than 70, 13% have Ki67%<10%, 35% KI67 10-20%, 30% KI67 21-30% & 18% Ki67>30%, 12% tumor <1cm, 59% 1-2cm and 27% tumor 2.1-5cm. RS distribution is the following: <18 (56%), 18-30 (35%) and >30 (9%). In addition, pre-ODX 60% and 48% patients had a treatment recommendation for chemo-hormonotherapy (CT-HT) in France and Italy respectively. Post-testing, the number of patients recommended CT-HT decreased to 29% and 31% for France and Italy respectively, highlighting that the test reduced unnecessary use of CT and homogenized treatment decisions.

Conclusions: In France and Italy, the use of the ODX test results in an overall reduction in CT recommendations, while also identifying patients more likely to benefit from CT.

Legal entity responsible for the study: Genomic Health SARL.

Funding: Genomic Health SARL.

Disclosure: S. Barni, F. Cognetti: Medical Consultant: Genomic Health. All other authors have declared no conflicts of interest.

195P Benefit of adjuvant chemotherapy in hormone receptor-positive, HER2-negative, invasive lobular carcinoma of the breast

A. De Nonneville[1], C. Jauffret[2], A. Gonçalves[1], J-M. Classe[3], M. Cohen[2], F. Reyal[4], C. Mazouni[5], M-P. Chauvet[6], N. Chopin[7], P-E. Colombo[8], E. Jouve[9], E. Darai[10], R. Rouzier[11], C. Coutant[12], P. Gimbergues[13], A-S. Azuar[14], C. Tunon de Lara[15], E. Lambaudie[2], G. Houvenaeghel[2]

[1]Department of Medical Oncology, Institute Paoli Calmettes, Marseille, France, [2]Department of Surgical Oncology, Institute Paoli Calmettes, Marseille, France, [3]Department of Surgical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [4]Department of Surgical Oncology, Institut Curie, Paris, France, [5]Department of Surgical Oncology, Institut Gustave Roussy, Villejuif, France, [6]Department of Surgical Oncology, Centre Oscar Lambret, Lille, France, [7]Department of Surgical Oncology, Centre Leon Berard, Lyon, France, [8]Department of Surgical Oncology, CLCC Val d'Aurelle, Montpellier, France, [9]Department of Surgical Oncology, Centre Claudius Regaud, Toulouse, France, [10]Department of Gynecologic and Breast Cancers, Hôpital Tenon, Paris, France, [11]Surgery, Institut Curie, Paris, France, [12]Department of Surgical Oncology, Centre Georges-François Leclerc (Dijon), Dijon, France, [13]Department of Surgical Oncology, Centre Jean-Perrin, Clermont-Ferrand, France, [14]Department of Surgical Oncology, Hôpital de Grasse, Grasse, France, [15]Department of Surgical Oncology, Institut Bergonié, Bordaux, France

Background: Invasive lobular carcinoma (ILC) is the second most common histologic breast cancer subtype and represent approximately 10% of all breast cancers. Despite this high frequency, benefit of adjuvant chemotherapy (CT) in ILC is still unclear.

Methods: Our objective was to investigate the impact of CT on survival in ILC. Patients were retrospectively identified from a cohort of 23,537 patients who underwent primary surgery in 18 French centres between 1990 and 2014. Only ILC, hormone-positive, HER2-negative patients who received adjuvant endocrine therapy (ET) were included. Endpoints were disease-free survival (DFS) and overall survival (OS). A propensity score for receiving CT was estimated using a logistic regression including age, tumour size, nodal status, lymphovascular invasion (LVI), grade, type of surgery, period and CT.

Results: Of a total of 2,318 patients with ILC, 1,485 patients (64%) received ET alone and 823 (36%) received ET+CT. Patients receiving ET+CT had more adverse prognostic features, such as young age, larger tumour size, high grade, macroscopic lymph-node involvement and LVI, received more adjuvant radiotherapy and underwent more often mastectomy. In a multivariate Cox model, we observed a beneficial effect of addition of CT to ET on both DFS and OS, (HR = 0.61, 95% CI [0.41-0.90]; p = 0.01 and 0.52, 95% CI [0.31-0.87]; p = 0.01, respectively). This effect was even more pronounced when propensity score-matching, aiming to compensate for baseline characteristics, was used. Ten-year estimates DFS in case-matched patients for propensity score analysis were 90% (95% CI [87%-93.4%]) in the ET+CT group vs. 66% (95% CI [61.4%-71.4%]) with ET alone and 10-year estimates OS were 96% (95% CI [93.8%-98%]) in the ET+CT group vs. 71% (95% CI [66.6% et 76.2%]) with ET alone. Regarding subgroup analysis, low-risk patients without CT did not have significant differences in DFS or OS compared to low-risk patients with CT.

Conclusions: Patients receiving adjuvant ET for hormone receptor-positive, HER2-negative ILC could derive significant DFS and OS benefits from CT. Our results highlight that patients with high-risk ILC should not be denied adjuvant CT because of such histologic subtype.

Legal entity responsible for the study: Gilles Houvenaeghel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

196P Baseline lymphocyte counts predict distant recurrence in early breast cancer

G.M. Kim[1], H.D. Koh[1], J.H. Kim[1], B-W. Park[2], Y.U. Cho[2], S.I. Kim[2], H.S. Park[2], J.Y. Kim[2], M.J. Kim[2], J.H. Jeong[1], J. Sohn[1]

[1]Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

Background: The presence of pretreatment lymphopenia or high NLR (neutrophil-lymphocyte ratio) has been reported as poor prognostic factor in breast cancer. Here, we investigated whether baseline lymphocyte counts and NLR are associated with overall survival (OS), breast cancer specific survival (BCSS), and distant recurrence free survival (DRFS) in large early breast cancer (EBC) patient cohort.

Methods: We reviewed demographic, clinical, pathologic, and survival data from Yonsei Breast Cancer Center Registry. Patients who underwent surgery with stage I-III

Table: 196P Baseline demographics

	All Patients (n = 5,252)	Baseline Lymphopenia (n = 158)	No Baseline Lymphopenia (n = 5,094)
Age			
Median (Range)	50 (19-92)	48 (31-77)	50 (19-92)
TNM Stage			
I	2672 (50.9)	81 (51.3)	2591 (50.9)
II	1890 (36)	53 (33.5)	1837 (36.1)
III	450 (8.6)	18 (11.4)	432 (8.5)
Subtype			
ER+/HER2-	3286 (62.6)	90 (57)	3196 (62.7)
ER+/HER2+	558 (10.6	19 (12)	539 (10.6)
ER-/HER2+	496 (9.4)	22 (13.9)	474 (9.3)
ER-/HER2-	912 (17.4)	27 (17.1)	885 (17.4)
Neoadjuvant chemotherapy			
Yes	983 (18.7)	124 (78.5)	4145 (81.4)
No	4269 (81.3)	34 (21.5)	949 (18.6)
Adjuvant chemotherapy			
Yes	2957 (56.3)	69 (43.7)	2226 (43.7)
No	2295 (43.7)	89 (56.3)	2868 (56.3)
Radiation therapy			
Yes	3755 (71.5)	49 (31)	1448 (28.4)
No	1497 (28.5)	109 (69)	3646 (71.6)
Endocrine therapy			
Yes	3799 (72.3)	108 (68.4)	3691 (72.5)
No	1453 (27.7)	50 (31.6)	1403 (27.5)
HBsAg test			
Positive	182 (3.5)	14 (8.9)	168 (3.3)
Negative	4419 (84.1)	126 (79.7)	4293 (84.3)
Unknown	651 (12.4)	18 (11.4)	633 (12.4)
Baseline Lymphopenia			
Yes	158 (3)		
No	5094 (97)		

EBC at the Yonsei Cancer Center between 2006 and 2015 were included. Baseline complete blood counts data were collected from electronic medical records system. Multivariable regression models adjusted for age, stage, neoadjuvant/adjuvant chemotherapy use, subtype were used to evaluate associations between baseline absolute lymphocyte count (ALC) and OS/BCSS/DRFS.

Results: A total of 5,785 stage I–III EBC patients were underwent breast surgery from 2006 to 2015; 533 patients were excluded due to lack of complete data (n = 262) and the diagnosis of second primary cancer (n = 270). Median follow up duration was 72.73 months (95% confidence interval (CI), 73.85-75.64). Of 5,252 eligible patients, only 159 (3.0%) had baseline lymphopenia (ALC < 1,000/mL). The incidence of baseline lymphopenia was similar among age group, stage, and subtype, but patients with HBsAg (+) showed higher baseline lymphopenia than HBV negative patients (7.7% vs. 2.9%, p = <0.001). In univariate analysis, baseline lymphopenia was significantly associated with poor OS, BCSS and DRFS. In multivariable analysis, baseline lymphopenia predicted lower DRFS [HR 0.502; 95% CI, 0.307–0.820]. The prognostic significance of baseline lymphopenia regarding to DRFS was highest in HER2 positive subtype.

Conclusions: Baseline lymphocyte counts predicted distant recurrence in early breast cancer.

Legal entity responsible for the study: Gun Min Kim.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

197P A propensity score analysis exploring the impact of the addition of adjuvant chemotherapy (aCT) to hormone therapy (aHT) in a multicenter series of resected luminal early stage pure invasive lobular breast carcinoma (ILC)

L. Carbognin[1], I. Sperduti[2], G. Arpino[3], M.V. Dieci[4], F. Schettini[5], G. Griguolo[6], M. Brunelli[7], V. Guarneri[8], R. Nortilli[1], E. Fiorio[9], S. Pilotto[10], E. Orvieto[11], E. Manfrin[7], P. Conte[6], S. de Placido[3], G. Scambia[12], G. Tortora[10], E. Bria[13]

[1]Medical Oncology, University of Verona, AOUI Verona, Italy, [2]Biostatistics, Regina Elena National Cancer Institute, Rome, Italy, [3]Dipartimento di Medicina Clinica e Chirurgia, AOU Policlinico Federico II, Naples, Italy, [4]Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padua, Italy, [5]Dipartimento di Medicina Clinica e Chirurgia, Azienda Universitaria Ospedaliera Federico II, Naples, Italy, [6]Department of Surgery, Oncology and Gastroenterology, University of Padova, Istituto Oncologico Veneto IRCCS, Padua, Italy, [7]Department of Diagnostics and Public Health, Section of Anatomical Pathology, University and Hospital Trust of Verona, Verona, Italy, [8]Department of Surgery, Oncology and Gastroenterology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [9]Medical Oncology, AOU Integrata Verona, Verona, Italy, [10]UOC Oncologia, Dipartimento di Medicina, Università di Verona, AOUI, Verona, Italy, [11]Department of Pathology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [12]Department of Woman and Child Health', Policlinico Universitario A. Gemelli I.R.C.C.S., Rome, Italy, [13]UOC Oncologia Medica, Università Cattolica del Sacro Cuore - Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy

Background: Patients (pts) resected for luminal early breast cancer are assigned to receive aCT according to international guidelines based upon clinico-pathological features, regardless of the histotype, given the lack of prospective data for ILC. Thus, the magnitude of the benefit of the addition of aCT to aHT for ILC is still not sizable. The aim of this analysis was to investigate the effect of aCT in a multi-center series of luminal early stage pure ILC.

Methods: Clinico-pathological data of consecutive pts affected by luminal pure ILC, undergone surgery between 2000 and 2014, were correlated with disease-free and overall survival (DFS/OS) using a Cox model. A propensity score analysis was performed to evaluate the prognostic impact of aCT. Kaplan-Meier curves were compared with Log-Rank analysis.

Results: Data from 576 pts were gathered (median age 58 years (yrs)). At median follow-up of 72 months, 5-/10-yrs DFS and OS were 81.5%/71.8% and 91.8%/80.4%, respectively. Tumor-size according to TNM (T, HR 1.78, 95% CI 0.91-3.49, p = 0.09) and lymph-node (N) status (HR 2.97, 95% CI 1.69-5.19, p < 0.0001) were independent predictors for DFS at multivariate analysis. N status (HR 3.93, 95% CI 1.79-8.70, p = 0.001), Ki67 (HR 2.66, 95% CI 0.92-7.70, p = 0.072), and age (HR 2.32, 95% CI 1.09-4.93, p = 0.029) were predictors for OS. A significant prognostic effect of aCT upon OS was found after adjusting for T, N, Ki67, grading and age at diagnosis with the propensity score method, as shown in the table. Particularly, aCT significantly prolongs DFS in pts with T > 2 (p = 0.03) and OS in pts with Ki67 >4% (p < 0.0001).

Table: 197P

Outcome	Category	5-yrs (%)	10-yrs (%)	Log-Rank
DFS	aHT	76.6	54.4	p = 0.08
	aCT + aHT	85.0	76.4.	
OS	aHT	80.9	55.6	p = 0.001
	aCT + aHT	98.1	95.9	

Conclusions: Despite the retrospective nature of this analysis, the propensity score analysis indicates that pts with luminal ILC may significantly benefit from the addition of aCT to aHT in terms of long-term survival, particularly for larger and more aggressive tumors.

Legal entity responsible for the study: University of Verona.

Funding: University of Verona.

Disclosure: All authors have declared no conflicts of interest.

198P Benefit of adjuvant systemic therapies in HR+ HER2- pT1ab node-negative breast carcinomas

A. De Nonneville[1], A. Gonçalves[1], J-M. Boher[2], J-M. Classe[3], M. Cohen[4], P-E. Colombo[5], F. Reyal[6], M-P. Chauvet[7], E. Jouve[8], E. Darai[9], G. Blache[10], C. Coutant[11], P. Gimbergues[12], C. Mazouni[13], R. Rouzier[14], R. Villet[15], P. Crochet[16], A-S. Azuar[17], E. Lambaudie[4], G. Houvenaeghel[4]

[1]Department of Medical Oncology, Institute Paoli Calmettes, Marseille, France, [2]Department of Clinical Research and Investigation, Biostatistics and Methodology Unit, Institute Paoli Calmettes, Marseille, France, [3]Department of Surgical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [4]Department of Surgical Oncology, Institute Paoli Calmettes, Marseille, France, [5]Department of Surgical Oncology, CLCC Val d'Aurelle, Montpellier, France, [6]Department of Surgical Oncology, Institut Curie, Paris, France, [7]Department of Surgical Oncology, Centre Oscar Lambret, Lille, France, [8]Department of Surgical Oncology, Institut Universitaire du Cancer Toulouse Oncopole, Paris, France, [9]Department of Gynecologic and Breast Cancers Hôpital Tenon, Paris, France, [10]Department of Surgical Oncology, Centre Leon Berard, Lyon, France, [11]Department of Surgical Oncology, Centre Georges-François Leclerc (Dijon), Dijon, France, [12]Department of Surgical Oncology, Centre Jean-Perrin, Clermont-Ferrand, France, [13]Department of Surgical Oncology, Institut Gustave Roussy, Villejuif, France, [14]Surgery, Institut Curie, Paris, France, [15]Department of Surgical Oncology, Hôpital des Diaconnesses, Paris, France, [16]Department of Surgical Oncology, Hopital de la Conception, Marseille, France, [17]Department of Surgical Oncology, Hôpital de Grasse, Grasse, France

Background: Hormone receptor-positive, HER2-negative, pT1ab N0 breast cancers (BC) are generally estimated as having a low risk of recurrence after locoregional treatment and adjuvant treatment decisions could be challenging. We examined the impact of endocrine therapy (ET) +/- chemotherapy on outcomes in this population.

Methods: A total of 4,788 patients with pT1ab N0 HR+ HER2- BC were identified from a large cohort of 22,475 consecutive patients who underwent primary surgery at 15 French centres between 2000 and 2014. Endpoints were disease-free survival (DFS) and overall survival (OS). Analyses of causal effect using propensity scores were realized using a logistic regression including age, tumour size, histology, grade, and lymphovascular invasion (LVI).

Results: Of 4,779 patients with pT1ab HR+ HER2- BC, 846 patients did not receive any adjuvant treatment and 3,933 received ET, among which 251 received chemotherapy. Age ≥ 70y, ductal histology, high grade and tumour size > 5mm were independently associated with ET prescription. Age ≤ 40y, LVI and high grade, were independently associated with chemotherapy prescription. At a median follow-up of 47.7 months, ET was independently associated with a significant DFS benefit in multivariate analysis (HR: 0.60 [0.41-0.89]; p = 0.011) with 5-year estimate DFS of 94% (CI95 [92-96%]) without ET vs. 96% (CI95 [95-97%]) with ET, while addition of adjuvant chemotherapy was not (HR: 0.90 [0.39-2.09]; p = 0.813). These results were supported by the analyses of causal effect using propensity scores (HR: 0.48 [0.28-0.83]; p = 0.009 for ET, and HR: 1.54 [0.11-21.8]; p = 0.78 for chemotherapy). OS was not significantly impacted by systemic treatments despite a trend for ET in multivariate (HR: 0.60 [0.36-1.00]; p = 0.051) and in propensity score analyses (HR: 0.52 [0.24-1.11]; p = 0.092).

Conclusions: Adjuvant endocrine therapy is associated with a survival benefit in pT1ab N0 HR+ HER2- BC even with a relatively short follow up. Consistent with current consensus guidelines that do not recommend adjuvant chemotherapy in these tumours, we did not find any benefit of adding chemotherapy to ET. These data provide additional clues to the issue of adjuvant systemic treatments in these tumours.

Legal entity responsible for the study: Gilles Houvenaeghel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

199P Anti-proliferative effect of oral metronomic vinorelbine in PAM50 Luminal/HER2-negative early breast cancer (SOLTI-1501 VENTANA): An open-label, randomized, three-arm, multicenter, window-of-opportunity study

A. Prat[1], B. Adamo[1], J.A. Perez Fidalgo[2], S. Blanch[3], N. Martinez[4], P. Gomez Pardo[5], A. López González[6], L. Murillo Juso[7], K. Amillano[8], M. Vidal[1], T. Pascual[9], L. Pare[10], J. Canes[11], P. Galvan[12], B. Gonzalez Farre[13], V. Ortega Cebrian[14], X. Gonzalez[15], M. Bellet Ezquerra[16], P. Villagrasa[11], E.M. Ciruelos[17]

[1]Medical Oncology, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain, [2]Medical Oncology, Hospital Clínico Universitario de Valencia / INCLIVA / CIBERONC, Valencia, Spain, [3]Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [4]Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, [5]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [6]Medical Oncology, Complejo Asistencial Universitario de León, León, Spain, [7]Medical Oncology, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain, [8]Medical Oncology, University Hospital St. Joan de Reus, Reus, Tarragona, Spain, [9]Medical Oncology, Hospital Clinic i Provincial de Barcelona / IDIBAPS / SOLTI Breast Cancer Research Group, Barcelona, Spain, [10]Bioinformatics, IDIBAPS / SOLTI Breast Cancer Research Group, Barcelona, Spain, [11]Scientific Department, SOLTI Breast Cancer Research Group, Barcelona, Spain, [12]Medical Oncology, IDIBAPS / Hospital Clinic i Provincial de Barcelona, Barcelona, Spain, [13]Pathological Anatomy, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain, [14]Medical Oncology, Hospital General de Granollers, Granollers, Spain, [15]Instituto Oncológico Dr Rosell, Hospital General de Catalunya / SOLTI Breast Cancer Research Group, Barcelona, Spain, [16]Medical Oncology, Vall d'Hebron University Hospital / Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [17]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: The anti-proliferative effect of oral metronomic vinorelbine (mVNB) alone or in combination with endocrine therapy in patients with hormone receptor (HR)-positive/HER2- breast cancer has been scarcely addressed.

Methods: Postmenopausal women with untreated stage I-III breast cancer were randomized (1:1:1) to receive 3 weeks of letrozole (LTZ) 2.5mg/day, oral mVNB 50mg 3 days/week or the combination. The 1^{ary} objective was to evaluate, within PAM50 Luminal A/B disease, if the anti-proliferative effect of mVNB+LTZ was superior to monotherapy. An anti-proliferative effect was defined as the mean relative decrease of the PAM50 11-gene Proliferation Score in each arm. 2^{ary} objectives included safety and the comparison of the anti-proliferative effect between arms. An unplanned analysis of stromal tumor infiltrating lymphocytes (TILs) was performed. PAM50 analyses were performed using the nCounter®-based Breast Cancer 360^{TM} panel.

Results: A total of 61 patients were randomized and 54 paired samples (89%) were analyzed. Main patient characteristics were mean age 67, mean tumor size 1.7 cm, stage I (55.7%) and grade 1-2 (90%). Grade 3 toxicities occurred in 3.3% of cases. Most baseline samples were Luminal A (74.1%) or B (22.2%). The anti-proliferative effect of mVNB+LTZ (-73.2%) was superior to both monotherapy arms combined (-49.9%; $p = 0.001$) and mVNB (-19.1%; $p < 0.001$). The anti-proliferative effect of mVNB+LTZ (-73.2%) was higher compared to LTZ (-65.7%) but did not reach statistical significance ($p = 0.328$). Stromal TILs ($\geq$10% at week 3) were observed across arms in 6.6% (mVNB), 15% (LTZ) and 26% (mVNB+LTZ) of the cases. In tumors with $\leq$10% TILs at baseline, a significant increase in TILs was observed following VNB+LTZ (paired analysis $p = 0.012$).

Conclusions: mVNB is well-tolerated and presents antiproliferative activity alone and in combination with LTZ. Further investigation comparing these biological results with other metronomic schedules or drug combinations is warranted. Of note, the increase of TILs observed with the combination opens the possibility of studying this combination with immunotherapy.

Clinical trial identification: NCT02802748.

Legal entity responsible for the study: SOLTI Breast Cancer Research Group.

Funding: Pierre Fabre Médicament.

Disclosure: A. Prat: Consultancy: Pfizer, Eli Lilly, Novartis, Nanostring Technologies; Research funding: Novartis, Nanostring Technologies; Scientific advisory board: Oncolytics Biotech. J.A. Perez Fidalgo: Advisory board: Clinigen, Pharmamar, Clovis; Other: Substantiate relationships (speaker) Roche, Pharmamar, AstraZeneca, Ipsen. All other authors have declared no conflicts of interest.

200P Clinicopathologic significance of androgen receptor expression and discordant receptor status during progression in breast cancer

C.H. Park[1], E.Y. Kim[1], S-I. Do[2]

[1]General Surgery, Kangbuk Samsung Hospital Sungkyunkwan University, Seoul, Republic of Korea, [2]Pathology, Kangbuk Samsung Hospital Sungkyunkwan University, Seoul, Republic of Korea

Background: The role of androgen receptor (AR) as a prognostic marker has been proposed in breast cancer. This study investigated AR status and its clinical significance in breast cancer, especially in triple negative breast cancer (TNBC). We also evaluated discordant AR status during the process of lymph node metastasis, locoregional recurrences (LRR) and distant metastasis.

Methods: From January 2005 to December 2010, we retrospectively reviewed 120 patients including 55 TNBC patients diagnosed as invasive carcinoma with no special type (NST), who were treated at the Kangbuk Samsung Hospital. Tissue microarray was constructed and immunohistochemical expression of AR was performed for 120 invasive carcinomas, NST specimens and matching samples from 28 lymph node metastasis, 2 LRR and 8 distant metastases.

Results: AR expression was found in 35.0% (42/120) of the total patients and 14.5% (8/55) of those diagnosed as TNBC. Positive expression of AR was significantly correlated with smaller tumor size, early T stage, fewer lymph node metastases, early AJCC stage, lower histologic grade, estrogen receptor/progesterone receptor positivity, more luminal A type, less TNBC, longer disease-free survival and overall survival, fewer distant metastasis and no deaths from breast cancer (all $P < 0.05$). AR was a favorable prognostic marker for disease free survival in univariate analysis ($P = 0.041$). The discordance rate of AR status between primary and recurrent/metastatic disease was 21.6%.

Conclusions: AR expression was associated with favorable clinicopathological outcomes in the whole study population. AR status can be altered during tumor progression.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

201P The outcomes of early breast cancers utilizing the oncotype Dx recurrence score (RS) instead of clinico-pathological (CP) factors for prognostic risk assessment: A single institution experience

A.N. Alsayed[1], T. Al-Twejeri[1], K. Suleman[1], A. Tulbah[2], D. Ajarim[1]

[1]Oncology Centre, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [2]Pathology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: Genomic profiling of hormone receptor positive breast cancer outperforms CP factors in predicting the outcomes. This has led to wider application of genomic testing for risk stratification. This can lead to avoidance of chemotherapy in patients with favorable outcomes.

Methods: Patient with T1, T2, node negative estrogen and or Progesterone receptor positive Her 2 Negative breast cancer, regardless of age, menopausal status, Grade or Ki67 were eligible for risk prediction using the Oncotype DX RS. All patient who had RS were included from March 2012- September 2017. The test was sent out and done in reference laboratory (Genomic Health). The original cut off of Low RS (<18), Intermediate RS18-31 and high RS > 31 was used. Patient with low RS were spared chemotherapy. While those high score received chemotherapy. Intermediate risk was preferably given chemotherapy. The changes in therapy based on RS score were reordered as compared to CP factors (St. Gallen Criteria). The disease free and overall survival was analyzed.

Results: Complete data was available for 141 Patients. Median age was 51 years (30-78). 54% premenopausal. 97% ductal histology. Grade correlated with RS with higher grade having higher RS. There was 67% reduction in use of adjuvant chemotherapy when compared to decision based on CP factors while 1 patient had escalation of therapy based on RS. Median follow up was 32 months (3-73 months). The 5 year estimated DFS was 95%. The overall survival was 98%. Only recurrence score correlated with DFS $p = 0.04$ while age, Ki67, grade, tumor size did not.

Conclusions: Our data in a younger group of mainly premenopausal women with early breast cancer is consistent with the published date about the prognostic value of RS. A substantial percentage of these patient can be spared chemotherapy and its related toxicity without adversely affecting the long-term outcomes. Utilizing RS in decision making may potentially be cost effective.

Legal entity responsible for the study: The breast cancer group at KFSH.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

202P Circulating tumor cells as a prognostic marker in non-metastatic breast cancer patients

S.M. Elmorshidy[1], O.N. Abd Elffatah[1], H.H. Essa[1], A.K. Ibrahim[2], D. Sayed[3], S. Shehata[1]

[1]Clinical Oncology, Assiut University Hospitals, Assiut, Egypt, [2]Community Medicine Department, Assiut University Hospital, Faculty of Medicine, Assiut, Egypt, [3]Clinical Pathology, South Egypt Cancer Institute, Assiut, Egypt

Background: Still, there is no clinically reliable marker to detect micro-metastasis or breast cancer relapse. This study aimed to evaluate the role of circulating tumor cells (CTCs) as a biomarker in non-metastatic breast cancer patients.

Methods: CTCs quantification was carried out using flow cytometry for 50 breast cancer patients post-operatively on three intervals; before starting, after three cycles and at the end of adjuvant chemotherapy. The relationship between CTCs and other tumor characteristics and outcomes were studied.

Results: The median follow-up duration was 35 months. Before starting adjuvant chemotherapy, CTCs were positive (cut off point $\geq$5) in 36% of the patients and dropped to 20% after finishing chemotherapy ($P = 0.04$). There was a strong negative correlation (r=-0.89) between change in the CTC levels from baseline till mid-treatment (3 cycles)

and from this point to the end of treatment (6 cycles) (R2=79.2). CTCs were detected in 88.9% (n = 16 of 18) of node-positive patients and in 11.1% of node-negative patients (n = 2 of 18, p-value =0.04). No significant association was found with tumor size, grading, or hormone receptor status. Distant metastasis was detected in 20% (n = 10 of 50) of patients and was significantly associated with CTCs ≥ 5 in 80 % of them (n = 8 of 10) p-value =0.01. The presence of ≥ 5 CTCs at baseline was associated with reduction in both the disease-free survival and overall survival (p-value <0.001 and =0.003, respectively) . Baseline CTCs ≥5 were confirmed as an independent prognostic factor in multivariate cox hazard regression analysis for DFS (HR = 3.71; 95% CI = 1.62-8.48; p-value=0.002 and OS (HR = 3.14; 95% CI = 1.34-7.37;p-value= 0.009).

Conclusions: The findings of the current work suggested that the presence of ≥ 5 CTCs at baseline would predict early disease recurrence and reduce the overall survival in primary, non-metastatic breast cancer patients receiving adjuvant chemotherapy. Thereby, peripherally detected CTCs could be used as a new prognostic marker for identification of early relapse and survival reduction.

Legal entity responsible for the study: Assiut University, Egypt.

Funding: Assiut University Hospitals, Egypt.

Disclosure: All authors have declared no conflicts of interest.

203P Molecular subtyping of breast cancer by dedicated breast PET

S. Sueoka, S. Sasada, E. Suzuki, N. Goda, K. Kajitani, A. Emi, N. Masumoto, T. Kadoya, R. Haruta, T. Kataoka, M. Okada

Breast Surgery, Hiroshima University Hospital, Hiroshima, Japan

Background: Therapeutic strategies for treating breast cancer differ according to molecular subtype. We investigated whether dedicated breast PET (DbPET), a high-resolution molecular breast imaging system, could stratify breast cancer by subtype.

Methods: We included 390 patients with invasive breast cancer who underwent ring-type DbPET between January 2016 and March 2018. The association between SUV_{max} and various tumor characteristics such as size, nuclear grade, estrogen receptor (ER) status, human epidermal growth factor receptor 2 (HER2) status, and Ki-67 labeling index, were assessed. Tumor subtypes were classified as luminal A-like, luminal B-like, ER+/HER2+, ER-/HER2+, or triple negative on the basis of the St. Gallen International Expert Consensus.

Results: The median patient age was 57 years, the median tumor size was 1.5 cm, and the median SUV_{max} on DbPET was 6.9. The number of patients with each subtype was luminal A-like in 113, luminal B-like in 185, ER+/HER2+ in 40, and ER-/HER2+ in 12, and triple negative in 40 patients. SUV_{max} significantly correlated with tumor size ($P < 0.001$), nuclear grade ($P < 0.001$), ER status ($P = 0.004$), HER2 status ($P < 0.001$), and Ki-67 labeling index ($P < 0.001$). The median SUV_{max} values of the luminal A-like, luminal B-like, ER+/HER2+, ER-/HER2+, and triple negative subtypes were 4.6, 8.2, 9.5, 16.1, and 10.4, respectively (Table, all values of $P < 0.001$ relative to luminal A-like). Thus, DbPET distinguished luminal A-like tumor subtype from other subtypes.

Table: 203P

SUVmax on dedicated breast PET according to molecular subtypes.

Subtypes	Median SUVmax (IQR)	P value reffered to luminal A-like
Luminal A-like	4.6 (3.0-6.8)	
Luminal B-like	8.2 (4.6-12.4)	< 0.001
ER+/HER2+	9.5 (5.5-16.6)	< 0.001
ER-/HER2+	16.1 (7.5-20.2)	< 0.001
Triple negative	10.4 (4.2-17.0)	< 0.001

Conclusions: DbPET can be used to classify breast cancer into molecular subtypes, which may help determine the necessity of adjuvant chemotherapy. SUV_{max}, as assessed on DbPET, may thus contribute to the selection of proper therapeutic strategies in invasive breast cancer.

Legal entity responsible for the study: Hiroshima University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

204P Analytical validation of OncoMasTR, a multigene test for predicting risk of distant recurrence in hormone receptor-positive early stage breast cancer

T. Loughman[1], A. Chan-Ju Wang[1], P. Dynoodt[1], B. Fender[1], C. Lopez Ruiz[1], S. Barron[1], S. Stapleton[1], D. O'Leary[1], A. Fabre[2], C. Quinn[2], B. Nodin[3], K. Jirstrom[4], A. Bracken[5], W.M. Gallagher[6]

[1]OncoMark Limited, NovaUCD, Dublin, Ireland, [2]Histopathology, St. Vincent's University Hospital, Dublin, Ireland, [3]Oncology and Pathology, Clinical Sciences, Lund, Sweden, [4]Department of Clinical Sciences, Lund University, Lund, Sweden, [5]Smufit Institute of Genetics, Trinity College Dublin, Dublin, Ireland, [6]UCD Conway Institute, University College Dublin, Dublin, Ireland

Background: OncoMasTR is a new multigene prognostic test that was discovered via a novel transcriptional network analysis method that identified upstream Master Transcription Regulators (MTRs), which regulate previously identified prognostic biomarkers. The optimised OncoMasTR signature incorporating clinicopathological information has been shown to be significantly prognostic for predicting distant recurrence in two independent cohorts (TransATAC & a subset of TAILORx from participating Irish centres). The analytical performance characteristics of the OncoMasTR test, comprising solely three prognostic MTRs, were determined.

Methods: Relative gene expression levels were measured by RT-qPCR. Assay precision and input ranges were determined using a panel of samples representative of low and high recurrence risk tested across a number of runs incorporating different sources of variation. Serial dilutions of a pooled patient RNA sample was used to establish the linear range and efficiency of the individual gene assays.

Results: The overall standard deviation of the OncoMasTR risk score was 0.15, which represents less than 2% of the 10-unit risk score range. The majority of the variability in OncoMasTR results was related to within-run variation (78.2%) with other between-run variation sources contributing relatively little (PCR instrument (0.6%), assay operator (5.2%), reagent lots (7.3%) or loading position (8.7%)). Consistent risk scores were measured for individual samples from 40ng down to < 1ng RNA per PCR reaction. Individual gene assays were linear over >500-fold RNA input range corresponding to C_T values of 23 – 36, demonstrating the ability of the test to reliably detect low level expression of the OncoMasTR panel. Importantly, PCR efficiencies were similar for the individual MTR and reference gene assays which ranged from 79 – 95%.

Conclusions: The OncoMasTR prognostic test displays robust analytical and clinical performance and is being launched as a CE-marked test. The concise nature of the three gene signature and a simplified workflow that can be readily adopted using standard laboratory equipment will enable convenient qualification by local laboratories for decentralised use.

Legal entity responsible for the study: OncoMark Limited.

Funding: EU Horizon 2020 SME Instrument.

Disclosure: T. Loughman, A. Chan-Ju Wang, P. Dynoodt, B. Fender, C. Lopez Ruiz, S. Barron, S. Stapleton: Employee: OncoMark Limited. D. O'Leary, W.M. Gallagher: Director and shareholder: OncoMark Limited. A. Fabre, C. Quinn: Consultant histopatholgist: OncoMark Limited. A. Bracken: Co-inventor and patent holder for OncoMasTR. All other authors have declared no conflicts of interest.

205P Comparing the prognosis of favourable-histology breast cancers between younger women of less than 45 years of age at diagnosis with their older counterparts

G.E. Lee[1], W.H. Hor[2]

[1]Medical Oncology, National Cancer Center, Singapore, [2]Business School, Imperial College London, Singapore

Background: Tubular, cribriform and mucinous carcinomas account for <10% of all breast cancer histology. They have excellent prognosis and aggressive treatment with chemotherapy is usually not warranted. Younger age at breast cancer diagnosis is often associated with a poorer prognosis in early breast cancers, however little is known about the natural history of favourable-histology breast cancers for younger women compared to their older counterparts. We aim to compare the prognosis of younger women less than 45 years of age with their older counterparts for early breast cancers with favourable histology.

Methods: Using the SEER dataset from 1988-2015, we identified 20 577 women diagnosed with early stage breast cancers of favourable histology i.e. tubular, cribriform, and mucinous carcinoma. We extracted the information on age of diagnosis, estrogen receptor (ER) status, progesterone receptor status (PR), HER2 status, ethnicity, cause of death, and survival months. The survival was compared between women < 45 years of age at diagnosis versus ≥ 45 years using log-rank test and cox-regression to give a univariate and multi-variate analysis.

Results: Among 20577 women with early stage favourable-histology breast cancers, we identified 1308 (6.4%) tubular, 6486 (31.5%) cribriform, and 12 783 (62.1%) mucinous breast cancer. The median age of diagnosis is 42 and 64 years of age for the younger group of < 45 years of age and older group of ≥ 45 years of age respectively. 85% of the breast cancer in younger women were ER+ while 88% in the older age group were ER+. In a univariate analysis, the median breast cancer specific survival for early stage favourable histology breast cancer was 120 months for women < 45 years of age and 100 months for women ≥ 45 years of age ($p < 0.001$). In multi-variate analysis,

accounting for tumour size, nodal status, stage, grade, hormone receptor status, HER2 receptor status, histologic type and year of diagnosis, younger age still predicts for a better outcome ($p < 0.001$).

Conclusions: Younger women diagnosed with early stage favourable-histology breast cancers have a better prognosis compared to older women. This will help in counselling on prognosis and management of younger patients.

Legal entity responsible for the study: Guek Eng Lee.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

206P TNBC universe: A monocentric retrospective analyses of TILs and AR as prognostic markers

A. Losurdo[1], R. De Sanctis[1], B. Fernandes[2], V. Errico[3], A. Sagona[3], G. Masci[1], M. Zuradelli[1], E. Agostinetto[1], R. Torrisi[1], W. Gatzemeier[3], A. Testori[3], M. Roncalli[2], M. Alloisio[3], C. Tinterri[3], A. Santoro[1]

[1]Medical Oncology and Hematology, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy, [2]Pathology, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy, [3]Breast Surgery, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy

Background: TILs have been proposed as a prognostic biomarker in many tumor types both in the adjuvant and neoadjuvant setting. In TNBC, TILs are present at the highest level and have been demonstrated to be associated with better prognosis. TNBC is a highly diverse group of cancers and subtyping is necessary to better identify patient-tailored therapies. Cluster analysis by gene expression identified 6 TNBC subtypes among which the so called "luminal androgen receptor subtype".

Methods: We retrospectively collected 160 early stage TNBC consecutively treated at our Institution from 2006 to 2015. Data were obtained for clinico-pathological patients' characteristics. On IHC archive slides we analyzed stromal TILs scored as a continuous variable and androgen receptor's (AR) percentage and intensity of expression. We performed Cox analyses for DFS and for OS, and we used chi-square and Fisher test to evaluate the correlation between TILs, AR and other clinical variables. To define high vs low TILs, an internal dataset cut-off of 10% was considered.

Results: 150 patients were eligible for IHC analyses of TILs and AR. With a median follow-up of 6.5 years, 41 local and/or distant relapse events were observed and 28 patients died of disease. Interestingly, TILs were found to be significantly associated with nodal status (N0 vs N1-3), grading (G2 vs G3) and Ki-67 ($<20\%$ vs $\geq 20\%$) ($p = 0.007$, $p = 0.055$ and $p = 0.002$, respectively). AR was also significantly associated with proliferation, specifically AR-positive cases presented mostly with a Ki-67$<20\%$ ($p = 0.008$). Probably due to the paucity of events, no statistically significant association of TILs and AR with either DFS or OS was observed.

Conclusions: TILs are a promising prognostic marker, but still prospective validation is needed to integrate them into clinical practice. Among TNBC, the identification of AR-expressing luminal subtype might provide a targeted therapy chance for a low proliferation TNBC subtype. Larger prospective trials are likely to validate TILs prognostic role and to explore the universe of TNBC subtypes targeted therapies opportunities.

Legal entity responsible for the study: Istituto Clinico Humanitas.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

207P Genomic spectrum of Asian breast cancer based on targeted next-generation sequencing in 150 consecutive primary breast cancer

C. Cha[1], S.J. Bae[1], C-I. Yoon[1], S.E. Park[1], Y. Kim[2], S.G. Ahn[1], K.A. Lee[2], J. Jeong[1]

[1]Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Department of Laboratory Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Background: Application of next-generation sequencing (NGS) enables to reveal genetic diversity of malignant tumors. Here we report our experience with targeted NGS in Asian patients with primary breast cancer.

Methods: We identified 150 Asian patients who had genotyping by targeted NGS between April 2017 and Mar 2018 in a single institution. The genetic mutation patterns of the patients were analyzed retrospectively. Targeted NGS with the Oncomine^{TM} comprehensive panel including 143 genes was conducted on Ion Torrent S5 XL (Thermo Fisher Scientific, Waltham, MA, USA). All patients had stage I-III by AJCC 7th edition.

Results: Targeted NGS was conducted in a total of 150 primary breast cancer including 98 (65.3%) patients of the luminal/HER2-negative subtype, 28 (18.7%) patients of the HER2 subtype, and 24 patients of the (16.0%) TNBC subtype. Of the 150 patients, 138 patients had 432 genomic alterations including 306 mutations and 126 aberrant copy number variations (CNV). The most common genetic mutation was PIK3CA mutation (64 patients, 42.7%), followed by TP53 mutation (48 patients, 32.0%), TET2 mutation (26 patients, 17.3%) and ERBB2 mutation (6 patients, 4.0%). Of the 6 patients with ERBB2 mutations, 5 patients were in the luminal/HER2-negative subtype and 1 in the HER2 subtype. When ERBB2 amplification excluded, most common CNV was found in FGFR1 (12 patients, 8.0 %) followed by CCND1 (10 patients, 6.7 %). In 35 ER-positive/HER2-negative patients who agreed to receive Oncotype DX assay, 18 patients (48.6%) had PIK3CA mutation. In patients with PIK3CA mutation, 13 (72.2%) had a low RS, and 5 patients (27.8%) had an intermediate RS. A patient with RS of 27, which is recognized as high score by the criteria of TAILORx trial, had co-mutations as PIK3CA^{H1047R} and P53^{K132N}.

Conclusions: Our data with targeted NGS panel suggested that genomic landscape of Asian breast cancer is in accordance with previous NGS studies with Western women. In addition, our subgroup study with Oncotype DX supports early notion that ER-positive breast cancer patients with PIK3CA mutation show a better prognosis compared with those without PIK3CA mutation.

Legal entity responsible for the study: Chihwan Cha.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

208P The impact of the 21 gene recurrence score (RS) on chemotherapy (CHemoRx) prescribing in hormone receptor (HR) positive, lymph node positive (LN+) early-stage breast cancer (BC) in Ireland: A national, multi-centre, prospective study (CTRIAL-IE 15-34)

A. Hassan[1], N. Keegan[1], C. O'Leary[1], L. McSorley[1], T. Mahgoub[1], S. O'Reilly[2], J. Walshe[3], M.J. Kennedy[4], L. Coate[5], M. O'Connor[6], M. Keane[7], C.M. Kelly[8], M. Milewski[1], S. Molloy[1], K. Eagan[1], V. Murphy[9], O.S. Breathnach[1], L. Grogan[1], B. Hennessy[1], P.G. Morris[1]

[1]Cancer Clinical Trials and Research Unit, Beaumont Hospital, Dublin, Ireland, [2]Department of Medical Oncology, Cork University Hospital, Cork, Ireland, [3]Department of Medical Oncology, St Vincent's University Hospital, Dublin, Ireland, [4]Oncology Directorate, St James's Hospital, Dublin, Ireland, [5]Department of Medical Oncology, Mid-Western Cancer Centre, University Hospital Limerick, Dooradoyle, Ireland, [6]Department of Medical Oncology, University Hospital Waterford, Waterford, Ireland, [7]Department of Medical Oncology, University Hospital Galway, Galway, Ireland, [8]Department of Medical Oncology, Mater Misericordiae University Hospital University College Dublin, Dublin, Ireland, [9]Translational Research Unit, Cancer Trials Ireland, Dublin, Ireland

Background: The 21 gene RS has improved the selection of patients (pts) for ChemoRx in early BC. Internationally, the RS is used in LN+ disease, but has not been reimbursed for this indication in Ireland. We conducted a prospective study to determine the extent to which use of the RS could alter Oncologists' ChemoRx recommendations in pts with LN+ BC.

Methods: Eligible patients had 1-3 LN+, HR+ HER2- BC. All pts gave written informed consent. Baseline demographics were collected. Questionnaires were completed by a Consultant Oncologist before and after the RS, which examined expectations of tumour chemo-sensitivity, strength of ChemoRx recommendation and type of planned ChemoRx. The primary endpoint was the % reduction in pts recommended ChemoRx ($N = 75$).

Results: RS was available on 74/75 pts; median age 54 (range 32-78) years. Most pts had T1 (43%) / T2 (47%), grade 2 (72%) tumours with 1 LN + (68%). The RS was <11 in 10 (13%), 11-25 in 56 (76%) and >25 in 8 (11%) pts. Access to the RS led to a 27% reduction in ChemoRx recommendations from 68 (92%) to 48 (65%) pts. This was most notable in pts with 1 LN + (46 vs 24) and 2 LN + (13 vs 7). Access to the RS led to a reduction in physician perception of tumour chemosensitivity and strength of ChemoRx recommendation (Table). Use of the RS led to a decrease in Anthracycline (A)-Taxane (T) ChemoRx (30 vs 17 pts) and T-based ChemoRx (30 vs 21 pts) with a resultant increase in non-A, non-T ChemoRx (8 vs 10 pts). The use of the RS did not impact on ChemoRx recommendations in women <40yrs (all got ChemoRx). The biggest reduction in ChemoRx occurred in women age 51-70 with 1LN + (28 vs 18 pts). Overall, in 47 (64%) cases, Oncologists thought the RS significantly changed their treatment recommendations.

Table: 208P

Physician questionnaires before and after RS

1. How sensitive will the tumour be to ChemoRx?				
1	2	3	4	5
Not very sensitive				Very sensitive
Before RS				
10 (13)	32 (43)	21 (28)	10 (13)	1 (1)
After RS				
21 (28)	26 (35)	15 (20)	11 (15)	5 (7)
2. How strongly do you recommend ChemoRx?				
1	2	3	4	5

Continued

Table: 208P *Continued*

Physician questionnaires before and after RS				
Not very strongly				Very strongly
Before RS				
7 (9)	22 (30)	20 (27)	20 (27)	5 (7)
After RS				
23 (31)	16 (22)	10 (13)	21 (28)	4 (5)

Conclusions: Broader access to the 21 gene RS could result in a reduction in the use of ChemoRx in Ireland.

Legal entity responsible for the study: Cancer Trials Ireland.

Funding: Genomic Health Company.

Disclosure: P.G. Morris: Honoraria: Genomic Health Company. All other authors have declared no conflicts of interest.

209P Lymphocyte-predominant breast cancer has a significant lower mean of absolute neutrophil counts compared to non-lymphocyte-predominant breast cancer: Analyses with 576 cases

D.Y. Lee, S.E. Park, C. Cha, C-I. Yoon, S.J. Bae, S.G. Ahn, J. Jeong

Department of Surgery, Gananam Severance Hospital, Seoul, Republic of Korea

Background: Tumor-infiltrating lymphocytes (TILs) in surgical-specimen might be associated with host-cell mediated immunity, which could be partly reflected by blood cell counts from peripheries. We investigated whether peripheral blood cell counts are associated with TILs in 577 patients with breast cancer.

Methods: Between August 2016 and April 2018, we evaluated the percentage of stromal TILs in breast cancer patients who underwent primary surgery according to standardized methodology proposed by the international TIL Working Group. Lymphocyte-predominant breast cancer (LPBC) was defined as tumors having high TIL levels ($\geq$ 50%). Blood cell counts including absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), percentages of ANC and ALC, and neutrophil-to-lymphocyte ratio (NLR) was obtained from pretreatment laboratory data.

Results: Of 577 tumors, 99 (17.2%) was LPBC, and 478 (82.8%) was non-LBPC. When 5 markers of peripheral blood counts were compared, LPBC had a significantly higher mean ANC than non-LPBC (3,671 vs. 3,336; $P = 0.004$), but other means were not different. Further, in luminal/HER2-negative breast cancer, mean ANC of LPBC was still higher than that of non-LPBC ($P = 0.025$), whereas it tended to be higher in LPBC in other subtypes ($P = 0.385$ in HER2, $P = 0.260$ in TNBC).

Conclusions: Our results suggest that low peripheral ANC might be linked with LPBC, supporting the hypothesis that systemic immune cell counts might be associated with tumor-immune microenvironment. Further study on an association between peripheral ANC and tumor-associated neutrophil consisting tumor micromileu is warranted.

Legal entity responsible for the study: The Institutional Review Boards of the Gangnam Severance Hospital, Yonsei University, Seoul, Korea.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

210P Genetic alterations of early-stage breast cancers by next-generation sequencing (NGS)

Y. Xu[1], M. Zhang[2], R. Chen[2], X. Xia[2]

[1]General Surgical Department, Daping Hospital of Chongqing, Chongqing, China, [2]Medical Center, Geneplus-Beijing Institute, Beijing, China

Background: Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women. Patients diagnosed with early stage generally have better survival. However, disease free survival differed significantly for different molecular subtypes. Understanding the genetic alterations of early-stage breast cancer may help to identify patients at high risk for relapse.

Methods: We retrospectively reviewed genetic profiling of 53 early-stage breast cancer samples in our institute. Surgical specimens were analyzed using hybridization capture-based NGS ER-seq method, white blood cells as control, which enables simultaneously assess single-nucleotide variants (SNV), insertions/deletions (indel), rearrangements and somatic copy-number variation(CNV) of 1021 genes.

Results: Fifty-three surgical specimens from 51 female patients with early-stage breast cancer were analyzed, including two bilateral primary breast cancers with different molecular subtypes. There were 29 HR+/HER2-, 6 HER2+, 6 HR+/HER2+ and 12 TNBC. The median diagnosis age was 43(range 31-67). In addition to TP53, there were 16 genes carried actionable mutations identified (details in table). The most frequently mutant genes were TP53 and PIK3CA, in all molecular subtypes. Among PIK3CA mutations, the H1047R/L were tested in all subtypes. Other gene alterations were highly heterogeneous in different molecular subtypes. HRAS or KRAS mutation was always identified with other genes. For instance, HRAS/PIK3CA and KRAS/AKT1 concurrent in 2 HR+/HER2-, KRAS/PIK3CA concurrent in 1 TNBC. Interestingly, for the two bilateral primary breast cancers, one patient had no overlapping mutation in 2 samples within total 6 variants, the other one only had common HER2 CNV in 2 samples within total 13 variants.

Table: 210P

Signaling Pathways	Genetic Alterations	HR+/HER2-(29)	HER2+(6)	HR+/HER2+(6)	TNBC(12)
p53	TP53	14	5	4	11
PI3K/AKT/mTOR	PIK3CA	12	3	1	3
	AKT1	6	-	-	-
	PTEN	3	-	-	-
	NF1	1	-	-	-
	FLCN	1	-	-	-
Homologous recombination repair	BRCA1(gm)	-	-	-	1
	BRCA1(sc)	-	1	-	-
	BRCA2(gm)	2	-	-	-
	BRCA2(sc)	-	1	-	-
	ATM(gm)	-	-	1	-
Ras/Raf/MAPK	HRAS	1	-	-	-
	KRAS	1	-	-	1
Cell cycle	RB1	1	-	-	-
	CDKN2A	1	-	-	-
	CCND1	1	-	-	-
RTKs	FGFR1	1	-	1	-
	HER2 CNV	-	4	5	-
	EGFR CNV	-	-	-	1

sc, somatic mutation; gm, germline mutation.

Conclusions: Genetic alterations were highly heterogeneous in different molecular subtypes of early-stage breast cancers. And this may contribute to the different relapse risk.

Legal entity responsible for the study: Geneplus-Beijing.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

211P Oncotype Dx results in patients ≤40 years: Does age matter? New insights

F. Namuche[1], R.E. Ruiz[2], Z.D. Morante Cruz[2], D. Urrunaga[3], G. Ziegler[4], R. Mantilla[4], M. Leon Rivera[5], M. Chavez Mac Gregor[6], H.L. Gomez Moreno[7]

[1]Oncology, Oncosalud, Lima, Peru, [2]Oncology, Instituto Nacional de Enfermedades Neoplasicas - INEN, Lima, Peru, [3]Medicine, USMP, Lima, Peru, [4]Mastology, URP, Lima, Peru, [5]Oncology, Clinica Ricardo Palma, Lima, Peru, [6]Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [7]Medicine, Instituto Nacional de Enfermedades Neoplasicas - INEN, Lima, Peru

Background: The 21-gene recurrence score (RS) predicts the benefit of adjuvant chemotherapy (CT) in ER-positive, HER2-negative breast cancer (BC) and has been validated in a population where women under 40 are underrepresented. Young BC pts are more likely to receive adjuvant chemotherapy (CT) in addition to endocrine therapy (ET). Our objective was to assess the RS results in young ($\leq$40 yo) vs older (>40 yo) pts and evaluate the impact of age on clinical decision making according to RS categories.

Methods: We retrospectively reviewed electronic medical files of all patients with early stage hormone receptor BC for whom RS was available between 2007 and 2017 in 3 specialized cancer centers. We used the Mann-Whitney and Chi-squared tests to assess differences between age group. Similarly, we evaluated the association between age groups and treatment, within each ODx category. To determine if age was associated with CT use in the low-risk category, a logistic regression model was constructed.

Results: A total of 551 pts were included, 53 (9.6%) $\leq$40 yo and 498 (90.4%) >40 yo. No statistical differences were found between the younger and older groups in T ($p = 0.874$), N ($p = 0.794$), stage ($p = 0.188$), or grade ($p = 0.791$). Young patients underwent radical surgery more frequently than their older counterparts (41.5% vs 25.7%, $p = 0.014$). Statistically significant differences were also observed in ER mean, which was lower in the younger group (80% vs 90%, $p < 0.001$). The median RS result was significantly higher in the younger group (19 vs 16, $p = 0.009$). Also, high-risk recurrence score category was significantly more frequent in the younger group (22.6% vs 9.2%, $p = 0.009$). In the intermediate-risk category there were no differences in the

proportion of patients who received CT according to age groups ($p = 0.484$). In the low-risk category, 28.0% of patients ≤40 years vs 11.3% of patients >40 years received CT ($p = 0.037$).

Conclusions: Our results indicate that RS tends to be higher in patients with BC ≤ 40 yo and that the frequency of high-risk RS is significantly higher in the younger group, suggesting biological differences between groups. 28% of young patients with low-risk RS from our cohort are overtreated. Based on these results, it should be considered to develop a test adjusted to the age of the patients.

Legal entity responsible for the study: Oncosalud.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

212P Impact of BRCA status on outcomes and survival in high-risk early breast cancers

E. Klajer[1], S. Paget-Bailly[2], G. Meynard[1], A. Meurisse[2], F. Bazan[1], L. Chaigneau[1], E. Dobi[1], N. Meneveau[1], P. Montcuquet[1], C. Villanueva[1], A. Thiery-Vuillemin[1], E. Kalbacher[1], C. Populaire[3], M.-A. Collonge-Rame[3], J. Gligorov[4], E. Curtit[1], X. Pivot[5], L. Mansi[1]

[1]Medical Oncology, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [2]Methodology and Quality of Life in Oncology Unit, UMR 1098, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [3]Medical Biologic Genetic and Clinical Oncogenetic, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [4]Medical Oncology APHP, CancerEst, Tenon University Hospital, Paris, France, [5]Medical Oncology, Centre Paul Strauss Centre de Lutte contre le Cancer, Strasbourg, France

Background: Relationship between the presence of the BRCA mutation (BReast CAncer) and outcomes is unclear, especially in high-risk breast cancers. The aims were to describe clinical and pathological outcomes considering mutational status and to assess the prognostic impact of germinal BRCA mutated status (BRCAm) in this high-risk population.

Methods: A multi-center retrospective cohort of patients treated in Franche-Comté between 2003 and 2013 for an early breast cancer (eBC) by neoadjuvant and/or adjuvant chemotherapy was analyzed. Clinical and pathological outcomes were described and distributions were compared in regards of mutational status group performing Fisher exact tests. Kaplan-Meier method and log-rank tests were used to compare survival in terms of overall survival (OS. Univariate and multivariate Cox proportional hazards models were estimated for OS.

Results: A total of 2,295 patients were included. Among them, 240 patients were tested (10.5%) including 60 patients diagnosed with BRCAm (2.6%). Among them, 36 were BRCA1 (1.6%), 22 BRCA2 (1%) and two BRCA1 and 2 (0.01%). Age at diagnosis ($p < 0.0001$), histological type ($p = 0.0043$), size ($p = 0.0021$), nodal status ($p < 0.0001$), histologic grade ($p = 0.0009$), triple negative status ($p < 0.0001$) and in situ component ($p = 0.0163$) were significantly different between BRCAm, BRCAwt and untested patients. BRCA1 mutated tumors were mostly triple negative tumors contrary to BRCA2 mutated tumors, which were mostly locally advanced luminal tumors. In multivariate analysis, OS was not associated with BRCAm status ($p = 0.5690$).

Conclusions: Among this French cohort of high-risk eBC, incidence of BRACm cases was 2.6%. BRCA1 and BRCA2 breast cancers were two distinct tumors in term of pathological outcomes. BRCAm status had no significant impact on OS.

Legal entity responsible for the study: CHU Besançon.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

213P Early breast cancer classified as intermediate risk by the Prosigna assay: Characteristics and treatment strategy

N. Hajjaji[1], Y.M. Robin[2], D. Bertin[2], J.M. Bonneterre[1]

[1]Breast Cancer Department, Centre Oscar Lambret, Lille, France, [2]Pathology, Centre Oscar Lambret, Lille, France,

Background: Genomic-based signatures are implemented in clinical practice to guide adjuvant treatment strategy in early breast cancer patients with luminal tumors. One of the main signatures, the PAM50-based Prosigna assay classifies patients into 3 risk categories based on their score of recurrence, thus providing clear guidance in low or high risk tumors. This study aimed at assessing in real life the proportion of patients with intermediate (ITD) risk results with the Prosigna assay, their tumor profile and the factors influencing treatment decision.

Methods: This monocentric retrospective study was conducted in 107 patients with luminal early-stage breast cancer treated at Oscar Lambret Cancer Center (Lille, France). Their tumors were analyzed with the Prosigna assay from July 2016 through April 2018.

Results: The Prosigna assay classified 15% of the patients in the low risk group, 41% were high risk, and 44% ITD risk. In this group, approximately one third were node negative and two third node positive. The tumor profiles with the highest proportion of ITD risk results had the following characteristics: 14≤Ki67≤20% and grade 2 in node negative or positive patients, or Ki67<14% and grade 2 in node positive patients (Table). 83% of the patients with an ITD risk result (39 of 47) were spared chemotherapy. Among them, 34 had luminal A and 5 luminal B tumors. Among the 8 patients proposed chemotherapy, luminal A and B tumors were evenly split. The main determinant of this decision was an estimated 10-year risk of relapse over 10 or 11%.
Table: Prosigna risk groups distribution within patients' main tumor profiles.

Table: 213P

	Prosigna risk groups						
	Low		Intermediate		High		
Main Tumor Profiles (99 of 107 patients)	n	%	n	%	n	%	Total (n)
14≤Ki67≤20% - G2 - N0	5	33	7	47	3	20	15
14≤Ki67≤20% - G2 - N1	0		10	59	7	41	17
Ki67<14% – G2 - N0	6	60	3	30	1	10	10
Ki67<14% – G2 - N1	0		13	65	7	35	20
Ki67>20% – G2 - N0	2	17	4	33	6	50	12
Ki67>20% – G2 - N1	0		1	9	10	91	11
Ki67>20% – G3 - N0 - T1	0		3	43	4	57	7
Ki67<14% – G1 - N1	2	29	4	57	1	14	7

G: grade; N0/N1: node negative / positive (1 to 3); T1: tumor size ≤ 20mm

Conclusions: Our study showed that a significant proportion of patients were classified in the intermediate risk group, and most were spared chemotherapy. A specific guidance is needed in this risk group.

Legal entity responsible for the study: Centre Oscar Lambret.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

214P Ki67 as an important predictor for oncotype Dx recurrence score risk groups in early breast cancer

F. Namuche[1], R.E. Ruiz[2], Z.D. Morante Cruz[2], D. Urrunaga[3], A. Aguilar Cartagena[4], H.L. Gomez Moreno[5]

[1]Oncology, Oncosalud, Lima, Peru, [2]Oncology, Instituto Nacional de Enfermedades Neoplasicas - INEN, Lima, Peru, [3]Medicine, USMP, Lima, Peru, [4]Oncology, Oncosalud SAC, Lima, Peru, [5]Medicine, Instituto Nacional de Enfermedades Neoplasicas - INEN, Lima, Peru

Background: The gene expression profiling assay OncotypeDx (ODx) prognosticates the risk of estrogen receptor positive (ER+) breast cancer (BC) recurrence and assesses the likely benefit from adjuvant chemotherapy in addition to endocrine therapy. There have been several attempts to develop algorithms that provide similar outcome prediction to the ODx assay with the use of routine clinicopathological characteristics. Ki67 is frequently incorporated into these assessments, although there is no standard cut-off for its use.

Methods: We retrospectively reviewed the electronic medical records of 330 patients with early stage ER+ BC for whom ODx recurrence score (RS) was available. Patients were diagnosed and treated at two specialized cancer centers between 2014 and 2017. Our objective was to determine the ki67's median differences between ODx risk groups. We used Spearman rho for the correlation between Ki67 and ODx score and used Kruskal-Wallis test for compare medians, pairwaise comparison for the intergroup relations.

Results: Mean age at diagnosis was 57.42 years (range 28-89). Mean tumor diameter was 15.67 mm. 78.9% were intermediate histologic grade and 9.7% patients had lymph node involvement. Median expression of ER and PR were 90% (5-100) and 70% (0-100), respectively. We assessed the correlation between Ki67 and ODx score, with a pearson r:0.31, $p < 0.001$. The data showed a directly proportional trend between Ki67 and ODx score. Median Ki67 was 20 (1-100). According to ODX RS, 61.5% of tumors were low risk, 30.3% were intermediate risk and, 8.2% were high risk. Median Ki67 within each category group is as follows: low: 15 (IQR:15), intermediate: 20 (IQR:18) and high: 40 (IQR:35), with a statistically significant difference between medians ($p < 0.001$). In the Pairwise comparison intergroup the data showed: Low-Intermediate ($p < 0.05$), Low-High ($p < 0.001$), Intermediate-High ($p < 0.001$).

Conclusions: The data showed directly proportional trend between Ki67 and ODx score. In our population there is a statistically significant difference between Ki67 medians according to ODx risk groups.

Legal entity responsible for the study: Oncosalud.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

215P Genetic signatures always suggest undertreatment? Experience with PAM50

C. Sales[1], I. Vieira[1], M. Cassiano[1], C. Oliveira[1], C. Vieira[1], M. Ferreira[1], A. Rodrigues[1], A. Ferreira[1], M.I. Pousa[1], R. Couto[1], C. Leal[2], J. Abreu[3], M. Teixeira[4], D. Pereira[1], S. Sousa[1], M.H. Abreu[1]

[1]Medical Oncology, Instituto Portugues de Oncologia Centro do Porto(IPO-Porto), Porto, Portugal, [2]Pathology, Instituto Portugues de Oncologia Centro do Porto(IPO-Porto), Porto, Portugal, [3]Surgical Oncology, Instituto Portugues de Oncologia Centro do Porto(IPO-Porto), Porto, Portugal, [4]Clinical Genetics, Instituto Portugues de Oncologia Centro do Porto(IPO-Porto), Porto, Portugal

Background: PAM50 (Prosigna®) identifies a gene-expression profile that categorises early breast cancer (BC) in intrinsic subtypes and gives prognostic estimation based on a 10 year-recurrence risk score (ROR). The purpose of this study was to evaluate the impact of PAM50's information on adjuvant treatment decisions.

Methods: Prospective collection of BC cases treated in a Cancer Centre in the last 10 months, in which PAM50 was used to define treatment strategy. Demographic, clinic and pathologic characteristics are described. Concordance between immunohistochemistry (IHC) and PAM50 subtypes were assessed as well as therapeutic decision changes according to risk stratification, using blind revision. Categorical variables were compared used chi-square test.

Results: Inclusion of 101 patients, median age of 52 years (34-79 years). Fifty-five patients (54.5%) were premenopausal, 71 (70.3%) had ductal carcinomas, 71 (70.3%) pT1c, 99 (98%) G2, 72 (71.3%) pN0, ER positive and HER2 negative. Eighty five(84.2%) had a PR expression above 20% and 63 (62.4%) had a Ki67≤15%. Overall discordance rate between BC subtypes by IHQ and PAM50 was 34%, ($p < 0.001$). By IHC, 51 (50.5%) were luminal A-like. Forty seven(92%) remained luminal A with PAM 50 [(low ROR: 28 (60%), intermediate:16 (34%), high:3 (6%)]. Four (8%) changed to luminal B [intermediate ROR:1 (25%), high:3 (75%)]. Of the 50 luminal B-like tumours (49.5%), 20 (40%) remained luminal B [intermediate ROR: 8 (40%); high:12 (60%)] and 30 (60%) changed to luminal A [low ROR:18 (60%), intermediate:12 (40%)]. Based on PAM50, adjuvant strategy was changed in 28 patients (28%), ($p = 0.001$): 15 (54%) changed from endocrine therapy (ET) only to chemotherapy (CT) also and 13 (46%) changed from CT and ET to ET only.

Conclusions: PAM50 availability results in 28% change in adjuvant plan with more cases of chemotherapy. The 34% discordance with classic IHC subgroups, especially in luminal B tumours, underlines the need for more accurate tests in this heterogeneous population to define the adequate adjuvant strategy. A longer follow up is important to evaluate the prognostic value of clinical decisions based on genetic signatures.

Legal entity responsible for the study: Breast Department - IPO-Porto.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

216P Significance of receptors expression, mitotic index and Ki67 in breast cancer patients with Nottingham Prognostic Index (NPI) poor prognosis score

M. Nesrine[1], H. El Benna[1], Y. Berrazegua[1], S. Labidi[1], N. Daoud[1], H. Boussen[2]

[1]Medical Oncology Abderrahmen Mami Hospital, Ariana, Tunisia, [2]Department of Medical Oncology, Hopital Abderrahman Mami, Ariana, Tunisia

Background: Nottingham Prognostic Index (NPI) is a used prognostic model for breast cancer patients, but new histological prognostic factors are today defined. We evaluated their effect within patients with poor prognosis NPI score.

Methods: We retrospectively selected 351 non-metastatic breast cancer patients with High NPI score (>5,4). They were classified according to surrogate definition of intrinsic subtypes of breast cancer (St Gallen 2015). Several prognostic factors were evaluated. We used log rank test, cox regression model to evaluate the significance of clinic-pathological factors.

Results: Median age of our population was 50 years. They were luminal A in 30%, Luminal B in 43%, HER overexpression in 10% and basal like in 17%. On univariate analysis, menopausal status (HR = 0,32 [0.13-0,76]), endocrine receptors expression (HR = 6,52 [2,57-16,54]), HER2 expression (HR = 3,08 [0.191-10.39]), Mitotic index (HR = 1,05 [1,02-1,09]) and obesity (HR = 3,49 [1,27-9,58]) were significant prognostic factors. There was no prognostic value of age<35 years, Ki 67 cut-off of 20% and nodal capsule rupture. There was a highly significant difference ($p < 0.0001$) in overall survival between the 4 intrinsic subtypes. Five-year overall survival was 95% for Luminal A, 90% for Luminal B, 56% for HER2 and 36% for basal-like. On multivariate analysis receptors expression and intrinsic subtype were significantly associated to survival ($p < 0.05$).

Conclusions: In NPI aggressive disease, the most important prognostic factors were receptors expression and intrinsic subtype. The elaboration of a histology-matched NPI score could afford better prognostic evaluation of early stage breast cancer.

Legal entity responsible for the study: Abderrahmen Mami Hospital, Medical Oncology Department.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

217P Subgroup analyses of efficacy from a phase III study comparing SB3 (trastuzumab biosimilar) with reference trastuzumab in early breast cancer patients

J. Cortes Castan[1], M. Pegram[2], X. Pivot[3], G. Curigliano[4], J.Y. Lim[5], S. Song[6], Y.C. Yoon[7]

[1]Breast Cancer and Gynecological Tumors, Vall d'Hebron University Hospital, Barcelona, Spain, [2]Medicine, Stanford Comprehensive Cancer Institute, Stanford, CA, USA, [3]Medical Oncology, Centre Paul Strauss Centre de Lutte contre le Cancer, Strasbourg, France, [4]Early Drug Development for Innovative Therapies Division, Istituto Europeo di Oncologia, Milan, Italy, [5]Clinical Development, Samsung Bioepis, Suwon, Republic of Korea, [6]Biometrics, Samsung Bioepis, Suwon, Republic of Korea, [7]Medical Affairs, Samsung Bioepis, Suwon, Republic of Korea

Background: SB3 has been approved by the European Commission as a biosimilar of reference trastuzumab (TRZ). Equivalence for efficacy between SB3 and TRZ based on breast pathologic complete response (bpCR) rates has been demonstrated and previously reported.[1] Here we report results of subgroup analyses of efficacy by baseline disease characteristics and demographics.

Methods: Patients received either SB3 or TRZ for 8 cycles concurrently given with chemotherapy (docetaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide). Then patients underwent surgery followed by 10 cycles of SB3 or TRZ. The primary endpoint was bpCR rate. Subgroup analyses of bpCR rate, total pathologic complete response (tpCR) rate, and overall response rate (ORR) by region, age, ethnicity, hormone receptor status, breast cancer type, and menopausal status was performed.

Results: 800 patients (SB3, n = 402; TRZ, n = 398) were included in the per-protocol set (PPS). The bpCR rates were 51.7% for SB3 and 42.0% for TRZ with adjusted difference of 10.70% (95% CI, 4.13, 17.26). Subgroup analysis results are provided in the table. A trend of favourable efficacy of SB3 compared to TRZ was maintained in most of subgroup analyses. Similar trends were observed in the subgroup analysis of tpCR rate and ORR. Table: bpCR rates by baseline demographics and disease characteristics.

Table: 217P

	SB3 n/n′ (%)	TRZ n/n′ (%)	Adjusted difference (%) (SB3-TRZ, 95% CI)
Region			
Europe	53/108 (49.1)	44/98 (44.9)	3.44 (-9.63, 16.51)
Non-Europe	155/294 (52.7)	123/300 (41.0)	13.18 (5.59, 20.77)
Age			
Age <45	59/121 (48.8)	48/119 (40.3)	9.20 (-3.08, 21.48)
Age ≥45	149/281 (53.0)	119/279 (42.7)	11.51 (3.76, 19.26)
Ethnicity			
Asian	68/124 (54.8)	51/124 (41.1)	15.52 (4.27, 26.78)
White	135/269 (50.2)	112/264 (42.4)	8.45 (0.28, 16.62)
Hormone receptor status			
ER and/or PR positive	119/254 (46.9)	78/230 (33.9)	12.87 (4.45, 21.28)
ER and PR negative	89/148 (60.1)	89/168 (53.0)	7.34 (-3.14, 17.83)
Breast cancer type			
Operable	120/241 (49.8)	97/238 (40.8)	10.14 (1.44, 18.85)
Locally advanced	88/161 (54.7)	70/160 (43.8)	11.53 (1.58, 21.48)
Menopausal status			
Yes	105/198 (53.0)	92/198 (46.5)	7.65 (-1.33, 16.64)
No	103/204 (50.5)	75/200 (37.5)	12.97 (3.81, 22.14)

CI, confidence interval; ER, oestrogen receptor; PR, progesterone receptor; n, number of patients achieving bpCR; n′, number of patients with available assessment results.

Conclusions: Subgroup analysis results of bpCR, tpCR, and ORR showed a tendency of favourable efficacy in SB3 compared to TRZ, which were consistent with the overall bpCR analysis result. Reference: 1. Pivot X et al. J Clin Oncol. 2018; 36:968-74.

Clinical trial identification: EudraCT: 2013-004172-35.

Legal entity responsible for the study: Samsung Bioepis Co., Ltd.

Funding: Samsung Bioepis Co., Ltd.

Disclosure: J. Cortes Castan: Honoraria: Roche, Novartis, Eisai, Celgene, Pfizer; Consulting/advisor: Roche, Celgene, Aztrazeneca, Cellestia Biotech, Biothera, Merus. X. Pivot: Principle investor: phase III study of SB3; Consultant and honoraria: Samsung Bioepis. G. Curigliano: Fee for a seminar on the abstract. S. Song, Y.C. Yoon: Employment: Samsung Bioepis. All other authors have declared no conflicts of interest.

218P Autoimmunity and benefit from trastuzumab treatment in breast cancer: Results from the HERA phase III trial

A. Sonnenblick[1], A. Bailey[2], B. Uziely[3], M. Untch[4], I. Smith[5], L. Gianni[6], J. Baselga[7], C. Jackisch[8], D. Cameron[9], R. Bell[10], D. Zardavas[11], N. Al-Sakaff[12], R. Gelber[13], M. Dowsett[14], B. Leyland-jones[15], M. Piccart[16], E. de Azambuja[17]

[1]Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Frontier Science, Kingussie, UK, [3]Oncology, Hadassah Medical Center, Jerusalem, Israel, [4]Clinic for Gynecology, Gynecologic Oncology and Obstetrics, Helios Klinikum Berlin Buch, Berlin, Germany, [5]Oncology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [6]Oncology, IRCCS San Raffaele, Milan, Italy, [7]Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [8]Gynecology and Obstetrics, Klinikum Offenbach GmbH, Offenbach, Germany, [9]Oncology, Edinburgh Cancer Centre Western General Hospital, Edinburgh, UK, [10]Deakin University Waurn Ponds, Geelong, Australia, [11]Breast International Group, Brussels, Belgium, [12]F. Hoffmann-La Roche AG - Switzerland, Basel, Switzerland, [13]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA, [14]Royal Marsden Hospital, Academic Department of Biochemistry, London, UK, [15]Department of Molecular and Experimental Medicine, Avera Cancer Institute, Sioux Falls, SD, USA, [16]Medicine, Institute Jules Bordet, Brussels, Belgium, [17]Oncology, Institute Jules Bordet, Brussels, Belgium

Background: A growing body of evidence demonstrates that the immune system contributes to the therapeutic effects of trastuzumab. We sought to determine whether autoimmune background could identify patients with HER2 positive early breast cancer (EBC) who derive differential benefit from adjuvant primary trastuzumab-based therapy.

Methods: HERA (BIG 1-01) is an international, multicenter, open-label, phase 3 randomized trial of 5,102 women with HER2-positive EBC, who were enrolled after completion of their postoperative chemotherapy to receive trastuzumab for 1 year, 2 years, or no trastuzumab. In this exploratory analysis, we evaluated whether there is an interaction between autoimmune history and the magnitude of trastuzumab benefit with respect to disease-free survival (DFS) and overall survival (OS).

Results: A total of 5,099 patients were included in the current analysis: 4,774 patients (93.6%) had no history of autoimmune disease at baseline while 325 patients (6.4%) had autoimmune disease history, 295 of whom had active disease. Median follow-up was 11 years (IQR 10.09–11.53); 1,631 patients experienced a DFS event and 1,037 patients experienced an OS event. Random assignment to 1 or 2 years of trastuzumab compared with no trastuzumab yielded similar reductions in the risk of events for patients with no autoimmune history as for patients with autoimmune history (interaction $p = 0.95$ for DFS, and $p = 0.62$ for OS). Trastuzumab reduced the risk of DFS event for both the no autoimmune (HR 0.77, 95% CI 0.69–0.85) as well as the autoimmune history group (HR 0.76, 95% CI 0.51–1.12). The risk of death was also similarly reduced for both groups: no autoimmune history: (HR 0.74, 95% CI 0.65-0.84); autoimmune history: (HR 0.65, 95% CI 0.40-1.07).

Conclusions: We found no evidence of a differential benefit from trastuzumab in patients with a medical history of autoimmune disease.

Legal entity responsible for the study: BrEAST - Amir Sonnenblick.

Funding: HERA was conducted under the umbrella of the Breast international group (BIG), with sponsorship and funding provided by F Hoffmann-La Roche.

Disclosure: C. Jackisch: Advisory board: Roche; Travel grants: Roche. D. Zardavas: Research grants; Roche, Genentech, Pfizer, AstraZeneca. N. Al-Sakaff: Employment: F. Hoffmann-La Roche. R. Gelber: Contributions to clinical trials: Roche, Novartis, Pfizer, AstraZeneca, Ipsen, Ferring, GSK, Celgene. M. Piccart: Consultancy fees: Roche. E. de Azambuja: Research grant, Advisory board and honoraria: Roche; Travel grants: Roche / GSK. All other authors have declared no conflicts of interest.

219P Impact of hormone receptor status in HER2+ early breast cancer: A paradigm shift in the trastuzumab era

A. De Nonneville[1], A. Gonçalves[1], J-M. Boher[2], M. Cohen[3], F. Reyal[4], J-M. Classe[5], S. Giard[6], P-E. Colombo[7], X. Muracciol[8], E. Darai[9], E. Jouve[10], C. Mazouni[11], P. Gimbergues[12], A-S. Azuar[13], E. Barranger[14], R. Rouzier[15], R. Villet[16], N. Chopin[17], E. Lambaudie[3], G. Houvenaeghel[3]

[1]Department of Medical Oncology, Institute Paoli Calmettes, Marseille, France, [2]Department of Clinical Research and Investigation, Biostatistics and Methodology Unit, Institute Paoli Calmettes, Marseille, France, [3]Department of Surgical Oncology, Institute Paoli Calmettes, Marseille, France, [4]Department of Surgical Oncology, Institut Curie, Paris, France, [5]Department of Surgical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [6]Department of Surgical Oncology, Centre Oscar Lambret, Lille, France, [7]Department of Surgical Oncology, CLCC Val d'Aurelle, Montpellier, France, [8]Radiotherapy, Hopital de la Timone, Marseille, France, [9]Department of Gynecologic and Breast Cancers, Hôpital Tenon, Paris, France, [10]Department of Surgical Oncology, Centre Claudius Regaud, Toulouse, France, [11]Department of Surgical Oncology, Institut Gustave Roussy, Villejuif, France, [12]Department of Surgical Oncology, Centre Jean-Perrin, Clermont-Ferrand, France, [13]Department of Surgical Oncology, Hôpital de Grasse, Grasse, France, [14]Department of Surgical Oncology, Centre Antoine Lacassagne, Nice, France, [15]Surgery, Institut Curie, Paris, France, [16]Department of Surgical Oncology, Hôpital des Diaconnesses, Paris, France, [17]Department of Surgical Oncology, Centre Leon Berard, Lyon, France

Background: While hormone receptor-positive (HR+) and negative (HR-) HER2+ breast cancers (BC) are thought to be distinct diseases, only few studies have investigated the impact of HR status in the context of trastuzumab (TRZ)-treated BC. We evaluated the impact of HR status on outcomes of HER2+ early BC, before and after generalization of TRZ.

Methods: Patients were identified from a cohort of 23,374 women who underwent primary surgery in 18 centers between 2000 and 2017. Since the year 2005 marked the generalization of TRZ, we conducted distinct analyses in patients treated between 2000 and 2004 and those treated between 2005 and 2017. Impact of HR status analyses were done with censorship of events occurring after 5 years in both cohorts. Proportionality tests included all events.

Results: Of 970 HER2+ patients, 349 were treated between 2000 and 2004 without TRZ, and 621 between 2005 and 2017, with TRZ-based adjuvant chemotherapy. Endocrine therapy was received by 92 and 94% of HR+ patients, respectively. In the first group, HR status impacted disease-free survival (DFS) in univariate analysis (Hazard ratio: 2.44 [1.43-4.19]; $p < 0.001$, log-rank test). Conversely, HR status did not significantly impact DFS in the cohort with TRZ (1.34 [0.66-2.71], $p = 0.414$). Overall survival was also impacted by HR status in the group without TRZ (Hazard ratio: 2.49 [1.23-5.04]; $p = 0.009$), but not in the TRZ group (0.68 [0.23-2.00]; $p = 0.482$). These results were maintained in multivariate analysis including age, LVI, lymph node involvement, histology, grade and tumor size. Evolution of Hazard ratio over time for cumulative incidence of first recurrence according to HR status in patients without TRZ showed a non-proportionality of risks on metastatic ($p = 0.027$, AD-test) recurrences, with a decreasing risk for HR- over time. Conversely, the analysis of cumulative incidence of first recurrence did not show such a trend in patients treated with TRZ, suggesting the proportionality of the risks over time for HR status.

Conclusions: Instead patients treated without TRZ, HR status was no longer determinant of outcomes when patients received TRZ. These observations are supported by the analysis of Hazard ratio's evolution over time for cumulative incidence of first metastatic recurrence.

Legal entity responsible for the study: Gilles Houvenaeghel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

220P Safety profile of subcutaneous trastuzumab in patients with HER2-positive early breast cancer: The French HERMIONE non-interventional prospective study

J-P.P. Jacquin[1], L. Uwer[2], A. Savignoni[3], J-M. Ferrero[4], A. Lortholary[5], D. Solub[6], H. Attar-Rabia[7], S. Deblay[7], S. Pibre[7], Y. Belkacemi[8]

[1]Oncology Unit, Institut de Cancérologie de la Loire, Saint-Etienne, France, [2]Oncology Unit, Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandœuvre-lès-Nancy, France, [3]Pole Biométrie, Institut Curie, Paris, France, [4]Oncology Unit, Centre Antoine Lacassagne, Nice, France, [5]Oncology Unit, Hopital Prové du Confluent, Institut de Cancérologie Catherine de Sienne, Nantes, France, [6]Oncology Unit, Hôpitaux de Chartres, Chartres, France, [7]Oncology Unit, Roche S.A.S - France, Boulogne-Billancourt, France, [8]Henri Mondor Breast Cancer Center and Department of Radiation Oncology, AP-HP, Henri Mondor University Hospital, University of Paris-Est Créteil (UPEC), Créteil, France

Background: The HERMIONE study was conducted to assess, in HER2-positive early breast cancer, the safety profile of subcutaneous formulation of trastuzumab (SC T) in real life in France.

Methods: This prospective, multicenter, noninterventional study included 511 patients planned to be treated in both neoadjuvant and adjuvant settings with a follow-up (FU) of 12 months maximum. The safety analyses concerned 505 patients, either naïve (40.4%) or non-naïve (59.6%) of intravenous trastuzumab (IV T). According to routine practice, patients received concomitant locoregional radiotherapy (68.7%), endocrine therapy (59.9%) and chemotherapy (37.8%). Primary endpoint was the description of systemic and local Adverse Events (AEs) of SC T assessed by NCI-CTCAE. Congestive Heart Failure (CHF), hepatobiliary toxicity and suspected transmission of an infectious agent by SC T were AEs of Special Interest (AESIs). Secondary endpoints included description of patients, disease characteristics and modalities of SC T administration. Quality of life (QoL) was assessed by QLQ-C30.

Results: Patients were included in 101 sites between January and November 2015. The median age was 58 years. Over the FU period, AEs occurred in 422 patients (83.6%): 92 AEs (3.8%) were grade ≥ 3, 76 (3.1%) were serious, 87 (3.6%) were AESIs and 336 (13.7%) were related to SC T. Most frequent AEs (> 10% of patients) were asthenia, arthralgia, radiation skin injury, myalgia, hot flush and diarrhea. Main grade ≥ 3 events were radiation skin injury (1.8% of patients) and febrile neutropenia (1.4%). Serious AEs (SAEs) included febrile neutropenia (9.2% of SAEs) and pulmonary embolism (6.6%). Main AESI was CHF in 11.5% of patients and was related to SC T only in 4.5%. Injection site pain was the main SC Trelated AE (9.1% of patients). Few AEs (1.4%) led to permanent SC T discontinuation. Only 1 death assessed as not related to SC T (pulmonary thromboembolism) was reported. QoL analyses showed no deterioration of global health status.

Conclusions: The Hermione study showed that the safety of SC T (HERCEPTIN®) in a real-life setting is consistent with the known profile, without new safety concerns or QoL deterioration.

Clinical trial identification: NCT02286362.

Editorial acknowledgement: Stéphanie Mohsen, Aixial.

Legal entity responsible for the study: Hoffmann-La Roche.

Funding: Hoffmann-La Roche.

Disclosure: H. Attar-Rabia, S. Deblay, S. Pibre: Roche employee. Y. Belkacemi: Honoraria and consulting: Astellas, Roche, Genomic Health. All other authors have declared no conflicts of interest.

221P Real-life data on the cardiac toxicity of adjuvant fixed-dose subcutaneous trastuzumab in HER2-positive breast cancer

R. De Sanctis[1], F. D'Antonio[1], E. Agostinetto[1], A. Marinello[1], G. Masci[1], M. Zuradelli[1], A. Losurdo[1], D. Guiducci[2], C. Tinterri[3], A. Testori[3], W. Gatzemeier[3], V. Errico[3], R. Torrisi[1], A. Santoro[1]

[1]Medical Oncology and Hematology, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy, [2]Cardiology, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy, [3]Breast Surgery, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy

Background: Fixed-dose adjuvant subcutaneous (s.c.) trastuzumab (T) has been approved in the treatment of early HER2-positive breast cancer (BC), based on the evidence of its non-inferiority to standard intravenous (i.v.) infusion. Few data from real-life are available regarding cardiac toxicities associated with fixed-dose subcutaneous T administration. We conducted a retrospective study in order to compare cardiac toxicity profile of adjuvant fixed-dose s.c.-T and weight-based i.v.-T, according to anthropometric data which takes into account more than simply weight.

Methods: Patients treated with adjuvant T for HER2-positive breast cancer at Humanitas Research Hospital from December 2013 to October 2017 were evaluated. T was administered at a either fixed dose of 600 mg s.c. or 6 mg/kg i.v, respectively. Data regarding previous chemotherapy, Body Mass Index (BMI), and development of cardiotoxicity (decrease in LVEF >10% points, to a value < 50%) were extracted from medical records. Four BMI classes were considered: underweight (BMI < 18 kg/sqm), normal weight (18-24.9 kg/sqm), overweight (25-29.99), and obesity (≥30). All variables were compared with categorical tests (Pearson Chi-squared with Yates correction or Fisher exact test).

Results: A total of 260 HER2-positive BC patients receiving adjuvant T were analyzed. Median age was 56 (range, 32-88), median BMI 23.5 (range, 15.8-50.2 kg/sqm). 196 (75.38%) patients received s.c.-T and 64 (24.62%) i.v.-T. 156 had a normal weight, while 11 were underweight, 54 overweight and 39 obese. The incidence of cardiotoxicity was not different among the BMI classes according to the route of administration of T ($p = 0.28$). In the subset of the patients who had developed cardiac toxicity, BMI did not result as a risk factor, as well as a previous treatment with anthracyclines ($p = 0.89$).

Conclusions: Cardiac toxicity profile of fixed-dose s.c.-T is consistent with that of weight-based i.v.-T in the real-world setting regardless differences in anthropometric data as BMI. Our study confirms safety of subcutaneous T administration, which still represents a valid and more convenient alternative to intravenous administration.

Legal entity responsible for the study: Istituto Clinico Humanitas.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

222P Comprehensive evaluation of the pharmacokinetic profiles of SB3 and reference trastuzumab

X. Pivot[1], Y.J. Lee[2], J.Y. Lim[2], S.J. Song[3], H.S. Kim[4], Y.C. Yoon[5]

[1]Medical Oncology, Centre Paul Strauss Centre de Lutte Contre le Cancer, Strasbourg, France, [2]Clinical Development, Samsung Bioepis, Suwon, Republic of Korea, [3]Biometrics, Samsung Bioepis, Suwon, Republic of Korea, [4]Clinical Bioanalysis, Samsung Bioepis, Incheon, Republic of Korea, [5]Medical Affairs, Samsung Bioepis, Suwon, Republic of Korea

Background: SB3 has been approved by the European Commission as a biosimilar of reference trastuzumab (TRZ). Physicochemical and functional studies showed that SB3 was highly similar to TRZ. Here, the pharmacokinetic (PK) results comparing SB3 and TRZ in cynomolgus monkeys, healthy male subjects, and early breast cancer patients are reported.

Methods: PK profiles were evaluated in cynomolgus monkeys following intravenous administration of 25 mg/kg of SB3 or TRZ every week for 4 weeks. In healthy male subjects, the PK equivalence between SB3 vs. EU-TRZ, between SB3 vs. US-TRZ, and between EU-TRZ vs. US-TRZ were assessed in a Phase I, 6 mg/kg single dose study.[1] The trough concentration was evaluated in a Phase III study of early breast cancer patients receiving either SB3 or EU-TRZ in combination with neoadjuvant chemotherapy.[2] Equivalence was to be concluded if the 90% confidence interval (CI) for the ratio of geometric lead squares means (LS Means) of the PK parameters were within the standard margins of 80.00% to 125.00%.

Results: Maximum concentration C_{max}, time to reach C_{max} (T_{max}), and the area under the concentration-time curve from time zero to 168 hour ($AUC_{0\text{-}168}$) were similar in cynomolgus monkeys treated with SB3 or TRZ. In 108 healthy subjects, the 90% CIs for the AUC from time zero to infinity (AUC_{inf}), AUC from time zero to the last quantifiable concentration (AUC_{last}) and C_{max} for all pairwise comparisons were within the pre-defined equivalence margin. The PK population in Phase III study consisted of 313 patients (SB3, n = 161; TRZ=152). Mean trough concentrations were similar from cycle 3 to 8 of SB3 ranging from 37.71 to 55.80 µg/mL and TRZ ranging from 39.83 to 53.13 µg/mL and the corresponding 90% CIs fell within the pre-defined equivalence margin. The proportion of patients with C_{trough} exceeding 20µg/mL was similar between the treatment groups at each cycle.

Conclusions: In addition to the non-clinical study in cynomolgus monkeys, similar PK profiles were well demonstrated between SB3 and TRZ in healthy subjects and in breast cancer patients. Reference 1. Pivot X et al. Clin Ther. 2016; 38:1665-73; 2. Pivot X et al. J Clin Oncol. 2018; 36:968-74.

Clinical trial identification: EudraCT: 2013-004172-35.

Legal entity responsible for the study: Samsung Bioepis Co., Ltd.

Funding: Samsung Bioepis Co., Ltd.

Disclosure: X. Pivot: Principle investigator: Phase III study of SB3; Consultant and honoraria: Samsung Bioepis. S.J. Song, Y.C. Yoon: Employment: Samsung Bioepis. All other authors have declared no conflicts of interest.

223P The impact of neoadjuvant dual HER2 targeting with pertuzumab and trastuzumab on pathological complete response (pCR) rates: Kent Oncology Centre (KOC) experience

S. Forner, V.R. Sim, J.L. Glendenning, R. Burcombe

Oncology, Maidstone Hospital Maidstone & Tunbridge NHS TRUST, Maidstone, UK

Background: Neoadjuvant chemotherapy (NACT) with dual HER2 targeting improved pCR rates (ypT0ypN0) compared with Herceptin plus chemotherapy in the TRYPHAENA and NeoSphere registration trials. Pertuzumab-containing regimens were adopted at KOC following NICE approval (December 2016).

Methods: A retrospective case notes study of 110 (stage 1-3) HER2+ breast cancer patients receiving HER2-directed NACT at KOC was conducted. Age, clinical stage, ER status, treatment regimen and pCR status were recorded.

Results: Single targeting treatment (S) used FEC-TH. Dual targeting (D) regimens were FEC-THP or TCHP. Patients were well matched for age, clinical stage and ER status. Overall, dual targeting increased pCR rates: 62% vs 31% (S). pCR rates were higher with dual targeting regardless of ER or nodal status. The highest pCR rate was seen amongst ER negative patients receiving D (81%). Amongst D regimens, an excess of ER+ patients was seen in the TCHP group (75% TCHP vs 37% FEC-THP). Despite this, pCR rates were comparable (61% TCHP vs 63% FEC-THP). All 9 ER negative patients treated with TCHP achieved pCR (100%) compared with FEC-THP (67%). Table: Demographics and pCR rates for single and dual HER2 targeted NACT.

Table: 223P

	Single targeting (S)	Dual targeting (D)
Time period	Oct 15-Nov 17	Dec 16-Nov 17
N	55	55
Age Median (range)	55 (36-78)	53 (29-77)
Regimen		
FEC-TH	55	
FEC-THP		19
TCHP		36
ER status		
ER +	31 (56%)	34 (62%)
ER -	24 (44%)	21 (38%)
Node status at diagnosis		
N +	37 (67%)	29 (53%)
N -	18 (33%)	26 (47%)
pCR [n (%)]	17 (31%)	34(62%)
ER +	11 (35%)	17 (50%)
ER -	6 (25%)	17 (81%)
N +	11 (30%)	22 (76%)
N -	6 (33%)	12 (46%)

Conclusions: A substantial increase in pCR rates was observed with dual targeting, regardless of ER and nodal status, reproducing the registration trial data in real world clinical practice. pCR rates were greatest in ER negative patients, regardless of regimen. The small subgroup most likely to achieve pCR were ER negative patients treated with TCHP.

Legal entity responsible for the study: Kent Oncology Centre, Maidstone Hospital.

Funding: Has not received any funding.

Disclosure: R. Burcombe: Honorarium and advisory board: Roche in 2017 for writing an article (BJN) on HER2 directed therapy for MBC. All other authors have declared no conflicts of interest.

224P Neoadjuvant trial of nab-paclitaxel and atezolizumab (Atezo), a PD-L1 inhibitor, in patients (pts) with chemo-insensitive triple negative breast cancer (TNBC)

J.K. Litton[1], S.L. Moulder[1], K.R. Hess[2], S. Damodaran[3], G.M. Rauch[4], R. Candelaria[5], B.E. Adrada[4], F. Symmans[6], R.K. Murthy[1], T. Helgason[1], A. Clayborn[1], S. Prabhakaran[1], V. Valero[1], A.M. Thompson[7], E.A. Mittendorf[8]

[1]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Breast Medical Oncology, The MD Anderson Cancer Center, Houston, TX, USA, [4]Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [5]Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]Pathology, MD Anderson Cancer Center, Houston, TX, USA, [7]Breast Surgery, MD Anderson Cancer Center, Houston, TX, USA, [8]Surgical Oncology, Dana-Farber Cancer Insitute, Boston, MA, USA

Background: Achieving a residual cancer burden (RCB) 0-1 portends an excellent prognosis for TNBC pts receiving neoadjuvant (NACT) anthracycline (AC) and taxane chemotherapy while pts with high residual disease (RCB II-III) have a 40-80% recurrence risk. The GeparTrio and Aberdeen trials demonstrated that pts with poor response by ultrasound (US) during NACT had pathologic complete response (pCR) rates of 2-5% even if NACT was changed based on US response. Immunotherapy is a promising strategy for chemo-insensitive TNBC; however, given toxicity and potential for long-term morbidity, pt selection is important.

Methods: Pts identified as having chemo-insensitive TNBC with AC using US or through previous participation in a separate trial, ARTEMIS, were eligible. To identify insensitive TNBC, ARTEMIS used an algorithm combining a CLIA-certified chemosensitivity mRNA gene signature with US response to AC X4. Eligible pts then received weekly nab-paclitaxel (100 mg/m2 IV for 12 weeks) and atezo (1200mg IV q 3 weeks). Atezo continued for 3 months after surgery. Using a 2-stage Gehan-type design, if > 1 pt had an RCB 0-I in the first 19, the protocol would continue to accrue a total of 37 pts to estimate an RCB-0/I rate for atezo + nab-paclitaxel in chemo-insensitive TNBC for future trials. We report the interim analysis of the first 19 pts.

Results: 19 pts enrolled from 02/2016- 12/12/2017. One pt received 1 cycle, then withdrew consent. Median age was 54 (range 35-75). Presenting clinical stage was II in 7 pts and III in 12 pts. Final pathology status was: RCB 0=5; RCB I = 1; RCB II = 5 and RCB III=7. RCB 0-I= 6/19 (32%). Toxicity included 6 serious adverse events in 3 pts: fever, elevated creatinine and post-surgical pain. Most common toxicities included fatigue, neuropathy, pain, anemia, rash, elevated transaminases, hyperglycemia, nausea and dyspnea. Six pts required atezo to be held and/or discontinued.

Conclusions: The combination of nab-paclitaxel and atezo resulted in moderate toxicity but increased the expected RCB 0-I rates from 5% to 32% for TNBC patients with chemotherapy-insensitive disease. Given these promising results, this study will continue to full accrual.

Clinical trial identification: NCT02530489.

Legal entity responsible for the study: Jennifer Litton.

Funding: MD Anderson Moonshot Program, Genentech.

Disclosure: J.K. Litton: Advisory boards (without personal compensation): AstraZeneca and Pfizer; Research studies: GSK, EMD Serono, Genentech, Pfizer, AstraZeneca, Novartis; CME with uptodate, med learning group, PER Guidelines; NIH PDQ and NCCN guidelines. E.A. Mittendorf; Advisory board: Merck and Sellas; Principal investigator: Genentech sponsored trials. All other authors have declared no conflicts of interest.

225P Prognostic implications of circulating tumor cells (CTCs) after neoadjuvant chemotherapy for triple negative breast cancer (TNBC)

C. Hall[1], K.R. Hess[2], L. Ravenberg[3], A. Clayborn[4], G.M. Rauch[5], R. Candelaria[6], E.A. Mittendorf[7], S.L. Moulder[4], A. Thompson[8], A. Lucci[8]

[1]Breast Surgical Oncology, MD Anderson, Houston, TX, USA, [2]Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Breast Medical Oncology, MD Anderson, Houston, TX, USA, [4]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [5]Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [7]Surgical Oncology, Dana-Farber Cancer Insitute, Boston, MA, USA, [8]Breast Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Background: ARTEMIS (A Randomized, TNBC Enrolling trial to confirm Molecular profiling Improves Survival) is a randomized trial to determine if precision guided neoadjuvant chemotherapy (NACT) impacts rates of pathologic complete response in the breast and axillary nodes (pCR). We hypothesized that CTCs in peripheral blood at the time of surgery, after completion of NACT, would be prognostic in TNBC.

Methods: Venous Blood taken following completion of NACT and immediately prior to surgery was assessed for CTCs after NACT as part of two IRB approved studies, ARTEMIS (2014 – 0185/PA15-1050) and LAB04-0698. CTCs (per 7.5 ml blood) were identified using the Cell Search® System (Menarini Silicon Biosystems). Samples with one or more cells having morphologic criteria for malignancy were deemed CTC+. Log-rank test and Cox regression analysis were applied to evaluate associations between CTC+, pCR, and overall survival.

Results: pCR was achieved in 24/68 (35%) patients with TNBC. Twenty four patients (35%) were CTC+. 3 year overall survival was evaluated in 4 groups of patients: pCR-no CTCs (n = 20), pCR-CTC + (n = 4), non-pCR-no CTCs (n = 24) and non-pCR-CTC + (n = 20). Three year OS was higher in the pCR-no CTCs cohort (100%), compared to pCR-CTC + (50%), non-pCR-no CTCs (83%), non-pCR-CTC + (19%); log rank $p < 0.0001$. In this data set, the presence of CTCs was associated with significant risk of death at 3 years [hazard ratio of 12.3 (95% CI 3.4-454, $p = 0.00002$)], whereas a favorable, but non-significant trend was noted for pCR [hazard ratio of 0.2 (95% CI 0.0, 1.4, $p = 0.11$)].

Conclusions: The presence of CTCs at the time of surgery after NACT has prognostic significance beyond that of pCR and should be considered in evaluation of patients for adjuvant clinical trials.

Legal entity responsible for the study: University of Texas, MD Anderson.

Funding: University of Texas, MD Anderson.

Disclosure: All authors have declared no conflicts of interest.

226P A prediction model for pathological complete response after neoadjuvant chemotherapy of HER2-negative breast cancer patients

L. Häberle[1], R. Erber[2], P. Gaß[1], A. Hein[1], S.M. Jud[1], H. Langemann[1], C. Rauh[1], C.C. Hack[1], R. Schulz-Wendtland[3], A. Hartmann[2], M.W. Beckmann[1], M.P. Lux[1], P.A. Fasching[1]

[1]Department of Gynecology and Obstetrics, Erlangen University Hospital, Erlangen, Germany, [2]Institute of Pathology, Erlangen University Hospital, Erlangen, Germany, [3]Institute of Radiology, Erlangen University Hospital, Erlangen, Germany

Background: Pathological complete response (pCR) is an established surrogate marker for survival in breast cancer (BC) patients treated with neoadjuvant chemotherapy. Prediction of pCR based on clinical information available at biopsy, particularly the biomarkers estrogen receptor (ER), progesterone receptor (PgR) and Ki-67 expression, might assist in the identification of patients who benefit of preoperative chemotherapy. Although biomarker assessment is mostly reported as the percentage of positively stained cells with values from 0 to 100%, cut-off points are used to classify patients into groups. Aim of this study was to examine established cut-off points and to develop a prediction tool estimating a patient's pCR likelihood obtained from clinical predictors and these biomarkers as assessed during clinical routine or categorically with established or newfound thresholds.

Methods: This study included all HER2-negative BC patients from one German institution treated with neoadjuvant chemotherapy from 2002 to 2017, having complete observations (N = 829). Various logistic regression models for predicting pCR which differ from each other by the usage of the biomarkers were set-up: (M1) continuous biomarkers from 0 to 100% as assessed during clinical routine, (M2) categorical (positive/negative) biomarkers with established thresholds, (M3) categorical biomarkers with newfound thresholds. Prediction accuracy (e.g., AUC) was assessed using cross-validation.

Results: A total of 163 (19.7%) patients achieved a pCR. The optimal cut-off points for ER, PgR and Ki-67 were 30%, 10% and 35%, respectively. The prediction model M1 with continuous biomarkers was more precise (cross-validated AUC, 0.863) than the prediction models M2 and M3 (both 0.854). The most accurate model M1 had a sensitivity of 0.80 at a specificity of 0.78. Beside these biomarkers, a patient's likelihood of achieving a pCR depended on age at diagnosis, clinical tumor stage and grading.

Conclusions: Using biomarkers as continuous variables yielded more precise predictions than when used categorically. Therapy decisions should base on predicted pCR probabilities obtained from multivariable prediction models rather than single biomarker values.

Legal entity responsible for the study: Erlangen University Hospital, Erlangen.

Funding: Has not received any funding.

Disclosure: A. Hartmann: Personal fees: AstraZeneca, BMS, MSD; Grants: Biontech, Nanostring; Personal fees and non-financial support: Roche, Sysmex; Grants: Janssen, Cepheid outside the submitted work. P.A. Fasching: Grants and personal fees: Novartis; Personal fees: Pfizer, Roche, Teva, Celgene; Grants: Biontech, outside the submitted work. All other authors have declared no conflicts of interest.

227P Evaluation of the MammaTyper® as a molecular predictor for pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) and outcome in patients with different breast cancer (BC) subtypes

P.A. Fasching[1], M. Laible[2], K.E. Weber[3], R.M. Wirtz[4], C. Denkert[5], K. Schlombs[6], S. Schmatloch[7], O. Camara[8], H.J. Lück[9], J. Huober[10], T. Karn[11], M.T. van Mackelenbergh[12], F. Marme[13], V. Müller[14], C. Schem[15], E. Stickeler[16], U. Sahin[17], S. Loibl[18], M. Untch[19]

[1]Department of Gynecology and Obstetrics, Universitätsklinik Erlangen, Erlangen, Germany, [2]Gynäkologie, BioNTech Diagnostics GmbH, Mainz, Germany, [3]Statistic, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [4]STRATIFYER Molecular Pathology GmbH, Cologne, Germany, [5]Institute of Pathology, Charite Berlin Mitte, Berlin, Germany, [6]BioNTech Diagnostics GmbH, Mainz, Germany, [7]Brustzentrum, Elisabeth Krankenhaus, Kassel, Germany, [8]Brustzentrum, Hufeland Klinikum, Bad Langensalza, Germany, [9]Gynäkologie, Gynäkologisch-Onkologische Praxis, Hannover, Germany, [10]Gynecol. & Obstetrics, Universitaetsfrauenklinik Ulm, Ulm, Germany, [11]Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Frankfurt (Johannes-Wolfgang Goethe Institute), Frankfurt am Main, Germany, [12]Clinic for Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Kiel, Germany, [13]Gynecologic Oncology, Nationales Zentrum für Tumorerkrankungen (NCT), Heidelberg, Germany, [14]Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany, [15]Mammazentrum Hamburg, Hospital Jerusalem, Hamburg, Germany, [16]Gynäkologie und Geburtsmedizin, Uniklinik RWTH, Aachen, Germany, [17]Management, BioNTech AG, Mainz, Germany, [18]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [19]Geburtshilfe und Gynäkologie, Helios Klinikum Berlin Buch, Berlin, Germany

Background: According to molecular and genetic features BC can be divided into subtypes which show differences in the response to systemic therapy and in long-term outcome. Thus, effective and reliable molecular analysis of tumor material at the time of BC diagnosis is needed.

Methods: Total RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor samples of BC patients (pts) enrolled in the single arm phase II TECHNO (Untch et al. JCO 2011) and the randomised phase III PREPARE (Untch et al. Ann Oncol. 2011) trials. MammaTyper®, a molecular in vitro diagnostic RT-qPCR test, was used to assess the expression of ERBB2 (HER2), ESR1 (ER), PGR (PR) and MKI67 (Ki67) genes as continuous and binary variables using predefined cutoffs. Pts were classified into 6 intrinsic BC subtypes according to St Gallen guidelines (Goldhirsch et al. Ann Oncol. 2013). In both trials the ER, PR, HER2 and Ki67 expression was assessed by immunohistochemistry (IHC). Predefined cutoffs for increased ESR1 (+1.8 Cq) and PGR (+3.7 Cq) expression defined a subgroup of ultra-high tumors. The study aimed to evaluate the MammaTyper® test for predicting pCR (ypT0 ypN0) after NACT and outcome in the BC subtypes. The degree of agreement between the MammaTyper® and the IHC test for determining BC subtypes was also estimated.

Results: A total of 418 pts were assessed. The BC subtypes defined by MammaTyper® and IHC showed good agreements (ERBB2/HER2, kappa [κ]=0.674; ESR1/ER, $\kappa = 0.815$; PGR/PR, $\kappa = 0.648$). MKI67 significantly predicted pCR (AUC=0.686, $p < 0.001$). In HER2+ pts from the TECHNO trial the ERBB2 significantly predicted pCR in ESR1-positive sybtype ($n = 59$, AUC=0.708, $p = 0.006$). HER2-negative pts from the PREPARE trial with ultra-high ESR1 and/or PGR expression had significantly better disease-free (DFS) and overall survival (OS) than the non-ultra-high pts ($n = 153$; DFS HR = 1.80, [95%CI 1.18-2.76], $p = 0.007$; OS HR = 2.54 [95%-CI 1.50-4.31], $p = 0.001$).

Conclusions: The MammaTyper® significantly predicts response after NACT in BC subtypes. A subgroup of pts with ultra-high ESR1/PGR expression had a good prognosis. Further analysis is required.

Legal entity responsible for the study: GBG Forschungs GmbH and BioNTech Diagnostics GmbH.

Funding: This study was financially supported by BioNTech Diagnostics GmbH, Mainz, Germany.

Disclosure: P.A. Fasching: Grants: Biontech, during the conduct of the study; Grants and personal fees: Novartis; Personal fees: Pfizer, Roche, Teva, Celgene, outside the submitted work. M. Laible: Patent WO 2015/024942, Commercialized as MammaTyper(TM) Kit; Relevant financial activities outside the submitted work: BioNTech Diagnostics GmbH (Employee of BioNTech Diagnostics GmbH). K.E. Weber: Grants and non-financial support: BioNTech Diagnostics GmbH, Mainz, Germany, during the conduct of the study; Patent EndoPredict issued. C. Denkert: Personal fees: Teva, Novartis, Pfizer, Roche, Amgen, MSD Oncology; Other: Sividon Diagnostics, outside the submitted work. K. Schlombs: Personal fees: BioNTech Diagnostics GmbH, outside the submitted work; Patent WO 2015/024942 pending; New Patent application pending. F. Marme: Personal fees: Roche, AstraZeneca, Pfizer, Tesaro, Novartis, Amgen, PharmaMar, GenomicHealth, CureVac, Eisai, outside the submitted work. S. Loibl: Grants: AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, Teva, Vifor during the conduct of the study and outside the submitted work. All other authors have declared no conflicts of interest.

228P Impact of clinical, morphologic and molecular characteristics on response to neoadjuvant systemic therapy (NAST) in metaplastic breast cancer (MpBC)

C. Yam[1], S. Seth[2], K.R. Hess[3], E.A. Mittendorf[4], R.K. Murthy[1], S. Damodaran[1], T. Helgason[1], L. Huo[5], A.M. Thompson[6], M. Barton[7], M.L. Huang[8], E.M. Arribas[8], D.L. Lane[8], G.M. Rauch[8], B.E. Adrada[8], M.Z. Gilcrease[5], J.T. Chang[9], S.L. Moulder[1]

[1]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]Surgical Oncology, Dana-Farber Cancer Insitute, Boston, MA, USA, [5]Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [7]Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [8]Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [9]Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: MpBCs are morphologically heterogeneous, frequently triple-negative and resistant to chemotherapy. To better understand why MpBCs are resistant to chemotherapy, we investigated associations between response to NAST and clinical, morphologic, as well as molecular characteristics in a cohort of MpBC patients (pts).

Methods: 19 MpBC pts were identified from a prospective cohort of 242 triple-negative breast cancer (TNBC) pts treated with anthracycline-based NAST. Histologic subtype of MpBC was determined by light microscopy. TNBC subtypes were determined using the Vanderbilt gene expression signatures (GES). Residual cancer burden (RCB) was assessed after surgery.

Results: Of the 19 MpBCs, 37% (7/19) were matrix producing and 63% (12/19) were not. Analysis of GES revealed the following subtype distributions: mesenchymal (M)=32% (6/19), mesenchymal stem-like (MSL)=11% (2/19), basal-like 2 (BL2)=32% (6/19), immunomodulatory (IM)=11% (2/19), unstable (UNS)=11% (2/19), basal-like 1 (BL1)=5% (1/19). Fifty-seven percent (4/7) and 33% (4/12) of the matrix producing and non-matrix producing MpBCs were of the M/MSL subtype, respectively. Twenty-one percent (4/19) of pts had a pathologic complete response (pCR)/minimal residual disease (RCB-I) following NAST. MpBCs that were matrix producing or of the M/MSL subtype were associated with worse response to NAST as none (0/11) of the pts with MpBC that was matrix producing and/or of the M/MSL subtype had a pCR/RCB-I, compared with 50% (4/8) of the remaining pts ($p = 0.018$).

Table: 228P Associations between response to NAST and clinical, morphological as well as molecular characteristics

	pCR/RCB-I (n = 4)	RCB-II/III (n = 15)
Median age (range)	57.3 (42.4-67.2)	57.8 (34.2-74.0)
Mean tumor size - cm (SD)	2.4 (1.2)	4.7 (3.8)
Clinical nodal status		
Negative - n (%)	4 (25)	12 (75)
Positive - n (%)	0	3 (100)
Stage		
I - n (%)	2 (40)	3 (60)
II - n (%)	2 (20)	8 (80)
III - n (%)	0	4 (100)
Histologic grade		
1 - n (%)	0	1 (100)
2 - n (%)	1 (25)	3 (75)
3 - n (%)	3 (21)	11 (79)
Metaplastic subtype		
Matrix producing - n (%)	0	7 (100)
Non-matrix producing - n (%)	4 (33)	8 (67)
TNBC subtype		
M/MSL - n (%)	0	8 (100)
BL1/2 - n (%)	3 (43)	4 (57)
Other - n (%)	1 (25)	3 (75)

Conclusions: Analysis of GES suggest that MpBC is enriched for subtypes less likely to achieve pCR/RCB-I with NAST (BL2, M, MSL). Matrix-producing (light microscopy) and the M/MSL subtypes (GES) appear to be associated with resistance to anthracycline-based NAST in MpBC.

Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center.

Funding: National Comprehensive Cancer Network (NCCN) Oncology Research Program, The MD Anderson Cancer Center Moonshots Program, CPRIT Multi-Investigator Research Award (MIRA).

Disclosure: All authors have declared no conflicts of interest.

229P Evaluation of human epidermal growth factor receptor 2 overexpression (HER2+) after administration of neoadjuvant treatment (NAT) and prognostic impact in breast cancer (BC)

D.H.R. Machado[1], F. Branco[2], F.F. Silva[3], S. André[4], M. Brito[5], M. Casanova[6], M. Nave[7], A. Moreira[1], J.L.C. Passos-Coelho[7]

[1]Medical Oncology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E. (IPOLFG EPE), Lisbon, Portugal, [2]Medical Oncology, Hospital Beatriz Angelo-Loures, Loures, Portugal, [3]Medical Oncology, Hospital da Luz, Lisbon, Portugal, [4]Department of Pathology and Laboratory Medicine, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E. (IPOLFG EPE), Lisbon, Portugal, [5]Francisco Gentil de Lisboa, Instituto Portugues de Oncologia, Lisbon, Portugal, [6]Medical Oncology, Hospital Beatriz Ângelo, Loures, Portugal, [7]Oncology, Hospital da Luz, Lisbon, Portugal

Background: HER2+ occurs in 15-20% of BC and is associated with worse prognosis. While previous studies reported that NAT-associated changes in HER2 status adversely affect patients (pts) prognosis (Guarneri et al), others did not (Yoshida et al). To assess the efficacy of NAT in pts with HER2+ BC and its influence on HER2 status and associated prognostic impact. HER2 status was determined by immunohistochemically (IHC) or Silver in situ hybridization (SISH).

Methods: Retrospective chart review and pathologic evaluation of all consecutive pts with HER2+ BC (defined as IHC 3+ or IHC 2+ confirmed by SISH) submitted to NAT between Jan2010 and Oct2015 in 3 Portuguese Hospitals. All diagnostic tumor biopsies and surgical specimens were assessed for IHC.

Results: 108 female pts were included (median age 52yo, range 30-82; TNM stage was III in 68, II in 40. Hormone receptor (HR) were positive (ER and/or PR) in 68. HER2 status at diagnosis was IHC 3+ in 100 pts and IHC 2+ SISH amplified in 8. NAT included chemotherapy (CT) in all pts (anthracyclines (AC)/ taxanes (Tax) 102, AC/ non-Tax 3, non-AC regimen 3), trastuzumab (T) in 87 and T and pertuzumab (P) in 3. Pathological complete response (pCR) (ypT0/isN0) was achieved in 48 pts (44.4%): 28 of 70 HR+ and 20 of 38 HR neg ($p = 0.2$), 27 of 40 with stage II and 21 of 68 with stage III ($p < 0.001$). pCR rate was 46% after CT+T/P and 39% with CT alone ($p = 0.6$). With a median follow-up of 55 months, there were 5 disease free survival (DFS) events (4 relapses and 1 non-BC death) among pCR pts and 19 among non-pCR (16 relapses and 3 non-BC deaths) ($p = 0.02$, log rank test). Of the 60 pts with residual invasive tumor at surgery, 52 remained HER2+ and 8 (13.3%) lost Her2+. 5y-DFS and 5-OS is 70% and 84%, respectively, for pts whose tumors remained HER2 + (14 DFS events; 8 deaths), and 21% and 50% for pts whose residual tumors became HER2 negative (5 DFS events; 4 deaths) ($p = 0.02$ and <0,001, log-rank test).

Conclusions: We confirmed the negative prognostic impact of NAT-induced HER2 loss on residual tumor leading to worse DFS. Despite the retrospective design and small sample size, these results suggest the importance of retesting HER2 after NAT, to better refine pts prognosis.

Legal entity responsible for the study: José Luís Passos Coelho.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

230P Complete response (CR) to anthracycline-based chemotherapy using magnetic resonance imaging (MRI) predicts high rates of pathologic complete response (pCR) for triple negative breast cancer (TNBC) patients treated preoperatively with anthracycline and taxane-based regimens

M. Marin Alcala[1], G. Llort Pursals[1], J.H. Del Riego Ferrari[1], J. Giner[1], F.X. Andreu Navarro[1], S. Medina[1], O. Aparicio[1], E. Dalmau Portulas[1], P. Ribera Fernandez[1], H. Oliveres[1], C. Martinez Vila[1], J.M. Cabrera Romero[2], M.A. Segui Palmer[1], L.A. Fernandez Morales[1]

[1]Oncology, Hospital de Sabadell Corporacis Parc Tauli, Sabadell, Spain, [2]Medical Oncology, Hospital de Sabadell Corporacis Parc Tauli, Sabadell, Spain

Background: Predictors of pCR to neoadjuvant chemotherapy (NAC) for breast cancers have been studied extensively. We focused on CR to antracycline-based chemotherapy using MRI for prediction of pCR, in patients treated with NAC with anthracycline and taxane-based regimens.

Methods: Tumor measurements were done at diagnosis, after anthracyclines and at the end of taxanes. pCR was defined as absence of residual invasive foci and no lymph nodeinvolvement. Associations of clinicopathologic parameters with pCR were evaluated with the $\chi 2$ test. All test results with a p value of less than 0.05 were considered significant.

Results: A total of 114 TNBC patients were treated with NAC. Median age was 53 (28-77) years. 44 patients (38.6%)had stage II and 67(58.8%)stage III. Mutation in BRCA was detected in 9 patients and variants of uncertain significance in 5. 49 patients (43%) with tumor size by MRI > 50 mm, 49 (43%) with positive results on fine needle aspiration of axilla (FNAA), and 88 (77.2%) with histologic grade III. NAC regimen consisted in 108 patients (94.7%) of 4 cycles of epirrubicin+cyclophosphamide (CP) and in 3 patients (2.6%) 4 cycles of doxorubicin+CP, followed by taxane-based regimens. 43 patients (37.7%) had pCR. CR by MRI occurred in 22 patients (19.3%) after anthracycline-based regimen. At the end of NAC there were 37 patients (32.5%) with CR by MRI. Association of clinicopathologic parameters with pCR were: 62.8% pCR in patients with tumor size $\leq$ 50mm ($p = 0.389$); 58.1% in patients with FNAA + ($p = 0.238$); 81.4% in grade III tumors ($p = 0.700$); 46.5% pCR in patients with CR by MRI after anthracycline-based regimen ($p = 0.0001$) and 65.1% pCR in patients with CR by MRI before surgery ($p = 0.0001$). All the patients with CR by MRI after anthracycline-based regimen had a CR by MRI before surgery.

Conclusions: CR by MRI after treatment with anthracyclines could be a clinically useful predictor of pCR in patients with TBNC treated preoperatively with anthracylcines and taxane-based regimens and patients who not reach CR after anthraclines could benefit from improve taxans regimen.

Legal entity responsible for the study: Luis Antonio Fernandez Morales.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

231P Immunomonitoring of triple negative breast cancer patients undergoing neoadjuvant therapy (GBG89, Geparnuevo trial)

B. Seliger

Institute of Medical Immunology, Martin Luther University of Halle, Halle, Germany

Background: The Geparnuevo trial is a randomized, double-blind, multi-center phase II trial of neoadjuvant therapy in patients with early-stage triple negative breast cancer (TNBC) investigating the role of durvalumab, an anti-PD-L1 inhibitor in addition to standard chemotherapy with nab-paclitaxel followed by epirubicin plus cyclophosphamide.

Methods: In order to determine possible predictive and / or prognostic biomarkers, blood samples were taken before and during the different treatment phases and evaluated by multicolor flow cytometry.

Results: Evaluation of the absolute cell count in the whole blood highlighted a mixed behavior of the total leukocytes, whereas there was a statistically significant reduction in the lymphocytes, particularly during the last phase of the treatment. Further dissection into the different immune populations highlighted an almost complete loss of B cells that in some patients was also accompanied by a reduction of NK cells, mostly regarding the $CD16^+$ subset. However, the loss of $CD4^+$ and $CD8^+$ T cells has been less pronounced resulting in an overall enhancement of their percentages within the total lymphocytes. The different populations have also been evaluated for the expression of activation and exhaustion markers, whose behavior will be more deeply evaluated when the clinical outcome and the treatment received by the various patients will be made available.

Conclusions: We expect that with such analysis possible biomarkers for the treatment of TNBC patients will be identified thus leading to better patient selection for chemo/ immune combination therapy.

Legal entity responsible for the study: GBG.

Funding: AstraZeneca and Celgene.

Disclosure: The author has declared no conflicts of interest.

233P Impact of breast cancer subtype on survival after lumpectomy versus mastectomy for early stage invasive breast cancer

Y-C. Tsai, H.C. Cheng, C.C. Horng

Radiation Oncology, Koo Foundation Sun Yat-sen Cancer Center, Taipei, Taiwan

Background: Randomized clinical trials (RCT) have demonstrated equivalent survival for breast-conserving therapy with radiation (BCT) and mastectomy for early-stage breast cancer. Early stage breast cancer patients who underwent BCT or mastectomy was studied to observe whether outcomes of RCT were achieved in a single institution series, and whether survival differed by surgery type when stratified by breast cancer subtypes.

Methods: Information was obtained from the institutional breast cancer data base with stage I or II breast cancer between 1990 and 2010, who were treated with either BCT or mastectomy and followed for vital status through December 2014. Cox proportional hazards modeling was used to compare overall survival (OS) and disease-specific survival (DSS) between BCT and mastectomy groups. Analyses were stratified by breast cancer subtype.

Results: A total of 3486 women fulfilled eligibility criteria. Women undergoing BCT had improved OS and DSS compared with women with mastectomy (adjusted hazard ratio for OS = 0.69, 95% CI = 0.51-0.95, $p = 0.0.023$; adjusted hazard ratio for DSS =0.68, 95%CI =0.48 -0.96, $p = 0.029$). 10 year overall survival rate in women undergoing BCT was 95.2% in Luminal A, 94.8% in Luminal B, 84.8% in Luminal/HER2, 91.5% in HER2 enriched and 92.1% in Triple negative. 10 year overall survival rate in women with mastectomy was 91.2% in Luminal A, 82.3% in Luminal B, 89.5% in Luminal/HER2, 86.2% in HER2 enriched and 88.4% in Triple negative.The group achieving greatest benefit in OS and DSS with BCT relative to mastectomy were stage II

luminal B patients (adjusted hazard ratio for OS = 0.28, 95% CI = 0.1-0.82, p = 0.02; adjusted hazard ratio for DSS =0.31, 95%CI =0.11 -0.91, p = 0.0329).

Conclusions: Among patients with early stage breast cancer, BCT was associated with improved DSS and OS. These data provide confidence that BCT remains an effective alternative to mastectomy for early stage disease. The group achieving greatest benefit in DSS and OS with BCT relative to mastectomy were stage II Luminal B patients.

Legal entity responsible for the study: Koo Foundation Sun Yat-sen Cancer Center, Taipei, Taiwan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

234P Survival outcomes of dose dense neoadjuvant and adjuvant chemotherapy in triple-negative breast cancer patients: Indian scenario

T. Sood[1], A. Rauthan[1], P. Patil[1], S. Kulkarni[1], S.P. Somashekhar[2], S. Zaveri[3], V. Ahuja[3], K.R. Ashwin[3]

[1]Medical Oncology, Manipal Comprehensive Cancer Center Manipal Hospital, Bangalore, India, [2]Surgical Oncology, Manipal Comprehensive Cancer Care, Bangalore, India, [3]Surgical Oncology, Manipal Comprehensive Cancer Center Manipal Hospital, Bangalore, India

Background: Breast cancer is the most common cancer in Indian women. Triple negative breast cancer (TNBC) is associated with poor prognosis at any stage of diagnosis. It is an aggressive disease with a 5-year survival rate of 77% compared to 93% for other subtypes. Prevalence of TNBC in India is higher compared to western populations, making it an important target for early detection and treatment. Potential superiority of dose-dense chemotherapy in comparison with conventional regimen has been recently demonstrated in a meta-analysis in 2017 across various subsets of breast cancer. Aim of this study was to analyse survival outcomes in TNBC treated with dose dense chemotherapy at a tertiary care centre in India.

Methods: Retrospective analysis of patients diagnosed with TNBC stage I-III in last 8 years treated with 2 weekly dose dense AC regimen (adriamycin at 60mg/m^{2}and cyclophosphamide at 600mg/m^2 for 4 cycles followed by 2 weekly Paclitaxel at175 mg/m^2 for 4 cycles or weekly Paclitaxel at 80 mg/m^2 for 12 cycles) with growth factor support in adjuvant or neoadjuvant (NACT) setting. Locally advanced breast cancer (LABC) was defined as T > 5cm and ≥N2 disease. Kaplan–Meier method and log rank test were used to estimate survival functions.

Results: 97 patients with ER, PR and Her2neu receptor negative status were evaluated. Median age at diagnosis was 44 years (range 26 - 68 years). 56.7% had stage II disease, 36% stage III and rest stage I (7.2%). Disease free survival (DFS) rate ± SE at 2 years and 5 years was 90% ± 3% and 75% ± 5% respectively. Overall survival (OS) rate ± SE at 5 years was 82% ± 6%. 24 patients received NACT out of which 12 (50%) patients had pathCR. The DFS rate did not differ significantly between adjuvant and neoadjuvant subgroups. Early breast cancer and LABC subgroups had a statistically significant difference in DFS rates (p = 0.0002).

Conclusions: To our knowledge, this is the first study in India to evaluate survival outcomes of dose dense therapy in TNBC. The improved DFS (75%) and OS (82%) in this high risk subgroup are very promising, especially in patients with early disease. We advocate use of dose dense regimen in all patients of TNBC in curative setting.

Legal entity responsible for the study: Manipal Hospital Ethics Committee.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

235P Prognostic factors associated with pathological complete response in early breast cancer patients undergoing neoadjuvant chemotherapy: The importance of Ki-67 and molecular subtype

B.L. Rapoport[1], J.A. Barnard-Tidy[1], T. Smit[2], S.J. Nayler[3], C.A. Benn[4]

[1]Medical Oncology, The Medical Oncology Centre of Rosebank, Sandton, South Africa, [2]Pharmacy, The Medical Oncology Centre of Rosebank, Sandton, South Africa, [3]Anatomical Pathology, Grtizman & Thatcher, Parklands, South Africa, [4]Surgery, Breast Care Centre of Excellence, Parklands, South Africa

Background: Ki-67 immunohistochemical determination is a widely used biomarker of cell proliferation in patients (pts) undergoing endocrine treatment for breast BC. The role of Ki-67 in pts undergoing neoadjuvant chemotherapy (NAC) for early BC remains controversial.

Methods: We analyzed retrospectively data on 137 patients undergoing taxane and/or anthracycline, transtuzumab based NAC. Luminal A was documented in 6 pts, Luminal B in 29 pts, Her-2 positive in 30 pts and triple negative breast cancers (TNBC) in 72 pts. Pathological complete response (pCR) was defined as the complete disappearance of the invasive cancer in the breast and absence of tumor in the axillary lymph nodes examined by axillary clearance.

Results: The pCR rate of the entire cohort was 41.6%. At 2 years 92% of pts who attained a pCR were disease free compared to 80% of pts who did not attain a pCR (log rank test p < 0.0147). On univariate analysis factors associated with higher pCR included primary tumor size (T1 68% vs. T2 41% vs. T3 or T4 0%, Chi^2=20.05, p < 0.00017), nodal disease (N0 49% vs. N1 39% vs. N2 8%, p < 0.02948), ER receptor status (negative 59% vs. positive 14%, p < 0.00000), PR receptor status (negative 53% vs. positive 17%, p < 0.00002), molecular subtype (TNBC 53.4%, Her2=50% and Luminal A + B was 8.5%, p < 0.00002), Ki67 (>40=55% vs. 15-39=34% vs. <15=0%, p < 0.00060) and Stage (I = 85% vs. IIA=49% vs. IIB=36% vs. III=5%, p < 0.00006). Factors not associated with a higher pCR included age, menopausal status, extranodal spread and lympho-vascular invasion. In a logistic regression model Ki-67 as a continuous variable (p < 0.01203) and molecular subtype (p < 0.02228) retained its significance; while tumor size, stage of disease, nodal status, ER and PR loss significance.

Conclusions: Ki67 and molecular subtype (Her-2 positive disease and TNBC) are independent prognostic factors of pCR in pts with early BC undergoing NAC.

Legal entity responsible for the study: The Medical Oncology Centre of Rosebank.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

236P The accuracy of sentinel lymph node biopsy following neoadjuvant chemotherapy in clinically node positive breast cancer patients: A single institution experience

N. Sistany Allahabadi[1], H. Yahyazadeh[1], M. Hashemian[1], M. Rajabpour[1], S. Aminmozaffari[1], M. Zaree[1], A. Rezazadeh Mafi[2]

[1]Milad General Hospital, Clinical Cancer Research Center, Tehran, Iran, [2]Radiation Oncology, Shahid Beheshti University of Medical Sciences, Teheran, Iran

Background: Sentinel lymph node dissection (SLND) after neoadjuvant chemotherapy (NAC) is of questionable accuracy. In this study we evaluated the feasibility and accuracy of SLND in breast cancer patients with clinically positive axillary nodes.

Methods: We conducted a prospective cross-sectional study on breast cancer patients diagnosed at Milad Hospital of Tehran, Iran from June 2014 to February 2015. Biopsy-proven node positive patients who converted to clinically node-negative following NAC and had a successful SLND (more than three identified SLNs) were included in the study. We used a 2 × 2 contingency table to analyze the feasibility of SLNB (sensitivity, specificity, false negative ratio, and accuracy). STATA statistical software (version 13.0, StataCorp LP, Texas, USA) was used for statistical analysis.

Results: Among 52 patients who entered the study, 47 had a successful SLND (more than three identified SLNs) in whom we achieved a sensitivity of 100% (16/16), false-negative rate of 0% (0/21), a negative predictive value of 100% (16/16), and an overall accuracy of 89.4%.

Conclusions: SLND seems to be feasible and accurate in clinically lymph node positive breast cancer patients who achieve a clinically negative node status following neoadjuvant chemotherapy.

Legal entity responsible for the study: Iran University of Medical Sciences.

Funding: Milad General Hospital - Iran National Social Security Organization.

Disclosure: All authors have declared no conflicts of interest.

237P Index BRCA1/2 testing under a multidisciplinary program

D.H.R. Machado[1], S. Fragoso[1], A. Opinião[1], A. Clara[1], S. Bento[2], A.C. Luís[1], I. Miguel[1], S. Santos[3], P. Machado[3], P. Rodrigues[2], J. Parreira[2], F. Vaz[2]

[1]Medical Oncology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E. (IPOLFG EPE), Lisbon, Portugal, [2]Risk Family Clinic, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E. (IPOLFG EPE), Lisbon, Portugal, [3]Molecular Pathology, Investigational Center, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E. (IPOLFG EPE), Lisbon, Portugal

Background: Germline BRCA1/2 mutations are the main cause of Hereditary Breast and Ovarian Cancer syndrome (HBOC). Whenever possible, Index testing should be done in a family member with a previous breast or ovarian cancer (affected individuals, AI) and not in non-affected individuals (NAI). In here we review the characteristics, decisional process and BRCA1/2 mutation detection rate of index testing in AI and NAI.

Methods: Analysis of all consecutive HBOC files registered from November 2000-December 2017. The BRCAPRO model was applied to affected patients (pts) and the Tyrer-Cuzick model to all non-affected female individuals. Comprehensive BRCA1/2 analysis was done, including MLPA and c.156_157insAlu testing (Machado PM et al., 2007)

Results: 6112 individuals were counseled and 4642 (76%) consented on genetic BRCA1/2 testing: 3420 (56%) index pts and 1222 (20%) family relatives. Index pts: 3361 (98.3%) had a previous cancer diagnosis (AI) and 59 were NAI. Both groups included mostly women (AI-95.2%; NAI-97%). The mean age for NAI was 40.7 years (20-79) and 79% had at least one-first degree relative with breast or ovarian cancer. Testing decision for NAI: either affected relatives were dead (80%), refused testing (15%) or were unreachable (5%). The global BRCA1/2 detection rate for index pts was 10.44%, being higher (13.6%) for NAI index cases (8 pathogenic variants: 2 BRCA1, 6 BRCA2). The mean pretest BRCA mutation probability (P) for NAI was 10.72% (range

0.06-42.8). This P was 18,5% for those who tested positive and 9,45% for inconclusive results ($p > 0.05$). The pre-test lifetime breast cancer risk was 26.69% for all NA cases, being higher for those found to be BRCA1/2 carriers (36.07% vs 28.04%).

Conclusions: Our conservative approach allowed for a detection rate in NAI that compared favorably to affected index pts. Although some groups propose widespread BRCA1/2 screening we suggest that NAI should be tested as index only if no cancer relatives are available. Despite the small sample size, the BRCA pre-test probability of 10% or higher seems to increase the detection rate in this subgroup.

Legal entity responsible for the study: Fátima Vaz.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

238P BRCA1/BRCA2 germline mutations and chemotherapy-related hematological toxicity in breast cancer patients

A. Friedlaender[1], A. Vuillemier[1], V. Viassolo[1], A. Ayme[2], S. De Talhouet[3], J-D. Combes[4], J. Peron[5], A. Bodmer[1], S. Giraud[6], A. Buisson[6], V. Bonadona[7], I. Gauchat-Bouchardy[8], O. Tredan[3], P. Chappuis[1], S.I. Labidi-Galy[1]

[1]Department of Oncology, Hopitaux Universitaires de Geneve, Geneva, Switzerland, [2]Department of Genetics, Hopitaux Universitaires de Geneve, Geneva, Switzerland, [3]Department of Oncology, Centre Léon Bérard, Lyon, France, [4]Infections and Cancer Epidemiology Group, International Agency for Research on Cancer, Lyon, France, [5]Departement of Medical Oncology, Hospices Civils de Lyon, Pierre-Bénite, France, [6]Division of Molecular Genetics, Hospices Civils de Lyon, Pierre-Bénite, France, [7]Unit of Prevention and Genetic Epidemiology, Centre Leon Berard, Lyon, France, [8]Department of Genetic Medicine, Hopitaux Universitaires de Geneve, Geneva, Switzerland

Background: BRCA1 and BRCA2 proteins play a central role in DNA repair process. We hypothesize that BRCA1/BRCA2 germline mutation carriers may exhibit increased hematological toxicity when receiving genotoxic chemotherapy.

Methods: We included women with primary breast cancers treated with (neo)adjuvant chemotherapy and screened for BRCA1/BRCA2 germline mutations in Geneva (Swiss cohort). The primary endpoint was the incidence of febrile neutropenia following the first chemotherapy cycle (C1). Secondary endpoints were the incidence of grade 3-4 neutropenia, grade 4 neutropenia and hospitalization during C1, G-CSF use, and chemotherapy dose reduction during the entire chemotherapy regimen. Long-term toxicities (hematological, cardiac and neuropathy) were assessed in the Swiss cohort and a second cohort of patients from Lyon (French cohort).

Results: Overall, 221 patients were assessed for acute hematological toxicity, including 23 BRCA1 and 22 BRCA2 carriers. None of the patients received dose-dense (every 14 days) chemotherapy. Following the C1, febrile neutropenia had an incidence of 35% ($p = 0.002$), 14% ($p = 0.562$) and 10% among BRCA1, BRCA2 and non-carriers, respectively. Grade 4 neutropenia was found in 57% of BRCA1 ($p < 0.001$), 14% of BRCA2 ($p = 0.861$) and 18% of non-carriers. G-CSF support was necessary in 86% of BRCA1 ($p = 0.005$), 64% of BRCA2 ($p = 0.285$) and 51% of non-carriers. Among patients with triple-negative breast cancers, febrile neutropenia (35% vs. 12%, $p = 0.038$), grade 3-4 neutropenia (73% vs. 28%, $p = 0.003$) and grade 4 neutropenia (60% vs. 13%, $p = 0.001$) were significantly more frequent in BRCA1 carriers compared to non-carriers. Among BRCA1 carriers, the majority of patients were likely to have grade 3-4 neutropenia (88%; $p < 0.001$), but none of those having mutations located in the RING domain (0%, $p = 0.165$) compared to non-carriers. For long-term toxicity analysis, 898 patients were included (167 BRCA1-, 91 BRCA2- and 640 non-carriers). There was no difference between the three groups.

Conclusions: BRCA1 germline mutations predispose breast cancer patients to greater acute hematological toxicity. This has implication for primary prophylaxis with G-CSF.

Legal entity responsible for the study: Intidhar Labidi-Galy.

Funding: La Fondation Henriette Meyer.

Disclosure: All authors have declared no conflicts of interest.

239P PALB2 germ-line mutations in Russian breast cancer patients: Identification of recurrent alleles and analysis of phenotypic characteristics of the tumors

E.N. Imyanitov[1], E.V. Preobrazhenskaya[1], A.Y. Shlejkina[1], A.P. Sokolenko[1], E.I. Anisimova[2], A.O. Ivantsov[1], A.V. Togo[1]

[1]Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, St. Petersburg, Russian Federation, [2]Outpatient Department, Leningrad Regional Oncological Dispensary, St. Petersburg, Russian Federation

Background: PALB2 is a well-known gene for hereditary breast cancer (BC). However, PALB2-driven BCs are less studied as compared to BRCA1/2-related malignancies, due to rarity of PALB2 deleterious alleles.

Methods: PALB2 germ-line mutation analysis was performed using blood-derived DNA.

Results: Sequencing of the entire coding region of PALB2 gene in 190 BC patients, who had evident clinical features of hereditary disease, but lacked BRCA1/2 germ-line mutations, led to the identification of 5 PALB2 mutation carriers. In addition, we considered 4 PALB2 heterozygotes, which were identified in our earlier study [Sokolenko et al., 2015]. The mutation spectrum was represented by 7 distinct pathogenic alleles (c.1317delG, c.172-175delTTGT, c.509-510delGA, R414X (n = 2), Q921X, c.1592delT and Y1055X (n = 2)). These 7 mutations were further screened in 1126 consecutive BC cases. This analysis revealed 8 additional instances of PALB2 mutations (c.509-510delGA (n = 5), c.172-175delTTGT (n = 2), c.1592delT (n = 1)). None of the above mutations was detected in 638 elderly tumor-free controls. Among 18 patients with PALB2-related BC, only 8 women were younger than 50 years; 6 patients reported family history of BC disease and 4 suffered from bilateral BC. IHC data were available for 10 tumors: 1 case was triple-negative, 1 BC demonstrated HER2 activation coupled with negative staining for hormone receptors (HR), and the remaining 8 cases were HR+. Loss-of-heterozygosity (LOH) analysis of 8 chemonaive BCs revealed somatic deletion of the remaining PALB2 allele in 5 tumors and retention of heterozygosity in 3 cases. In addition, we analysed 2 residual BC samples obtained after neoadjuvant therapy and revealed the intact PALB2 wild-type allele in both cases.

Conclusions: PALB2 germ-line mutations contribute to a fraction of BC morbidity in Russia, with PALB2 c.509-510delGA allele being the most frequent pathogenic variant. Interpatient variability with regard to somatic inactivation of the wild-type PALB2 allele deserves attention, given that intratumoral PALB2 status is likely to influence the drug sensitivity of BC.

Legal entity responsible for the study: N.N. Petrov Institute of Oncology.

Funding: Russian Science Foundation.

Disclosure: All authors have declared no conflicts of interest.

240P Landscape of germline mutations in hereditary breast and ovarian cancer (HBOC) patients in Russia revealed by target panel sequencing

E. Shagimardanova[1], L.H. Shigapova[1], R.F. Enikeev[2], M. Druzhkov[2], A. Nikitin[3], O. Gusev[1], M. Gordiev[4]

[1]Institute of Fundamental Medicine and Biology, Kazan Volga Region Federal University, Kazan, Russian Federation, [2]Chemotherapy Department, Kazan Clinical Oncology Center, Kazan, Russian Federation, [3]Genetic Laboratory, Federal Research and Clinical Center, FMBA, Moscow, Russian Federation, [4]Laboratory of Molecular Genetics, Tatarstan Cancer Center, Kazan, Russian Federation

Background: Hereditary breast and ovarian cancer (HBOC) is one of the most frequent disorders among other cancers, caused by presence of germline pathogenic variants in patients. Awareness about presence of actionable mutations (BRCA1,2, ATM and others) is beneficial for patients with breast and ovarian cancer due to possibility of targeted treatment, monitoring risk groups among healthy carries and other aspects. In this study we reveal and characterize pathogenic germline mutations in HBOC patients from different regions in Russian Federation.

Methods: Individuals with "family history" were chosen to be included in this study according to the following criteria: (1) young age of disease onset, (2) the presence of relatives with breast or ovarian cancer diagnosis. Information about nationality, age at diagnosis, family cancer history, estrogen, progesterone and Her2 receptor status was collected. The NimbleGen SeqCap EZ Choice kit ("Roche") was used for target enrichment, and sequencing was performed using Illumina MiSeq ("Illumina") using paired-end 2 × 251 nucleotide single-index sequencing. HGMD Professional 2017.4 and BIC databases were used to identify pathogenic mutations.

Results: 568 patients with breast or ovarian cancer aged from 21 to 82 years old were included in this study. 103 woman has their first cancer diagnosis before 40 years old, 305 – between 40 and 60 years old, 160 - were older than 60. 193 patients had first degree kinship relatives suffered from HBOC syndrome and 165 patients had relatives with other cancers. Of the 568 patients, 22,5% (128) carried pathogenic or likely pathogenic mutation in BRCA1 gene, 9,2% (52) in BRCA2 gene, 17,6% (100) in one of other HBOC related genes, including CDK12, ATM, CDH1, APC, FANCI, CHEK2, FANCL, BARD1, RAD51C, MUTYH, RAD51D, PALB2, FANCA, XRCC2, RAD54L, CHEK1.

Conclusions: Among patients with fulfilling NCCN criteria of hereditary breast or ovarian cancer, only 30% of cases might be explained by BRCA1 or BRCA2 mutation. Panel sequencing is powerful strategy to find variants in other genes, which may play a role in cancer development. It has to be noted that many variants in non-BRCA genes were identified is of unknown significance (VUS) due to absence of database with common variants for Russian population.

Legal entity responsible for the study: Tatarstan Cancer Center.

Funding: The work is supported by the Russian Foundation for Basic Research № 18-415-160009 r_a and according to the Russian Government Program of Competitive Growth of Kazan Federal University.

Disclosure: All authors have declared no conflicts of interest.

241P Lynch syndrome-associated hereditary mutations cause breast and ovarian cancer: Results from Russian Heredetary Oncogenomics project

M. Gordiev[1], L.H. Shigapova[2], O. Brovkina[3], R.F. Enikeev[4], M. Druzhkov[4], A. Nikitin[5], E. Shagimardanova[2], O. Gusev[2]

[1]Molecular-Diagnostic Laboratory, Tatarstan Cancer Center, Kazan, Russian Federation, [2]Institute of Fundamental Medicine and Biology, Kazan Volga Region Federal University, Kazan, Russian Federation, [3]Genetic Laboratory, Federal Research and Clinical Center, FMBA of Russia, Moscow, Russian Federation, [4]Chemotherapy Department, Kazan Clinical Oncology Center, Kazan, Russian Federation, [5]Genetic Laboratory, Federal Research and Clinical Center, FMBA, Moscow, Russian Federation

Background: Lynch syndrome is a hereditary disease caused by mutations in DNA mismatch repair system (MMR), which includes ML1, MS2, MS6, PMS2, EPCAM genes. Clinical manifestation of the Lynch syndrome is usually colorectal cancer (CRC), endometrial cancer, ureteral cancer and kidney cancer. We aimed to analyze occurrence of mutations in MMR system genes in patients with hereditary breast and ovarian cancer.

Methods: We have analyzed 228 samples of blood from patients with hereditary breast (BC) and ovarian cancer (OC) in Tatarstan Regional Clinical Cancer Center, Russia. The criteria for inclusion was at least one out of three observations: Young age of manifestation of breast or ovarian cancer (before 50 y.o. for BC and 55 y.o. for OC), first or second-degree relatives with breast or ovarian cancer, primary-multiple BC and OC. The libraries for sequencing were prepared using NimblGen SepCapEZ Choice (Roche) with custom gene panel followed by sequencing on MiSeq platform.

Results: Eight out of 101 (8%) patients with hereditary OC and five out of 127 (4%) patients with hereditary BC carried pathogenic mutation in one of MMR genes. Average age of manifestation of BC and OC in the patients with Lynch syndrome was 54 y.o. in case of OC and 56 y.o. in case of BC group: 50 y.o. Nine women had first and second-degree relatives with either BC, OC, colon or esophagus cancer. The distribution of affected genes in HBOC cohort was as follows: 3 patients with mutation in MSH6 gene, 4 patients with mutation in PMS2 gene, 2 patients with mutation in MSH2 gene, 3 patients with mutation in mlH1 gene. One patient carried mutation in EPCAM gene.

Conclusions: To date, the clinical standard for screening for Lynch syndrome is the Amsterdam criteria II, which are not oriented to the occurrence of OC and BC in patients, as well as to the presence of these cancers in a hereditary history in patients with colorectal cancer. However, our experience shows that patients with signs of hereditary OC and BC also can be carriers of mutations in the genes of the MMR system, which determine the Lynch syndrome. Thus, impact of Lynch syndrome-associated germline mutation on other types of cancer should be reconsidered and studied in detail.

Legal entity responsible for the study: Tatarstan Cancer Center.

Funding: The work is supported by the Russian Foundation for Basic Research № 18-415-160009 r_a and according to the Russian Government Program of Competitive Growth of Kazan Federal University.

Disclosure: All authors have declared no conflicts of interest.

242P Impact of deleterious germline BRCA mutations, addition of taxanes and use of adjuvant endocrine therapy (ET) on anti-müllerian hormone (AMH) levels in early breast cancer (EBC) patients treated by adjuvant chemotherapy (CT)

N. Olympios[1], M. Lambertini[2], C. Calbrix[3], M. Saint-Ghislain[1], M. Fontanilles[1], A. Loeb[4], M. Leheurteur[1], I. Demeestere[5], F. Di Fiore[1], A. Perdrix[3], F. Clatot[1]

[1]Medical Oncology, Centre Henri Becquerel, Rouen, France, [2]Department of Medicine Institute Jules Bordet, Brussels, Belgium, [3]Biopathology, Centre Henri Becquerel, Rouen, France, [4]Medical Information Department, Centre Henri Becquerel, Rouen, France, [5]Fertility Clinic, Hopital Erasme, Brussels, Belgium

Background: AMH is a promising biomarker of treatment-induced gonadal damage. The impact of carrying a deleterious germline BRCA mutation, adding a taxane to anthracycline-based CT and using adjuvant ET on gonadal function following CT remains unclear. We assessed the influence of these 3 factors on AMH levels before and after adjuvant CT in EBC patients.

Methods: This monocentric retrospective study included consecutive EBC patients aged ≤40 years treated with adjuvant FEC CT between 2008 and 2016, known germline BRCA status and available frozen plasma samples before and after CT. AMH levels (ng/mL) were assessed before starting CT, 1 year and over 3 year after diagnosis.

Results: 148 patients were included. 35 (24%) patients harbored a deleterious germline BRCA mutation, 127 (86%) received a taxane following FEC CT and 90 (61%) had adjuvant ET after CT. Overall median age was 35 (range 22-40). In the whole cohort, median AMH levels dropped after adjuvant CT (from 1.69 to 0.06, $p < 0.0001$) and slightly recovered after 3 years (0.17, $p < 0.0001$). No difference in baseline (1.94 vs 1.66, $p = 0.53$), 1-year (0.09 vs 0.06, $p = 0.39$) or 3-year (0.25 vs 0.16, $p = 0.43$) AMH levels was observed between patients with or without a BRCA mutation. Significant lower AMH levels were observed for patients who received a FEC-taxane regimen as compared to those treated with FEC only CT 1 year after diagnosis (0.04 vs 0.22, $p = 0.0006$), with no difference at 3 years (0.18 vs 0.06, $p = 0.47$). Patients treated with adjuvant ET had slightly higher AMH levels than those who did not receive ET 1 year after diagnosis (0.12 vs 0.02, $p = 0.008$) with no difference at 3 years (0.11 vs 0.20, $p = 0.22$).

Conclusions: Use of adjuvant CT is associated with a significant and durable alteration in ovarian reserve measured by AMH levels. Addition of taxanes to FEC increased CT-induced gonadotoxicity immediately after CT exposure but not at longer follow-up. Carrying a germline BRCA mutation and using adjuvant ET following CT were not associated with additional negative impact on patients' ovarian reserve after treatment.

Legal entity responsible for the study: Centre Henri Becquerel, Rouen, France.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

243P Germline mutation status and therapy response in patients with triple-negative breast cancer (TNBC): Results of the GeparOcto study

E. Pohl[1], A. Schneeweiss[2], J. Hauke[1], V. Moebus[3], J. Furlanetto[4], C. Denkert[5], P.A. Fasching[6], C. Hanusch[7], H. Tesch[8], N. Weber-Lassalle[1], V. Müller[9], K. Rhiem[1], M. Untch[10], K. Luebbe[11], B. Lederer[4], C. Jackisch[12], V. Nekljudova[4], R.K. Schmutzler[1], E. Hahnen[1], S. Loibl[4]

[1]Center for Familial Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Medical Faculty, University of Cologne and University Hospital Cologne, Cologne, Germany, [2]National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany, [3]Department of Gynecology and Obstetrics, Klinikum Frankfurt Höchst, Academic Hospital of the Goethe University Frankfurt, Frankfurt, Germany, [4]German Breast Group Forschungs GmbH, Neu-Isenburg, Germany, [5]Institute of Pathology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [6]Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany, [7]Frauenklinik, Rotkreuzklinikum, Munich, Germany, [8]Hämatologisch-Onkologische Gemeinschaftspraxis, Bethanien-Krankenhaus, Frankfurt, Germany, [9]Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany, [10]Department of Gynecology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin, Germany, [11]Breast Center, Diakovere Henriettenstift, Hannover, Germany, [12]Department of Obstetrics and Gynecology, Sana Klinikum Offenbach GmbH, Offenbach, Germany

Background: The phase III neoadjuvant GeparOcto trial (NCT02125344) randomized patients with triple negative breast cancer (TNBC) to receive treatment with intensified dose-dense epirubicin (E), paclitaxel (P), and cyclophosphamide (C; iddEPC) or weekly paclitaxel/liposomal doxorubicin (PM), plus carboplatin (Cb). Data on germline mutational analysis of patients with TNBC and the correlation with pathological complete response (pCR ypT0/is ypN0) were analysed.

Methods: NGS-based germline mutational analysis of BRCA1/2 and further 16 BC predisposition or candidate predisposition genes was carried out in 393 patients (iddEPC n = 194, PMCb n = 199). Deleterious (IARC class 4/5) variants were validated by Sanger sequencing. Detection of copy number variations (CNV) was carried out using an in-house CNV detection tool and established open access tools. Validation of CNVs was performed by either multiplex ligation-dependent probe amplification or real-time PCR.

Results: Overall, 69 of 393 (17.6%) patients carry pathogenic mutations in the BRCA1/2 genes. In 324 BRCA1/2-negative patients, 30 patients carry mutations in at least one of the 16 further analysed genes (9.3%). Of those, two patients carry mutations in two genes (ATM/CHEK2, PALB2/XRCC2) and 28 carry mutations in one gene (n = 2 BARD1, n = 5 BRIP1, n = 1 CHEK2, n = 9 FANCM, n = 1 NBN, n = 8 PALB2, n = 1 RAD50, n = 1 RAD51C); no mutations were found in CDH1, MRE11A, PTEN, RAD51D, STK11, and TP53). Overall patients with a BRCA1/2 mutation had a pCR of 69.6% vs 46.0% without a mutation ($p < 0.001$). In the iddETC group, patients with a BRCA1/2 mutation had a pCR of 64.7% vs 45.0% without a mutation ($p = 0.040$); in the PMCb arm, patients with a BRCA1/2 mutation had a pCR of 74.3% vs 47.0% without a mutation ($p = 0.005$).

Conclusions: Our data confirm that BRCA1/2 germline mutations represent a predictive biomarker for the achievement of pCR following neoadjuvant anthracycline-taxane-containing chemotherapy for TNBC.

Clinical trial identification: NCT02125344.

Legal entity responsible for the study: German Breast Group (GBG).

Funding: German Breast Group (GBG).

Disclosure: A. Schneeweiss: Honoraria: Roche, Celgene, AstraZeneca, Novartis, and Pfizer during the past 2 years. C. Hanusch: Consulting or advisory role: Novartis, Roche, Amgen, and Celgene during the past 2 years; Speakers' bureau: Novartis, Roche, Amgen, Pfizer, and Celgene during the past 2 years. V. Müller: Honoraria: Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Pfizer, Novartis, Roche, and Teva during the past two years; Consulting or advisory role: Hexal, Roche, Pfizer, Amgen, Daiichi Sankyo, Nektar, and Eisai during the past 2 years; Travel, accommodation, or other expenses paid or reimbursed: Roche and Pfizer during the past 2 years. K. Luebbe: Consulting or advisory role: Roche and Novartis during the past 2 years. S. Loibl: Honoraria: Pfizer and Roche during the past 2 years (institution); Consulting or advisory role: Novartis, Pfizer, Roche, and SeaGen during the past 2 years (institution); Research project funding: Abbvie, Amgen, AstraZeneca, Celgene Novartis, Pfizer, Roche, SeaGen, Teva, and Vifor during the past 2 years (institution). All other authors have declared no conflicts of interest.

244P BRCA1/BRCA2 predictive genetic testing in an Irish population: A missed opportunity

D.E. O Reilly[1], L. Dooley[2], G. Watson[3], R. Clarke[3], A. Nolan[3], C. Nolan[3], E. Berkeley[3], M.P. Farrell[4], D. Gallagher[1]

[1]Medical Oncology, St James's Hospital, Dublin, Ireland, [2]Radiation Oncology, St Lukes Hospital, Dublin, Ireland, [3]Department of Cancer Genetics, St James's Hospital, Dublin, Ireland, [4]Department of Cancer Genetics, Mater Private Hospital, Dublin, Ireland

Background: The diagnosis of a BRCA1/2 mutation has significant implications for both probands and their families, with both screening and prophylactic surgical interventions available. Underutilisation of genetic testing services has been reported in other jurisdictions. BRCA1/2 testing is requested in only 29-53% of eligible women and 11-12% of eligible men, represented a missed cancer prevention opportunity. Possible explanations include lack of family disclosure, poor access or lack of awareness of genetic counselling services, or patient preference. We investigated the rates of BRCA1/2 predictive testing in an Irish population.

Methods: We performed a multicentre, retrospective analysis of 63 pedigrees from two Irish tertiary hospitals over a five-year period (2012-2017). By manually examining pedigrees, we identified eligible family members who should receive BRCA1/2 mutation testing as per national guidelines.

Results: A total of 1048 candidates for predictive BRCA1/2 mutation testing were identified. 318 (30.4%) proceeded to BRCA1/2 mutation testing including 215 (37.5%) females and 99 males (21.5%). Uptake of testing favouring women was statistically significant ($T = 3.7$, $p < .0002$).

Conclusions: We demonstrate suboptimal uptake of BRCA1/2 mutation testing in the Irish population, particularly among Irish males. Predictive BRCA1/2 testing and subsequent screening/surveillance/prophylactic intervention in mutation carriers can meaningfully impact breast cancer survival. This represents a missed cancer prevention opportunity for Irish society.

Legal entity responsible for the study: Department of Cancer Genetics, St. James' Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

245P Incidence and survival among young women with stage I-III breast cancer

A. Thomas[1], A. Rhoads[2], E. Pinkerton[2], M.C. Schroeder[3], J.J. Oelson[2], L.R. McNally[4], W.G. Hundley[1], K. Conway[2], C.F. Lynch[2], P.A. Romitti[2]

[1]Internal Medicine, Wake Forest University, Winston Salem, NC, USA, [2]Public Health, University of Iowa, Iowa City, IA, USA, [3]Pharmacy, University of Iowa, Iowa City, IA, USA, [4]Cancer Biology, Wake Forest University, Winston Salem, NC, USA

Background: De novo Stage IV breast cancer (BC) is increasing in premenopausal women. Less is known about current incidence and survival among these women with Stage I-III BC.

Methods: Women ages 20-29 ($N = 3,826$), 30-39 ($N = 34,585$), 40-49 ($N = 126,552$) and 50-59 ($N = 172,448$) diagnosed with Stage I-III BC from 2000-15 were identified from the US Surveillance, Epidemiology and End Results database. Age-adjusted, annual percentage changes (APC) in incidence and 10-year Kaplan-Meier survival curves were estimated by stage, hormone receptor (HR) status, and grade (low: well/moderately differentiated; high: poorly/undifferentiated) for each age decade.

Results: Stage III BC at presentation decreased with age (20-29 [23.9%], 30-39 [21.9%], 40-49 [16.1%], 50-59 [14.1%]); the opposite pattern was observed for Stage I (23.6%, 28.8%, 42.0%, 48.3%, respectively). HR+ high grade and HR- BCs also decreased with age (20-29 [34.5%, 36.5%], 30-39 [31.1%, 31.6%], 40-49 [23.9%, 21.4%], 50-59 [20.9%, 21.1%]). Among all BC presentations, age-adjusted APC in incidence was higher for women 20-29 (1.6) than those 30-39 (0.3), 40-49 (0.3) or 50-59 (-1.1). Incidence of HR+ low and high-grade BC increased for women <50 with the highest APC (5.7 and 3.8, respectively) for women 20-29; HR- BC incidence decreased for all ages. Among women 20-29, 10-year survival was lowest for those with HR+ high grade BC (Table); for this group, the greatest survival difference between HR+ high grade and HR- BC was for Stage I BC (79.8% vs 89.3%) compared to Stage II (77.2% vs 80.7%) or Stage III (44.9% vs 45.0%). Comparing Stage III BC across age decades, 10-year survival was lowest for women 20-29, notably for HR+ BC.

Table: 245P

Stage	HR Status	Grade	10-Year Survival % (Standard Error)			
			Age (years)			
			20-29	30-39	40-49	50-59
Any	+	Low	81.2 (1.9)	85.4 (0.5)	91.1 (0.2)	89.2 (0.1)
	+	High	67.7 (2.0)	75.3 (0.6)	80.2 (0.3)	77.1 (0.3)
	-		73.8 (1.5)	74.3 (0.5)	75.1 (0.3)	74.3 (0.3)
Stage III	+	Low	54.2 (5.7)	62.8 (1.6)	73.7 (0.7)	68.3 (0.7)
	+	High	44.9 (3.9)	55.7 (1.3)	60.1 (0.8)	54.2 (0.8)
	-		45.0 (3.5)	49.2 (1.2)	49.8 (0.8)	47.5 (0.7)

Conclusions: Among young women, HR+ BC is increasing in incidence and associated with reduced survival for those 20-29. Understanding the etiologies underlying these trends may inform strategies directed toward improving outcomes for these women.

Legal entity responsible for the study: University of Iowa.

Funding: United States Centers for Disease Control and Prevention (U01DD001035) and the Nealie Belk Stevens Fund for Breast Cancer Research.

Disclosure: All authors have declared no conflicts of interest.

246P Toxicity and clinical outcomes of partial breast irradiation (PBI) compared to whole breast irradiation (WBI) for early stage breast cancer: A systematic review and meta-analysis

H. Goldvaser[1,3], A. Fyles[2], D. Shepshelovich[1], E. Amir[1], Y. Korzets[2,3]

[1]Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [2]Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [3]Davidoff Cancer Center, Beilinson Hospital, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Background: There is uncertainty about efficacy and toxicity differences between adjuvant PBI and WBI in women with early-stage breast cancer treated with breast conservation.

Methods: We identified randomized trials that compared PBI to WBI in early-stage invasive breast cancer using PubMed. Odds ratios (ORs), 95% confidence intervals

Table: 246P

	OR, 95% CI	P value all/ subgroup difference	Weighted absolute difference
5-year local recurrence			
All	2.28 (1.66-3.15)	<0.001	1.47%
EBRT IORT Brachytherapy	0.64 (0.25-1.62) 3.1 (2.12-4.51) 1.44 (0.63-3.29)	0.004	
5-year regional recurrence			
All	1.49 (0.88-2.53)	0.14	0.3%
EBRT IORT Brachytherapy	1.96 (0.20-18.92) 1.45 (0.80-2.63) 1.56 (0.39-6.27)	0.97	
5-year contralateral breast cancer			
All	0.94 (0.59-1.47)	0.77	-0.1%
EBRT IORT Brachytherapy	0.85 (0.44-1.63) 1.54 (0.65-3.66) 0.64 (0.25-1.62)	0.37	
5-year death without breast cancer recurrence			
All	0.55 (0.41-0.73)	<0.001	-1.6%
EBRT IORT Brachytherapy	0.71 (0.42-1.20) 0.45 (0.29-0.69) 0.57 (0.29-1.13)	0.41	
5-year overall survival			
All	0.76 (0.61-0.95)	0.02	-1.1%
EBRT IORT Brachytherapy	0.79 (0.51-1.22) 0.78 (0.59-1.04) 0.61 (0.32-1.14)	0.75	

(CI) and absolute risks were computed for pre-specified efficacy and toxicity outcomes including cosmetics. Subgroup analysis evaluated the effect of PBI modality (external beam radiation treatment [EBRT], intraoperative radiation treatment [IORT] or brachytherapy) on efficacy. Meta-regression analysis explored the influence of median follow-up as well as patients and tumor characteristics on results.

Results: Eight trials comprising 10298 patients were included. Efficacy results, weighted absolute differences and subgroup analysis are shown in the table. PBI was associated with increased odds of local recurrence compared to WBI. However, PBI was associated with reduced odds of death without breast cancer recurrence and improved overall survival (OS). Subgroup analysis showed the effect on local recurrence was influenced by modality of radiation; odds of local recurrence were increased with IORT and brachytherapy, but not with EBRT. Nodal involvement was associated with higher local recurrence risk while larger tumors were associated with lesser improvement in death without breast cancer recurrence and OS. PBI was associated with higher odds of fat necrosis ($p = 0.002$). Worse cosmetic outcome with PBI approached significance ($p = 0.06$).

Conclusions: Compared to WBI, PBI is associated with higher odds for local recurrence and toxicity, but less death without breast cancer recurrence and improved OS. The balance between benefit and risk of PBI appears optimal for women with smaller ER positive tumors and without nodal involvement.

Legal entity responsible for the study: Hadar Goldvaser.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

247P Should anthracyclines always be present in the adjuvant treatment of breast cancer (BC)? A systematic review and meta-analysis of randomized controlled trials (RCTs)

R. Caparica[1], M. Bruzzone[2], F. Poggio[1], M. Ceppi[2], E. de Azambuja[3], M. Lambertini[1]

[1]CTSU, Institute Jules Bordet, Brussels, Belgium, [2]Biostatistics, IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [3]Medical Oncology, Institute Jules Bordet, Brussels, Belgium

Background: Anthracycline and taxane-based (A+T) chemotherapy (CT) is the current standard adjuvant CT for HER2-negative BC patients. However, anthracyclines can be associated with important short and long-term toxicities (e.g. cardiotoxicity and leukemias). After a phase 3 trial demonstrated that docetaxel+cyclophosphamide (TC) was more effective than doxorubicin + cyclophosphamide (AC), the use of TC has increased. Nevertheless, RCTs could not demonstrate that TC is non-inferior to the standard A+T. This is a systematic review and meta-analysis of RCTs comparing A+T versus TC as adjuvant CT in HER2-negative BC patients.

Methods: A literature search using PubMed, EMBASE, Cochrane, ASCO, ESMO and SABCS websites was performed up to March 30, 2018, to identify RCTs comparing TC vs A+T as adjuvant CT in HER2-negative BC patients. Disease-free survival (DFS) and overall survival (OS) were assessed. A subgroup analysis of DFS in hormone receptor positive (HR+) and negative (HR-) disease was also performed. Hazard ratios (HR) and 95% confidence intervals (CI) for DFS were extracted from each trial, and a pooled analysis was conducted using the random-effect model. The Higgins' I-Squared Test was used to quantify heterogeneity.

Results: A total of 8 RCTs that randomized 12,741 early BC patients were included. Five RCTs were published as pooled results: ABC trials comprised 3 RCTs, and PlanB + Success-C comprised 2 RCTs. The comparison of TC versus A+T demonstrated a non-significant benefit in favour of A+T for both DFS (HR 1.08, 95% CI 0.96 - 1.20) and OS (HR 1.05; 95%CI 0.90 – 1.22). The magnitude of the benefit of A+T was more pronounced in patients with HR- disease, (N = 1,947, HR 1.12, 95% CI 0.93 – 1.34) compared to those with HR+ disease (N = 4,867, HR 1.05, 95%CI 0.86 – 1.27).

Conclusions: Globally, our results showed that A+T was associated with a slight non-significant improvement in DFS and OS as compared to TC. Nevertheless, in selected patients such as those with HR+ disease, TC may be considered an alternative option to avoid the toxicities of anthracycline-based CT.

Clinical trial identification: CRD42018090962 - PROSPERO register.

Legal entity responsible for the study: Institut Jules Bordet.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

248P Taxane & cyclophosphamide vs anthracycline & taxane combination therapy as adjuvant treatment of breast cancer: A meta-analysis of randomized-controlled trials by the Hellenic Academy of Oncology (E.AK.O.)

P. Ntellas[1], N. Spathas[2], D. Zylis[3], S. Agelaki[4], E. Zintzaras[1], E. Saloustros[5]

[1]Biostatistics and Clinical Bioinformatics, Faculty of Medicine, University of Thessaly, Larissa, Greece, [2]Oncology Unit, Attikon University Hospital, Athens, Greece, [3]1st Department of Medical Oncology, Agios Savvas Regional Cancer Hospital, Athens, Greece, [4]Department of Medical Oncology, School of Medicine, University of Crete, Heraklion, Crete, Greece, [5]Oncology Unit, Venizeleio General Hospital, Heraklion, Greece

Background: Adjuvant chemotherapy has an indisputable value for early breast cancer. Taxane + cyclophosphamide combination (TC) has demonstrated superiority against cyclophosphamide + anthracycline (AC) in disease-free (DFS) and overall survival (OS). However, 5 randomized clinical trials (RCTs) failed to show non-inferiority of TC compared to an anthracycline-taxane combination (TaxAC). We conducted a meta-analysis of these RCTs to better estimate the cumulative evidence for non-inferiority of TC against TaxAC, in the adjuvant setting of HER2-negative, breast cancer.

Methods: The ABC trials, the Plan B trial and a trial by the Hellenic Oncology Research Group (HORG) were meta-analyzed. The DFS was the primary endpoint. A DFS-HR of 1.18 for TC versus TaxAC, was chosen to demonstrate inferiority, as it was the most conservative measure among the included studies. Secondary endpoints were OS and toxicity profile.

Results: Overall, 7,341 patients composed the meta-analysis population. We didn't encounter heterogeneity between the trials (Q-test $p = 0.55$, I^2:0%) and no publication bias was detected. Non-inferiority of TC was not established (DFS-HR=1.11, 95%CI: 0.95-1.30, $p = 0.18$). The combined DFS rates, according to the time points set by each study, were 89.04% versus 90.35% for TC and TaxAC respectively. Non-inferiority of TC was also not proven for the node-negative population either (HR = 1.05, 95%CI: 0.82-1.34, $p = 0.71$). Grade 3-4 leucopenia (OR: 1.2, 95%CI:1.068-1.348, $p = 0.002$) and thrombocytopenia (OR = 6.455; 95%CI:2.902-14.359, $p < 0.001$) prevailed in the TaxAC group, while cardiotoxicity was also increased (OR = 2.283; 95%CI:1.155-4.514, $p = 0.015$).

Conclusions: Although the TC combination was not proven to be non-inferior to TaxAC, the present analysis narrows the HR of recurrence risk of recurrence with a difference in the DFS rate of only 1,31%. Taking into account the more favorable safety profile of the TC combination, the question as to which treatment regimen should be preferred under what circumstances needs to be individualized according to patients' characteristics and desires.

Legal entity responsible for the study: Hellenic Academy of Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

249P Risk of cardiovascular late effects in breast cancer survivors: A population-based study

J. Lee[1], I.Y. Chung[2], Z. Kim[3], H. Hur[4], J.W. Lee[2], H.J. Youn[5]

[1]Surgery, Soonchunhyang University Hospital Seoul, Seoul, Republic of Korea, [2]Surgery, Asan Medical Center, Seoul, Republic of Korea, [3]Surgery, Soonchunhyang University Hospital, Bucheon, Republic of Korea, [4]Surgery, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea, [5]Surgery, Chonbuk National University Medical School, Jeonju, Republic of Korea

Background: Cardiovascular diseases are one of the late effects of breast cancer treatment that can impair survival. We reviewed the development of cardiac disease in breast cancer survivor using nationwide database.

Methods: A nation-wide retrospective cohort study was conducted using National Health Information Database which provides a whole set of claimed medical information, such as ICD-10 diagnosis and prescription data. We performed 1:5 age-sex matching with the non-cancer controls. Incidence of MI and CHF was evaluated for adjuvant treatment modalities, with adjustment of age and previous comorbidities (diabetes, hypertension, and hyperlipidemia).

Results: A total of 112,058 cases (554,801 person-years) and 560,290 controls (2,916,459 person-years) were evaluated. Risk of MI (hazard ratio (HR) 1.258, 95% confidence interval (CI) 1.168 - 1.355) and CHF (HR 1.86, 95% CI 1.753 – 1.973) was higher in breast cancer survivors than in non-cancer controls. Younger survivors (age 50 or less) showed the highest risk of MI (HR 1.73, 95% CI 1.512 – 1.979) and CHF (HR 3.557, 95% CI 3.174 – 3.986). Within one year of breast cancer diagnosis, the cumulative incidences of MI and CHF were significantly high in survivors. The cumulative incidence of CHF in breast cancer survivors was continuously higher than the control group, in contrast to that of MI showed similar pattern to controls. Taxane use was associated with development of MI (HR 1.284, 95% CI 1.074 – 1.534) and CHF (HR 1.65, 95% CI 1.444 – 1.887).

Conclusions: Incidence of MI and CHF were higher in breast cancer survivor than the non-cancer controls. The elevated risk of MI and CHF in early phase of survivorship should be noted, especially in young age group.

Legal entity responsible for the study: The Study of Multi-disciplinary Teamwork for breast cancer survivorship (SMARTSHIP).

Funding: Korean Breast Cancer Society.

Disclosure: All authors have declared no conflicts of interest.

250P Diagnostic value of contrast enhanced digital mammography versus contrast enhanced MRI for preoperative evaluation of breast cancer

E.Y. Kim, I. Youn, C.H. Park, S.H. Kook

General Surgery, Kangbuk Samsung Hospital Sungkyunkwan University, Seoul, Republic of Korea

Background: This study aimed to compare the diagnostic performance of pre-operative evaluation of contrast-enhanced digital mammography (CEDM) and contrast-enhanced magnetic resonance imaging (CEMRI) and to evaluate the effect of each modality to the surgical management in women with breast cancer.

Methods: This single-institution prospective study was approved by the Institutional Review Board and informed consent was obtained from all patients. From November 2016 to October 2017, 84 patients, who were diagnosed as invasive carcinoma (69/84) and ductal carcinoma in situ (DCIS) (15/84) underwent both CEDM and CEMRI, were enrolled. We correlated the imaging findings and surgical management with pathologic results, and compared the diagnostic performance of both modalities in the detection of index and secondary cancers (multifocality and multicentricity), and occult cancer in contralateral breast. We also evaluated whether CEDM or CEMRI made changes in surgical management of the affected breast attributed to imaging-detected findings.

Results: Eighty-four women were included for analysis. CEDM, in comparison to CEMRI, had a significantly higher specificity (66.7% vs 22.2%, $P = 0.021$), similar sensitivity (94.6% [78/84] vs 93.5% [81/84]), PPV (93.5% vs 86.0%) and a fewer false positive findings (66.7% [10/15] vs 93.3% [14/15]) in detecting index cancer. For detection of secondary cancers on ipsilateral breast and occult cancer in contralateral breast, no significant differences were found between CEDM and CEMRI (all $P > 0.05$). Regarding changes in surgical management, CEDM made less change (36.9% [31/84] vs 41.7% [35/84]) than CEMRI, owing to less false positive findings (48.4% [15/31] vs 54.3% [19/35]).

Conclusions: CEDM showed comparable diagnostic performance with CEMRI in depicting index, secondary cancers, and occult cancer in contralateral breast. The CEDM, owing to fewer false positive results, made less change in surgical management compared to CEMRI.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

252P Relationship between androgen receptor and tumor-infiltrating lymphocytes in triple-negative breast cancer

L.F. Sánchez-Cousido[1], A. López-González[1], E. Honrado Franco[2], E. Vallejo Pascual[3], O. Sanz[4], L. Lopez Gonzalez[5], I. Delgado[1], M. López-Flores[6], A. García Palomo[6]

[1]Oncology, Complejo Asistencial Universitario de León, León, Spain, [2]Pathology, Complejo Asistencial Universitario de León, León, Spain, [3]Economic and Statistic, Universidad de León, León, Spain, [4]General Surgery, Complejo Asistencial Universitario de León, León, Spain, [5]Radiology, Complejo Asistencial Universitario de León, León, Spain, [6]Oncología Médica, Complejo Asistencial Universitario de León, León, Spain

Background: Triple-negative breast cancer (TNBC) is considered a poor prognostic subtype and a heterogeneous entity. Its only treatment is chemotherapy. Immunotherapy and antiandrogen therapies are being tested. Androgen receptor (AR) is expressed in up to 53% of TNBC. It is associated with a better disease-free survival and overall survival. The relation between tumor infiltrating lymphocytes (TIL) and AR in urothelial cancers has been assessed, unlike in TNBC.

Methods: 50 stage I-III TNBC patients diagnosed between 2008 and 2013 were analyzed. Minimum follow-up was 57 months or until death. On these samples fixed in 10% formalin and included in paraffin, the evaluation of the expression of AR, CD20, CD4 and CD8 was performed by immunohistochemistry. AR+ was defined by more than 1% expression. Lymphocytes were evaluated as per the recommendations of the International Expert Consensus. We also analyzed total lymphocytes as high/low if they were over/under 80%. Data was analyzed by SPSS version 23.

Results: Clinical characteristics are as follows: mean age of 61 years old, and postmenopausal 68%. 74% of the patients did not relapse and progression-free survival (PFS) was 95,6 months. Main tumor characteristics were Ki67>20%, 67,3%; T1-T2 88%; high grade 67,4%; lymph node (N) positive 51%. Early stage (stage I-II) was the 80%. High level of lymphocytes (HiL) was present in 70% of them. AR + (26%) was associated with younger patients ($p = 0.009$), low Ki67 ($p = 0.014$) and N + ($p=0.025$). No relation was obtained between AR and TIL, tumor size, grade, stage or survival. CD8+ were more present in AR + ($p=0.002$) and so the proportion CD4/CD8 (CD8>CD4 in AR+; CD4>CD8 in AR-. $p = 0.026$) HiL was related with higher Ki67 ($p = 0.021$) and grade 3 ($p = 0.029$). However, lower relapse and also lower deaths were observed in those with HiL (15.4% vs 84.6%; 21.4% vs 78.6%). In HiL, percentage of CD8+ was inversely proportional ($p = 0.021$ mean 27,7%).

Conclusions: High grade tumors and higher Ki67 unleash a higher immune response, protecting from a worse prognosis. CD8+ lymphocytes are associated with AR expression. More studies are needed to understand the relationship between AR and TIL and also the role of AR blockade in TNBC and its role in immune-mediated lysis.

Legal entity responsible for the study: Complejo Asistencial Universitario de León.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

253P Use of red clover in premenopausal breast cancer patients receiving hormonal adjuvant treatment: Biological and clinical implications from a randomized clinical trial

C. Ferraris[1], B. Ballestra[1], V. Cappelletti[2], C. Listorti[1], P. Miodini[3], I. Pulice[4], L. Mariani[5], E. Ferrari[6], A. Gambaro[7], I. Maugeri[1], G. Martelli[1], S. Folli[1]

[1]S.C. Chirurgia Generale Indirizzo Oncologico 3 (Senologia), Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [2]Dipartimento di Oncologia Sperimentale e Medicina Molecolare, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [3]S.C. Biomarcatori, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [4]Direzione Scientifica Studi Clinici, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [5]Direzione Scientifica Statistica Medica, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [6]S. C. Farmacia, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [7]Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milan, Italy

Background: Premenopausal women with breast cancer (BC) experience early onset of treatment-induced menopausal syndrome with adjuvant hormone therapy (HT). Isoflavones in the red clover (RC) are biologically active agents providing a source of rapidly available phytoestrogens acting as natural selective estrogen receptor modulators. Aims of the study are: to improve quality of life reducing menopausal symptoms from HT in BC premenopausal women and preventing weight gain and metabolic syndrome with personal lifestyle intervention; to evaluate in vitro safety profile of RC used in combination with adjuvant anti-estrogenic HT.

Methods: Eighty-eight premenopausal BC women (DCIS, T1/T2N0-N1M0) receiving adjuvant HT were randomly assigned to have 80 mg/die of RC dry extract (MCE-11) (verum group) or a tablet without active principle (placebo group) for 2 years. Menopausal Rating Score (MRS) questionnaire was given every three months during the first year then biannually. Diet program was personalized with the WCRF/AICR recommendations and Mediterranean diet. Body Max Index (BMI), hip and waist circumference, homeostatic model assessment index (HOMA) and lipid profile (total LDL, HDL cholesterol, triglycerides) were recorded. Pool serum of women from the two groups was run for in vitro evaluation of the safety profile using specific cell lines selected to be representative of hormone-sensitive BC with high expression of estrogen receptor a (MCF7, T47D) and β (BT20).

Results: Menopausal symptoms significantly decreased in both groups over time ($p < 0.0001$). In the verum group BMI, hip and waist circumference were more reduced than in placebo group ($P < 0.0001$). HDL cholesterol significantly improved over time ($p < 0.01$). There was no significant difference in endometrial rhyme, while mammary density significantly decreased in both arms ($p < 0.0001$). In vitro, no significantly differences were observed in cell growth and induction of estrogen regulated/related genes in the cell lines treated with serum from women of the two arms.

Conclusions: Isoflavones can be safely used in premenopausal BC women under HT to contrast symptoms related to treatment.

Clinical trial identification: Protocol number INT 101/11 release date 25/06/2012 - EudraCT: 2011-005518-12 2-2-24-01-2012.

Legal entity responsible for the study: Cristina Ferraris.

Funding: Named S.p.A.

Disclosure: All authors have declared no conflicts of interest.

254P PROMs following breast-conserving therapy for breast cancer: Results from a prospective longitudinal monocentric study

I. Kindts[1], A. Laenen[2], M. van den Akker[3], C. Weltens[1]

[1]Radiation Oncology, University Hospitals Leuven - Campus Gasthuisberg, Leuven, Belgium, [2]Leuven Biostatistics and Statistical Bioinformatics Centre (L-Biostat), KU Leuven University, Leuven, Belgium, [3]Family Medicine, School CAPRI, Maastricht University, Maastricht, Netherlands

Background: To evaluate patient-reported outcomes (PROs) and long-term aesthetic outcome (AO) related to radiotherapy (RT) in the breast-conserving therapy setting for breast cancer over time. To explore the agreement between PROs and AO.

Methods: Patients treated with breast-conserving therapy at one institute between April 2015 and April 2016 were prospectively included in the cohort. The AO was scored by the patient and by the BCCT.core software. Further PROs were measured with the EORTC QLQ-C30, QLQ-BR23 and the BIBCQ. Patients were evaluated at preset time points over two years. First, we assessed the evolution in time of the PROs and AO. Second, we tested the differences in mean scale scores of the PROs between patients with a favourable and an unfavourable AO.

Results: 175 patients were included in the analysis. At baseline unsatisfactory levels were already present for several global, functional, symptom and body image scales. Most unsatisfactory PROs improved significantly up to one year after RT. Fatigue showed a small deterioration at the start of RT, but improved medium thereafter up to one year after RT (mean difference (MD) 7.6, -12.3, respectively and $p < 0.001$). Cognitive functioning showed a small decrease from at the start of RT with no further significant decrease (MD -4.73, -0.21 and p 0.003, 0.894, respectively). Breast symptoms significantly increased during RT but decreased afterwards up to two years after

RT to lower values than at baseline and were then considered satisfactory (MD 15.6, -19.7, -4.1 and $p < 0.001$, <0.001, 0.005, respectively). AO scored by the patient and with the BCCT.core associated well with each other and with the body image measures. There was no association between AO and global cancer-related QOL in the present cohort.

Conclusions: Small quality of life impairments present during RT with good recovery up to one year after RT. Body image is disturbed during RT and improves up to two years after RT. Around one third of patients score their long-term AO as unfavourable and these PROs correlate well with body image.

Legal entity responsible for the study: Caroline Weltens.

Funding: Kom Op Tegen Kanker.

Disclosure: All authors have declared no conflicts of interest.

255P Impact on disease-free survival (DFS) of the surgical waiting time (SWT) for patients (Pts) with early breast cancer (BC)

R. Nakamura[1], N. Yamamoto[1], T. Miyaki[2]

[1]Breast Surgery, Chiba Cancer Center Hospital, Chiba, Japan, [2]Breast Oncology, Chiba Cancer Center Hospital, Chiba, Japan

Background: SWT is distressing for patients and impairs their quality of life. There are few studies and no consensus in the literature concerning the impact of BC biology on SWT, particularly in each subtype. However, a randomized trial is not possible to study the SWT. We aimed to assess the impact of the SWT and the histological grade (HG) of tumor on DFS.

Methods: We retrospectively reviewed the data of Pts with invasive BC who received core needle biopsy (CNB) as diagnosis between January 2007 and June 2017. Pts who required neo-adjuvant chemotherapy were excluded. The primary analysis was a comparison of the DFS between patients who have SWT for 1 month or less (early group) and those who have them for longer than 1 month (late group). Propensity score matching in these groups was calculated based on the menopausal status, cT, cN, ER, PgR and HER2 status. Furthermore, we divided the Pts into 4 groups for the survival analysis as follows: the HH [high grade CNB/high grade surgical specimen (SS)], the LL (Low grade CNB/Low grade SS), LH (Low grade CNB/high grade SS) and the HL group (high grade CNB/low grade SS).

Results: We analyzed the data of 1513 patients. Based on the propensity score, the early group and late group had 530 matched patients each. The median age was 62 years, cT1:58%, cT2:36%, cN0:75%, cN1;25%, ER(+) 82%, PgR(+) 68%, HER2(+):12% in both groups. The median diagnosis to curative SWT was 24.2 days in the early group and 46.7 days in the late group. A propensity score-matched model showed the significant difference in the DFS between the early group and the late group (5-year DFS rate, 92.9 vs. 86.6%; $p = 0.0014$ HR:1.98 1.30 to 3.08). Multivariate analysis revealed that the prognostic factors were significantly associated with cT (HR:2.02 95% CI 1.34 to 3.07), cN (HR:2.68 95% CI 1.78 to 4.04) and SWT (HR: 1.98, 95% CI, 1.30 to 3.08). ER, PgR and HER2 were not independent prognostic factors. The LH group for early group had a shorter DFS than the HL, HH and LL group ($p = 0.0013$). The HG for late group was not associated with survival.

Conclusions: The late group was significant worse in DFS compared with the early group. The histological up-grading of tumor for the early group was associated with worse survival.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding

Disclosure: All authors have declared no conflicts of interest.

256P Oncological outcome of fat grafting for breast reconstruction after cancer

G. Griguolo[1], F. Miglietta[1], M.V. Dieci[1], V. Vindigni[2], F. Bassetto[2], E. De Antoni[2], I. Polico[3], A. Marchet[4], E. Baldan[3], G. Vernaci[1], T. Saibene[5], S. Michieletto[5], V. Guarneri[1]

[1]Department of Surgery, Oncology and Gastroenterology, University of Padova, Istituto Oncologico Veneto IRCCS, Padua, Italy, [2]Plastic Surgery Clinic, University of Padova, Padua, Italy, [3]Diagnostic Senology Unit, Istituto Oncologico Veneto - IRCCS, Padua, Italy, [4]Clinica Chirurgica 1, Azienda Ospedaliera di Padova, Padua, Italy, [5]Breast Surgery Unit, Istituto Oncologico Veneto - IRCCS, Padua, Italy

Background: Fat grafting (FG) has become widely used in breast reconstruction after breast cancer (BC). FG might express protumorigenic factors or alter radiological aspect of the breast, raising some concerns on its oncological safety. The aim of the study was to describe clinical outcome of patients (pts) undergoing FG.

Methods: Records of 424 pts who underwent FG between 2010 and 2017 at the Plastic Surgery Dept. of Padova University were reviewed. Pts without invasive BC or not followed at Istituto Oncologico Veneto were excluded, leaving 206 pts for analysis. Cumulative Incidence of relapse was calculated from first FG. Association between clinico-pathological factors and relapse was explored.

Results: Patients were mostly post-menopausal ($n = 115$, 56%) and the majority had HR+/HER2- BC ($n = 134$, 65%). Eight pts (4%) were BRCA-mut carriers. Disease stage at diagnosis was: I (42%), II (34%), III (24%). Median interval from surgery to first FG was 23 months (range 0-257). 336 FG interventions were performed (median per patient: 1, range 1-9). At median follow-up of 38.9 months, 35 pts relapsed (10 locoregional, 25 distant relapses). Cumulative Incidence of relapse according to clinico-pathological subgroups is reported in the table. Semestral hazard rates of relapse in the three years after FG were: 0.010, 0.053, 0.034, 0.007, 0.039, and 0.038, respectively. 59 pts (29%) underwent additional breast imaging over standard recommendation (range 1-6 per patient), and 40 (20%) pts underwent breast biopsies (range 1-4, 10 confirmed a local recurrence).

Table: 256P

Clinicopathological factors		Number of patients (%)	3-years cumulative incidence of relapse	Hazard Ratio (95% CI)
HR status	HR negative	26 (13%)	13%	ref
	HR positive	170 (87%)	16%	1.57 (0.47-5.18)
HER2 status	HER2 positive	46 (24%)	10%	ref
	HER2 negative	143 (76%)	16%	1.93 (0.74-2.05)
Stage at diagnosis	Stage I	81 (42%)	11%	ref
	Stage II	67 (34%)	17%	2.84 (1.06-7.62)
	Stage III	47 (24%)	23%	4.42 (1.68-11.63)
Interval from surgery to first FG	>2 years	99 (48%)	16%	ref
	<2 years	107 (52%)	17%	1.07 (0.55-2.08)
Type of breast surgery	Mastectomy	180 (87%)	15%	ref
	Conservative	26 (13%)	25%	1.53 (0.63-3.69)
Overall Population		206 (100%)	17%	-

Conclusions: This study describes a not negligible rate of recurrence in BC pts receiving FG, especially in stage III and conservative surgery pts. High risk of relapse in the first years after FG might suggest a potential relation between the procedure and events. Moreover, a significant proportion of pts underwent additional breast imaging and biopsies, which can adversely affect quality of life. A careful discussion in multidisciplinary setting is crucial for proper pts selection.

Legal entity responsible for the study: Valentina Guarneri.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

257P Changes in body weight over 18-months follow-up among Chinese patients after breast cancer diagnosis

W. Yeo[1], Y.Y. Lei[1], A.C. Cheng[2], C.C. Kwok[2], K.L. Cheung[1], I.C. Lee[1], R. Lee[1], S. Ho[3]

[1]Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, China, [2]Clinical Oncology, Princess Margaret Hospital, Kowloon, Hong Kong, China, [3]School of Public Health, The Chinese University of Hong Kong, Hong Kong, China

Background: Weight gain has commonly been reported among patients after breast cancer diagnosis in western countries. Based on limited data in the literature, weight gain in Asian counterparts appears to be less. In this prospective study, we investigate the weight changes among Chinese breast cancer patients during 18-month follow-up from diagnosis.

Methods: This is part of the ongoing Hong Kong NTEC-KWC Breast Cancer Survival Study (HKNKBCSS). Chinese patients with newly diagnosed early-stage breast cancer were consented. Studied patients had their weights recorded at breast cancer diagnosis (T0), at study entry (T1; within 12 months from T0) and at 18-month follow-up (T2). Potential associating factors including socio-demographic, lifestyle and clinical factors were assessed.

Results: A total of 1265 patients had detailed weight at the 3 time-points of assessment. The mean age at diagnosis was 51.8 years. The proportion of patients who received chemotherapy, radiotherapy and endocrine therapy were 77%, 70% and 72% respectively. Compared to T0, the median weight change was -0.5 kg (range: -11.4, 18.3) at T1 and 0 kg (range: -18.6, 19.5) at T2. At T1 and T2, 2.4% and 16.1% of women respectively gained weight between 2-5kg; 0.5% and 4.7% respectively gained >5kg, while 6.1% and 24.2% of women respectively had weight loss >2kg. On univariate analysis, patients who received radiotherapy had more weight loss at T1; no significant difference in weight change was noted with other factors including socio-demographic, lifestyle and clinical factors. When comparison was made between T0 and T2, patients who did not receive radiotherapy, those who remained premenopausal at T2 and those who were underweight at T0 were significantly associated with more weight gain.

Conclusions: In this cohort study, weight gain was not common among Hong Kong breast cancer patients within the first 18 months post-diagnosis. The findings from the present study differ from those conducted in western patient population, in whom average reported weight gains ranged between 1.0 and 6.0 kg over the first year after

breast cancer diagnosis. Funding: World Cancer Research Fund International (Grant Number WCRF 2010/249 and WCRF 2014/1197).

Legal entity responsible for the study: Joint CUHK-NTEC Clinical Research Ethics Committee and the KWC Research Ethics Committee.

Funding: World Cancer Research Fund International (Grant Number WCRF 2010/249 and WCRF 2014/1197).

Disclosure: All authors have declared no conflicts of interest.

258P Incidence of clinically significant toxicities in patients with high endoxifen concentrations

S.L. Groenland[1], A.B. Sanchez-Spitman[2], D.J.A.R. Moes[2], S.L. Koolen[3], V.O. Dezentjé[4], N. van Erp[5], R.H.J. Mathijssen[6], H-J. Guchelaar[2], A.D.R. Huitema[7], N. Steeghs[8]

[1]Department of Clinical Pharmacology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [2]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Medical Oncology, Erasmus University Medical Center, Rotterdam, Netherlands, [4]Department of Medical Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [5]Department of Clinical Pharmacy, Radboud University Medical Center (LUMC), Nijmegen, Netherlands, [6]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [7]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute and MC Slotervaart, Amsterdam, Netherlands, [8]Department of Medical Oncology & Clinical Pharmacology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: Tamoxifen is essential in the treatment of estrogen receptor positive breast cancer. Concentrations of its active metabolite endoxifen > 5.97 ng/mL have been associated with a 26% lower recurrence rate in the adjuvant setting (Madlensky 2011), providing a rationale for therapeutic drug monitoring. However, the risk of high endoxifen concentrations has not been established. Therefore, we investigated whether extremely high endoxifen levels are correlated with a higher incidence of clinically significant toxicities.

Methods: Patients receiving adjuvant tamoxifen treatment (20 mg) with a steady state endoxifen level above 25 ng/mL were retrospectively identified in databases of the CYPTAM study (n = 667, NTR 1509) and of samples collected in routine care (n = 1768). The percentage of patients with clinically significant toxicities, defined as toxicities leading to either dose reduction or treatment discontinuation, was compared to the overall tamoxifen population. As historical comparison, studies described in the EBCTCG overview (2011) in which patients received adjuvant tamoxifen (20 mg) and which reported clinically significant toxicities were selected.

Results: 26 patients (1.5%) had an endoxifen level > 25 ng/mL, of which 4 patients (15%) had clinically significant toxicities, compared to 10.2% in the overall tamoxifen population (p = 0.39, weighed average of 10 clinical trials, n = 9688, Baum (2002), Margolese (2016), Chirgwin (2016), Morales (2007), Bartlett (1987), Colleoni (2006), Bonneterre (2001), Kaufmann (2005), Bramwell (2010), Tevaarwerk (2014)). Reported toxicities were mood disturbances (n = 3), hot flushes (n = 2) and musculoskeletal disorders (n = 1). Median time on treatment was 28 months in patients with high endoxifen levels, compared to 47 months reported in literature.

Conclusions: The incidence of clinically significant toxicities is relatively low and is similar in patients with extremely high endoxifen levels and the overall tamoxifen population. Therefore, dose reductions are not indicated in patients with high endoxifen concentrations without toxicity.

Clinical trial identification: CYPTAM study: NTR 1509 (release date 27 October 2008).

Legal entity responsible for the study: The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital.

Funding: Has not received any funding.

Disclosure: N. van Erp: Research funding (all to the institution): Novartis, Astellas, Janssen-Cilag, AstraZeneca, GSK, Boehringer-Ingelheim, Gilead, Roche, Pfizer, Sanofi. R.H.J. Mathijssen: Research support: Astellas, Bayer, Boehringer Ingelheim, Cristal Therapeutics, Novartis, Pamgene, Pfizer, Roche and Sanofi; Consultation fees: Novartis, Servier; Travel Support: Astellas, Pfizer. N. Steeghs: Research funding (all to the institution): AstraZeneca, Bayer, BMS, Novartis, GSK, Pfizer, Roche, Boerringer Ingelheim, Blueprint. All other authors have declared no conflicts of interest.

259P Male breast cancer: Clinical and epidemiological patterns in the United States

M.A. Gouda

Department of Clinical Oncology, Faculty of Medicine - Menoufia University, Shebin El Kom, Egypt

Background: Male breast cancer is a rare disease that have different outcomes in comparison with the same disease in female counterparts. Due to rarity of its occurrence, data available on breast cancer in male population are relatively scarce. The aim of this study was to summarize data available in the SEER (National Cancer Institute Surveillance, Epidemiology, and End Results) program's database about male breast cancer. SEER incorporates data from 18 cancer registries all over the United States. Data about clinical and epidemiological patterns as well as survival were analyzed and are subsequently presented.

Methods: Data were obtained using SEER*Stat version 8.3.5 where (SEER 18 Regs Nov 2017 Submission) database was used as the data source. Only males diagnosed between 2000-2015 with malignant breast cancer, known age, and microscopic confirmation were included. Relative survival was calculated using Ederer II method. Further data analysis was made using SPSS version 21.

Results: A total of 6790 patients were identified with a median age of 68. White race constituted the majority of cases (81.3%; n = 5519). Incidence rate was 10.2 per million (95% CI 10 – 10.5) with increasing trend over time (annual percent change = 1.9%, $p < 0.05$). The disease showed slight predilection to occur on the left side (52.3%; n = 3550). Most cases were staged as regional (n = 2974) or localized (n = 3152) at time of diagnosis. The disease was the only primary cancer in 4502 patients (66.3%) and the first of 2 or more primaries in 787 cases (11.6%). It occurred as a second or later multiple primary in remaining cases (22.1%). Median observed survival was 117.2 months with a 5-years and 10-years observed survival of 70.6% (CI: 69.1%-71.9%) and 48.8% (CI: 46.9%-50.6%) respectively. 5-years relative survival was 84% (CI: 82.3%-85.6%) while 10-years relative survival was 71.1% (CI: 68.3%-73.7%).

Conclusions: Male breast cancer is a rare tumor with an incidence rate of 10.2 per million. This tumor is more likely to occur in old age and white race and occurs more on left side. Disease occurred as a second (or later multiple) primary in 22% of cases. 5-years relative survival is 84% with a median survival of 117.2 months.

Legal entity responsible for the study: Mohamed Alaa Gouda.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

260P The aesthetic results after oncoplastic surgery in early breast cancer

A. Zikiryahodjaev[1], A. Sukhotko[2], A. Tukmakov[1]

[1]Oncology and Plastic Surgery, P.A. Herzen Moscow Oncology Research Institute, Ministry of Health of Russia, Moscow, Russian Federation, [2]Oncology and Plastic Surgery, Herzen Cancer Research Institute, Moscow, Russian Federation

Background: To create of the new concept of surgical treatment as a component of multi-therapy treatment of patients with breast cancers on postoperative quality of life (Qol). According to Clough K. B. (2010), the advantage of the oncoplastic approach is the expansion of indications for operations in achieving the best aesthetic results. "Oncoplastic surgery is the' third way ' between standard organ preservation surgery and mastectomy."

Methods: We assessed 570 women who underwent breast conserving surgery (BCS) or total mastectomy (TM) with immediate reconstruction in P.A. Gertsen Moscow Research Institute from 2013 to 2017. Of the 437 patients, 300 (66,4%) had oncoplastic breast surgery. OBS included glandular reshaping (rotation flap, round-block technique, batwing mastopexy, wise pattern-inverted T, vertical pattern). The distribution of patients according to the stage of disease was as following: stage I-II – 348 (79,6%), IIIA – 89 (22,4%). A median follow-up period was 58 months. Only 94 (21,5%) patients received adjuvant polychemotherapy, combinations adjuvant polychemotherapy and radiation therapy – 27 (6,1%) or endocrine therapy – 37(8,5%).

Results: During a median follow-up period local recurrent were detected at 5 (0,8%), distant metastasis – 15 (2,6%) patients. Overall disease-free survival in patients with BCS stage I was 96,2%, IIA– 90%, IIB – 86,7%, IIIA – 86,2% (p>0,05). Overall disease-free survival in patients with SSM stage I was 92,9%, IIA– 91,2%, IIB – 84,4%, IIIA – 91,4% (p>0,05). The postoperative cosmetic result after BCS was assessed in 79,3% patients.

Conclusions: In breast reconstructive the most effective method is using breast tissue after BCS. Oncoplastic surgery contributes is the better phychological adaptation of patients. Variety of modifications and options of reconstructive surgery causes problem of choice, which should be solved with patient taking into account the clinical data. The extent of surgical intervention does not affect the performance of the 5-year overall and recurrent survival and depends on the distribution process.

Legal entity responsible for the study: P.A. Gerzen's Cancer Research Institute – The National Medical Research Radiologic Center of the Ministry of Health of the Russian Federation.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

261P The application of indocyanine green fluorescence navigation method to a sentinel lymph node biopsy after neoadjuvant chemotherapy in node-positive breast cancer

K. Yamagami[1], H. Matsumoto[1], T. Hashimoto[2], S. Yanai[1], S. Yuen[1], Y. Yata[1], Y. Ichinose[1], T. Deai[3], M. Toi[4]

[1]Department of Breast Surgery and Oncology, Shinko Hospital, Kobe, Japan, [2]Breast Surgery, Hashimoto Clinic, Kobe, Japan, [3]Breast Surgery Deai Clinic, Kobe, Japan, [4]Department of Breast Surgery, Kyoto University, Kyoto, Japan

Background: Approximately 40% of patients with node positive in axilla (N1) will have axillary pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC). The application of sentinel lymph nodes (SNs) biopsy (SNB) following NAC for initially node-positive breast cancer is unclear because of high false-negative results in previous studies (SENTINA, ACOSOG Z1071). These trials, using blue dye (BD) and/or radioisotope (RI) agent, showed the diagnostic accuracy of SNB was closely related to the number of SNs. We presented the efficacy of indocyanine green (ICG) fluorescence navigation method for SNB in clinically node-negative (cN0) patients (ASCO2008). The fluorescent ICG method can provide higher number of SNs. Moreover, some reports showed that florescence SNs with metastases could not be identified by radioactivity. To determine the detection rate, the false-negative rate of SNs using the fluorescent ICG method after NAC for biopsy-proved N1 breast cancer retrospectively.

Methods: Of 2301 patients (January 2010 - March 2018), 135 women with N1 (fine needle aspiration or core needle biopsy proved) received NAC. Node status after NAC was evaluated by ultrasound findings: Group 1 (N1 converted ycN0, n = 105) and Group 2 (N1 remained ycN1, n = 30). All patients underwent SNB using both ICG- and BD-method and axillary lymph node dissection.

Results: The average number of SNs removed were Group 1 (ICG: 3.65, BD: 1.37), Group 2 (ICG: 2.99, BD: 0.93). Detection rate of SNs: Group 1 ICG 97.1% (95% CI 91.9-99.0, 102 of 105), BD 77.1% (95% CI 68.2-84.1, 81 of 105), Group 2 ICG 86.7% (95% CI 70.3-94.7, 26 of 30), BD 53.3% (95% CI 36.1-69.8, 16 of 30). Resulting of a false-negative rate: Group 1 ICG 7.69% (95% CI 2.65-20.3, 3 of 39), BD 35.7% (95% CI 20.7-54.2, 10 of 28), Group 2 ICG 11.5% (95% CI 4.00-29.0, 3 of 26), BD 18.8% (95% CI 6.59-43.0, 3 of 16). Axillary pCR was 46.7% (63 of 135).

Conclusions: In patients whose axillary nodal status converted from N1 to ycN0, the fluorescent ICG method with higher number detection of SNs showed a remarkable high detection rate and a low false-negative rate of SNs, compared with those of Blue dye which is one of conventional method.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

262P Use of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with cytology proven axillary node-positive breast cancer at diagnosis

H.J. Choi[1], S.M. Jung[1], J.M. Ryu[2], I. Kim[1], S.J. Nam[1], S.W. Kim[2], J. Yu[2], S.K. Lee[2], J.E. Lee[2]

[1]Breast Surgery, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Department of Surgery, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: This study aimed to evaluate the prognostic effects of sentinel lymph node biopsy (SLNB) on recurrence and survival after neoadjuvant chemotherapy (NAC) in patients with cytology-proven axillary node metastasis breast cancer.

Methods: This study is a registered medical record review based on a prospectively collected cohort. We selected 506 patients who were diagnosed with invasive breast cancer and axillary lymph nodes metastasis and treated with NAC followed by curative surgery at Samsung Medical Center between January 2007 and December 2014. We classified patients into three groups: Group A, negative SLN status and no further dissection; Group B, negative SLN status with backup axillary lymph node dissection (ALND); and Group C, no residual axillary metastasis on pathology with ALND regardless of clinical response. We analyzed and compared outcomes including prognoses and survival among all groups.

Results: The median age at the time of surgery was 44.4 years. The median follow-up time was 47.0 months (range: 3-115 months) and the median number of retrieved SLNs was 5.0. The SLN identification rate was 98.3% (234/238 patients), and the false negative rate (FNR) of SLNB after NAC was 7.5% (8/106 patients). There was no significant difference in disease-free survival (DFS, p = 0.578) or overall survival (OS, p = 0.149) among Groups A, B, and C.

Conclusions: These results suggest that SLNB can be feasible and oncologically safe after NAC for node-positive breast cancer and could help reduce arm morbidity by avoiding standard ALND in negative SLN patients.

Legal entity responsible for the study: Samsung Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

263P Omission of axillary lymph node dissection after positive sentinel lymph node: Validity and safety among early breast cancer patients treated with mastectomy

A. Matsumoto, Y. Umemoto, H. Jinno

Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

Background: ACOSOG Z0011 trial showed that axillary lymph node dissection (ALND) had no impact on recurrence and survival in patients with positive sentinel lymph node (SLN) after breast-conserving surgery. However, it is still unknown if omission of ALND can be applicable to patients treated with mastectomy. The aim of this study was to evaluate whether ALND could be safely omitted for patients with SLN–positive breast cancer after mastectomy.

Methods: From a prospective database of 296 patients with clinically node-negative breast cancer who underwent mastectomy and sentinel lymph node biopsy (SLNB) from March 2006 to December 2016, 81 patients who had positive SLNs were analyzed. Patients treated with neoadjuvant chemotherapy were excluded from the analysis. Lymphatic mapping was performed with a combined method of blue dye and radioisotope.

Results: The median age was 57.0 (range: 32-85) years and the median tumor size was 2.5 (range: 0.6-7.9) cm. Of 81 patients, 23 (28.4%) patients omitted ALND. Patients with SLNB alone were more likely to have smaller SLN involvements ($p < 0.001$): micrometastasis was identified in 13 (56.5%) patients in SLNB-alone group and 9 (15.5%) patients in ALND group. The number of positive SLN was comparable between SLNB-alone (median: 1.0, range: 1-6) and ALND groups (median: 1.0, range: 1-5) (p = 0.063). There was no significant difference in characteristics including age, tumor size and tumor subtypes between the two groups. Post-mastectomy radiotherapy was performed in 5 (21.7%) patients with SLNB alone and 16 (27.6%) patients with ALND (p = 0.588). The majority of patients with macrometastatic SLN received adjuvant chemotherapy in both groups (83.3% vs. 75.5%, p = 0.562). After a median follow-up of 54.7 months, no axillary recurrence was observed in both groups and 5-year disease-free survival was not significantly different between the two groups (75.0% vs. 88.8%, p = 0.489). Lymphedema was observed significantly more often after ALND than after SLNB (22.4% vs. 4.3%, p = 0.045).

Conclusions: These data suggested that ALND could be safely omitted in SLN-positive breast cancer patients treated with mastectomy and appropriate systemic therapy.

Legal entity responsible for the study: Akiko Matsumoto.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

264P Pathologic response as a strong predictor of survival irrespective of phenotype in early breast cancer

A. Gasol Cudos[1], S. Morales Murillo[1], J. Veas Rodriguez[2], F. Vilardell Vilellas[2], D.R. Sanchez Guzman[2], E. Iglesias Martinez[1]

[1]Breast Cancer Unit, Hospital Arnau de Vilanova, Lleida, Spain, [2]Oncology, Hospital Arnau de Vilanova, Lleida, Spain

Background: Pathologic complete response after neoadjuvant chemotherapy is considered as a surrogate of survival by most authors, although there are special phenotypes, such HER2 positive, where their potential as apredictor of survival is stronger.

Methods: Overall survival was analyzed according to pathologic response in a cohort of early breast cancer patients (all subtypes) treated with standard neoadjuvant chemotherapy. Between March 2000 to October 2016, 459 breast cancer patients were treated with neoadjuvant chemotherapy with anthracicline and taxane regimens.

Table: 264P

Phenotype	RCB type 0	RCB1 type I	RCB type II	RCB type III
Overall	Median DFS:167 HR: 1	Median DFS:156 HR: 2,6	Median DFS:130 HR: 4,5	Median DFS:85 HR: 9,6
HER 2 positive	Median DFS: 126 HR: 1	Median DFS: 90 HR: 1,6	Median DFS:100 HR: 2,5	Median DFS:96 HR: 4,4
Luminal	Median DFS: 176 HR: 1	Median DFS: 160 HR: 2,8	Median DFS:115 HR: 4,8	Median DFS: NA HR: NA
Triple negative	Median DFS:188 HR: 1	Median DFS: 141 HR: 8,8	Median DFS: 117 HR: 16,7	Median DFS:122 HR: 28.4

Results: Median age was 52 (range 28-87), 173 tumors (38%) were classifyed as HER2 positive, 148 (32%) triple negative and 138 (30%) as luminal breast cancer. Median initial size was 34 mm (10-100) and 237 patients (51%) had initial node involvement. We achieved a total of 152/459 complete pathologic response with a 43% rate in HER2 positive, 44% in triple negative and 9% in luminal breast cancer patientes. Ten years disease free survival in the whole serie was 83%, with a 72% for patients without complete pathologic response versus 90% for complete pathologic response (long rang <0,00001). A strong correlation between pathologic response and survival wass found in all subtypes (long rang p:0,033; 0,028 and 0,027 in HER2 positive, luminal and triple negative respectively). A table with survival results according the RCB response by Symmans method in the whole series and different phenotypes is attached.

Conclusions: Pathologic response is a strong predictor of overall survival in all breast cancer phenotypes althoug in the triple negative has the highest magnitude with a HR of 28,4 in patients with worse pathologic response (RCB type III). Neoadjuvant chemotherapy should be considered in the majority of patients who are candidates to chemotherapy, specially in triple negative and HER2 positive; however, in luminal phenotype a better selection for neoadyuvant chemotherapy is needed.

Legal entity responsible for the study: Hospital Universitari Arnau de Vilanova.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

265P Nomogram to predict non-sentinel lymph node status of breast cancer using total tumor load determined by one-step nucleic acid amplification (OSNA)

P. O-charoenrat, D. Sa-nguanraksa, A. Kulprom

Surgery, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Axillary dissection might be omitted in selected breast cancer patients with positive sentinel node (SLN). Total tumor load (TTL) in SLN expressed by cytokeratin 19 (CK19) mRNA, detected by automated molecular technique-one-step nucleic acid amplification (OSNA), can quantitatively determine tumor burden in SLN. This study aimed to create nomogram to predict non-sentinel lymph node (NSLN) status.

Methods: Breast cancer patients were recruited at Division of Head Neck and Breast Surgery, Department of Surgery, Siriraj Hospital, Mahidol University, Thailand from November 2015 to January 2018. The patients with invasive breast cancer T1-T3, clinically negative axillary lymph node and able to give informed consent underwent SLN biopsy assessed by OSNA. The patients with positive SLN underwent axillary lymph node dissection. Correlations between TTL, clinicopathological parameters and NSLN status were analyzed by chi-square statistic and logistic regression. Model discrimination was evaluated using receiver-operating characteristic (ROC) analysis.

Results: Total number of the patients who underwent SLN biopsy was 262. There were 85 patients with positive SLN. Mean age at diagnosis of the patients in this group was 54.52±11.66 years. NSLNs were positive in 37 patients. Larger tumor size (25.35±9.02 mm vs 37.78±16.88 mm) and presence of lymphovascular invasion (24.5% vs 67.6%) were the independent factor that predict positive NSLN. TTL expressed by CK19 mRNA copy number can discriminate NSLN status with the area under ROC curve of 0.784 (95%CI 0.683-0.885). At the cut off level at 6550 copies/μL, sensitivity, specificity, and negative predictive value were 86.49%, 57.14%, and 84.85%, respectively. Nomogram containing tumor size and SLN status can predict NSLN involvement with area under ROC curve of 0.827 (95%CI 0.737-0.918).

Conclusions: Nomogram using the results by OSNA technique can predict NSLN status and help in decision for axillary lymph node dissection.

Legal entity responsible for the study: Pornchai O-charoenrat.

Funding: Sysmex.

Disclosure: All authors have declared no conflicts of interest.

266P Detecting bone density in early breast cancer survivors: The arm-DXA method

Y. Al-Farhat

Department of Oncology, Tolna County Teaching Hospital, Szekszard, Hungary

Background: Breast cancer survivors who are on adjunct therapy with Aromatase Inhibitors (AIs) or premature menopause due to chemotherapy are known to have an increased risk of osteoporosis and bone fracture. Being at high risk for osteoporosis, these patients should be screened using with dual energy X-ray absorptiometry (DXA) to measure bone mineral density (BMD) according to national guidelines. This study screened the population of patients with early Breast cancer utilizing the Arm-DXA as a user friendly and efficient method.

Methods: All Breast cancer patients at the Tolna County Cancer Center, Szekszárd who are diagnosis of early invasive breast cancer were scanned using Arm-DXA during their regular visit to the center. Cancer patients under hormone therapy were scanned annually. Patients who have metastatic disease or known to have osteoporosis were excluded from the study. A total of 431 patients were subject of an arm-DEXA scan for BMD during the period February 2015 to September 2017.

Results: Out of the 431 patients, normal T score −1,5 detected in 223 patients (51,7%), clinically significant osteopenia (CSO) T score −1,5, −2,5 detected in 129 patients (29,9%), and osteoporosis T score < −2,5 detected in 79 patients (18,3%). For the 224 Patients who were under hormone therapy or/and chemotherapy about 29,9% (n: 67) had a CSO, and 20,5% (n:46) had osteoporosis.

Conclusions: This study highlights the fact that osteoporosis is under-detected in early breast cancer survivors who are on or after hormone and chemotherapy. About 48% of early breast cancer survivors found to have osteoporosis or clinically significant osteopenia in our study. Our BMD test results shows that half the 224 patients who were under hormone therapy need to take treatment (zoledronic -acid or denosumab) to prevent bone fracture.

Legal entity responsible for the study: Al-Farhat Yousuf.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

267P Voluntary deep inspiration breathhold (DIBH) experience in the radiotherapy for left sided breast cancer

I.V. Gueorguiev, N. Nedev, A. Avramov, A. Tonev, N. Velikova

Radiation Oncology, Acibadem City Clinic Cancer Center, Sofia, Bulgaria

Background: The adjuvant radiotherapy to the whole breast or the chest wall is an integral part of the treatment of breast cancer. This study is aimed at evaluating the potential for sparing the heart and lung using voluntary deep inspiratory breath-hold (DIBH) technique for radiotherapy of left sided breast or chest wall.

Methods: During the period 09.2016 – 09.2017, 95 patients with breast cancer had planning CT scans in the both respiratory phases, using Varian Real Time Positioning Management System® for monitoring of the respiratory chest wall excursions. Each patient had two planning CT scans: one during free breathing (FB) and another one with voluntary deep inspiration breath-hold (DIBH). The Planning Target Volume (PTV) included the whole breast/chest wall with or without the supraclavicular nodal groups (SCL). For each patient, two radiotherapy plans were prepared using the FB and the DIBH planning scans.

Results: The DIBH was very well tolerated. The mean anterior-posterior chest wall shift during FB was 3.1 mm. With the DIBH, the front chest wall position was between 10 mm and 18 mm anteriorly to its mid-FB position. In the post-lumpectomy cases the portion of the heart that received more than 50% of the prescribed dose, was decreased from 2.07% to 0% (39.7 % max dose). At the same time, relative lung volume irradiated to > 50% of the prescribed target dose was reduced from 17.63% (for FB) to 13.2% (for DIBH). In one extreme case with SCL, the volume of the heart, receiving more than 50% of the prescribed dose, was: 5.74% for FB and 0% for DIBH (36% max dose); the ipsilateral lung received: 21.2% with FB and 8% with DIBH. The median ipsilateral relative lung volume receiving >50% was higher for DIBH – 14.17% and 10.91% for FB.

Conclusions: This is the first study in Bulgaria, which demonstrates the dosimetric benefits of breathing adapted radiotherapy (BART). Our results showed that irradiated cardiac volumes can be consistently reduced for left-sided breast cancers by using DIBH.

Legal entity responsible for the study: Ivan Gueorguiev.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

268P Psychological distress and health-related quality of life in women recently diagnosed with breast cancer in the Epi-GEICAM study

N. Fernández-De-Larrea[1], B. Pérez-Gómez[2], A. Ruiz[3], A.M. Casas[4], B. Bermejo[5], J.M. Baena-Cañada[6], S. Antolin[7], P. Sánchez Rovira[8], M. Ramos Vázquez[9], J.A. Garcia-Saénz[10], A. Anton Torres[11], M. Muñoz[12], C. Jara[13], M. Gil-Gil[14], E. Adrover[15], A. Oltra[16], J. Brunet[17], S. Bezares[18], M. Martín[19], M. Pollán[20]

[1]Cancer Epidemiology Unit, Faculty of Medicine, National Center for Epidemiology, CIBERESP, University of Alcalá, Madrid, Spain, [2]Cancer Epidemiology Unit, National Center for Epidemiology, CIBERESP, Madrid, Spain, [3]Medical Oncology Unit, Instituto Valenciano de Oncología, GEICAM, Valencia, Spain, [4]Medical Oncology Unit, Hospital Virgen del Rocío, GEICAM, Sevilla, Spain, [5]Medical Oncology Unit, Hospital Clinico de Valencia, GEICAM, Valencia, Spain, [6]Medical Oncology Unit, Hospital Puerta del Mar, INiBICA, GEICAM, Cadiz, Spain, [7]Medical Oncology Unit, Complejo Hospitalario Universitario A Coruña, GEICAM, A Coruña, Spain, [8]Medical Oncology Unit, Complejo Hospitalario de Jaén, GEICAM, Jaén, Spain, [9]Medical Oncology Unit, Centro Oncológico de Galicia, GEICAM, A Coruña Spain, [10]Medical Oncology Unit, Hospital Clínico Universitario San Carlos, GEICAM, Madrid, Spain, [11]Medical Oncology Unit, Hospital Miguel Servet, GEICAM, Zaragoza, Spain, [12]Medical Oncology Unit, Translational Genomics and Targeted Therapeutics, Hospital Clinic I Provincial, Institut d'Investigacions Biomèdiques Pi i Sunyer-IDIBAPS, GEICAM, Barcelona, Spain, [13]Medical Oncology, Hospital Universitario Fundación Alcorcón, Universidad Rey Juan Carlos, GEICAM, Madrid, Spain, [14]Medical Oncology, Institut Catalá d'Oncologia Hospital Duran i Reynals, GEICAM, Barcelona, Spain, [15]Medical Oncology Unit, Complejo Hospitalario Universitario de Albacete, GEICAM, Alicante, Spain, [16]Medical Oncology Unit, Hospital Virgen de los Lirios, GEICAM, Alicante, Spain, [17]Medical Oncology, Josep Trueta University Hospital, Catalan Institute of Oncology, GEICAM, Girona, Spain, [18]Scientific Department, GEICAM, Madrid, Spain, [19]Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain, [20]Cancer Epidemiology Unit, National Center for Epidemiology, CIBERESP, GEICAM, Madrid, Spain

Background: Breast cancer (BC) diagnosis may have a high emotional impact in patients. Health-related quality of life (HRQL) can be impaired by the psychological impact of the diagnosis, by choices having to be made about treatment and by treatments themselves.

Methods: Cross-sectional analysis of HRQL in BC women from the Epi-GEICAM case-control study carried out in 23 Spanish hospitals. Women fulfilled a questionnaire about sociodemographic and lifestyle factors, HRQL (SF-36), mental health (GHQ-28) and social support (Duke-UNC). Spanish population norm-based scores were calculated for the SF-36 scales. Physical (PSS) and mental (MSS) summary scores $\geq$5 points under the norm were considered suboptimal. Psychological distress (PD) was defined as GHQ-28 >5. Factors associated with PD and suboptimal PSS were identified by multivariable mixed logistic regression models.

Results: Among 1017 cases, 896 had complete SF-36 and GHQ-28. Median time since diagnosis was 77 days, 82% had been operated on, and 41% were on radiation/chemotherapy. Prevalence of PD was 54.4% (95% CI: 51.1-57.6). PD increased with TNM stage (p = 0.03). Other factors associated with PD were chemotherapy (OR = 1.7; 95% CI: 1.2-2.6), low social support (OR = 2.0; 95%CI: 1.2-3.5) and low education (OR = 2.1; 95% CI: 1.2-3.8). SF-36 scores are described in the table. Factors related to suboptimal PSS were surgery (OR = 3.2, 95% CI: 2.0-5.1), low education (OR = 1.9, 95% CI: 1.1-3.6) and number of comorbidities (OR = 1.3, 95% CI: 1.0-1.5). No differences in PD or PSS were observed according to BC subtype.

Conclusions: PD is very frequent during the initial stages of BC diagnosis and treatment. Advanced disease stage, lack of social support and low education are strong determinants of PD. The highest impact in HRQL was observed in the role-physical domain. PD and low PSS are interrelated and both are more frequent in patients with low education.

Table: 268P

	Mean*	95% CI	
Physical function	41.2	40.3	42.1
Role physical	36.8	36.0	37.5
Bodily pain	45.0	44.4	45.7
General health	46.9	46.2	47.5
Vitality	46.8	46.1	47.5
Social function	41.3	40.4	42.1
Role emotional	44.6	43.8	45.5
Mental health	46.7	46.1	47.4

*<50: under the norm

Legal entity responsible for the study: GEICAM Spanish Breast Cancer Group.

Funding: GEICAM Spanish Breast Cancer Group.

Disclosure: All authors have declared no conflicts of interest.

232TiP A multicentre, international neoadjuvant, double-blind, randomized phase III trial comparing fulvestrant to a combination of fulvestrant and palbociclib (CDK 4/6 inhibitor) in patients with operable luminal breast cancer responding to fulvestrant (SAFIA study)

J-M. Nabholtz[1], K. Al Saleh[1], A. Bounedjar[2], H. Abdel-Razeq[3], H. Errihani[4], A. Saadeddin[5], M. Al Foheidi[6], M. Ghosn[7], H. El Zawahry[8], A. Kandil[9], N. Abdel-Aziz[1], F. Dabouz[10], S. Kullab[1]

[1]Oncology Center, Medical Oncology, King Saud University Medical City (KSUMC), Riyadh, Saudi Arabia, [2]Oncologie Médicale, Centre Hospitalo Universitaire de Blida, Blida, Algeria, [3]Hematology and Medical Oncology, King Hussein Cancer Center, Amman, Jordan, [4]Oncologie Médicale, Institut National d'Oncologie Université Mohammed V, Rabat, Morocco, [5]Medical Oncology, National Guard Health Affairs (NGHA) - King AbdulAziz Medical City, Riyadh, Saudi Arabia, [6]Medical Oncology, National Guard Health Affairs (NGHA) - King AbdulAziz Medical City, Jeddah, Saudi Arabia, [7]Hematology - Oncology Department, Hôtel-Dieu de France, Université Saint-Joseph, Beirut, Lebanon, [8]Medical Oncology, National Cancer Institute (NCI)/ Cairo, Cairo, Egypt, [9]Department of Clinical Oncology and Nuclear Medicine, Clinical Research Center, Faculty of Medicine, Alexandria University, Alexandria, Egypt, [10]Clinical Research/ Data Management, International Cancer Research Group (ICRG), Sharjah, United Arab Emirates

Background: Neo-adjuvant (NA) chemotherapy (CT) +/- anti-Her2 treatment of operable breast cancer (BC) is considered a standard option in the management of BC. However, pathologic complete response (pCR) rates with CT in hormonal receptor+/Her2 negative BC are usually low: 7% (Luminal A) to 16% (Luminal B). Alternatively, NA endocrine therapy (ET) has not been established as a standard treatment because of low pCRs (i.e. 5% using 8 months of ET).

Trial design: This is a multicenter phase III, 3rd generation neo-adjuvant trial performed in 34 centers and 8 countries of Middle-East and Maghreb with the objective to investigate the potential role of the addition of a CDK 4/6 inhibitor (Palbociclib) to ET (Fulvestrant+/- Goseriline) compared to ET alone as neo-adjuvant therapy of HR+/Her2- operable BC sensitive to ET. The question Is whether or not ET plus CDK 4/6 inhibitor would yield high enough pCR rates to establish this strategy as a reasonable therapeutic option in this group of patients (pts) with luminal HER2- BC. A total of 400 pts with stage II and IIIA are planned to be recruited in this trial. Oncotype DX will be performed upfront in order to eliminate CT candidates. All pre/peri and post-menopausal pts with a recurrence score < 31 will be treated with 4 months of Fulvestrant (500 mg Day (d.) 1, 14, 28 then q. 28 d. (+/- Goseriline 3.6 mg q.28 d.). Patients with responding/stable disease will then be randomized in double blind fashion to Fulvestrant (+/- Goseriline) either with Palbociclib 125mg po daily 3 weeks/4 or placebo. Four additional cycles will be delivered before surgery. The study primary endpoint is pCR while clinical/radiological response, rate of conservative surgery, safety, disease-free and overall survival are secondary endpoints. Exploratory endpoints encompass biomarker serial analysis of liquid biopsies with Quantum Optic and DNA methylation technologies. The SAFIA trial aims to identify a new neo-adjuvant standard with ET plus CDK 4/6 inhibitor in luminal - Her2 negative operable BC.

Clinical trial identification: SAFIA Study (ICRG 1201); NCT03447132.

Legal entity responsible for the study: International Cancer Research Group (ICRG).

Funding: AstraZeneca, Pfizer and Genomic Health.

Disclosure: J-M. Nabholtz, F. Dabouz, S. Kullab: Research grants: AstraZeneca, Pfizer, Genomic Health. All other authors have declared no conflicts of interest.

269TiP Multicenter study to evaluate the efficacy and standardize radiofrequency ablation therapy for early breast cancer (RAFAELO study)

T. Kinoshita[1], S. Ohtani[2], H. Doihara[3], M. Takahashi[4], T. Fujisawa[5], N. Yamamoto[6], K. Aogi[7], T. Hojo[8]

[1]Division of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Breast Surgery, Hiroshima City Hospital, Hiroshima, Japan, [3]Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan, [4]Department of Breast Surgery, Hokkaido Cancer Center, Sapporo, Japan, [5]Breast Oncology, Gunma Prefectural Cancer Center, Gunma, Japan, [6]Division of Breast Surgery, Chiba Cancer Center, Chiba, Japan, [7]Department of Breast Oncology, Shikoku Cancer Center, Matsuyama, Japan, [8]Department of Breast Surgery, National Cancer Center Hospital East, Chiba, Japan

Background: Given the increasing number of early-stage breast cancers detected by screening mammography, we aim to establish RFA as a minimally invasive, cost-efficient, and cosmetically acceptable local treatment. In our Phase I study, localized tumors with a maximum diameter of 2 cm, preoperatively diagnosed by imaging and histopathology, were treated with RFA. A 90% complete ablation rate was confirmed histopathologically.

Trial design: The objective of our study is to demonstrate the non-inferiority of RFA compared with standard treatment in terms of local recurrence-free survival, which is the best index of local control. The inclusion criteria are untreated pts with histologically confirmed ductal carcinoma with a single localized tumor of 1.5 cm or less in the greatest dimension on preoperative imaging, no prior treatment for breast cancer.

RFA is defined as a procedure in which a radiofrequency electrode needle is inserted into the breast lesion from the surface of the body under imaging guidance and thermal

ablation with radiofrequency waves is performed. The Cool-tip™ RF Ablation Single Electrode Kit (Medtronic, Boulder, CO, USA) is recommended to standardize the evaluation of the effect of ablation. All pts receive RT and systemic therapy according to the ER, HER2, tumor grade and lymph node status of the primary breast cancer after RFA. Residual lesions after RFA will be assessed in all patients approximately 3 months after RT using imaging studies and pathological examination. VAB will be performed in all patients regardless of imaging results. If biopsy specimens reveals suspicious of viable tumor, additional excision will be performed. Follow-up evaluation for residual tumor every 12 months after RFA included clinical breast examination, diagnostic imagings (ultrasound, magnetic resonance, and mammography). The primary endpoint is 5-year local recurrence-free survival, and the secondary endpoints are residual lesion rate after treatment, overall survival, distant recurrence-free survival and adverse events of RFA. The pts accrual was started in August 2013. From 9 participating institutions, enrollment of 372 pts is planned over a 5-year accrual period.

Clinical trial identification: UMIN-CTR: UMIN000005586.

Legal entity responsible for the study: Takayuki Kinoshita.

Funding: The Japan Agency for Medical Research and Development.

Disclosure: All authors have declared no conflicts of interest.

270TiP Mutanome engineered RNA immuno-therapy (MERIT) for patients with triple negative breast cancer (TNBC)

L. Heesen[1], K. Frenzel[1], S. Bolte[2], V. Bukur[3], M. Diken[4], E. Derhovanessian[5], S. Kreiter[4], A. Kuhn[6], K. Kühlcke[7], M. Löwer[8], H. Lindman[9], S. Pascolo[10], M. Schmidt[11], A. Schneeweiss[12], T. Sjöblom[13], K. Thielemans[14], L. Zitvogel[15], Ö. Türeci[16], U. Sahin[17]

[1]Project Management, BioNTech AG, Mainz, Germany, [2]Clinical Research, BioNTech AG, Mainz, Germany, [3]Genomics, BioNTech AG, Mainz, Germany, [4]Immunotherapies & Preclinical Research, BioNTech AG, Mainz, Germany, [5]GxP Analytics, BioNTech AG, Mainz, Germany, [6]RNA Biochemistry & Manufacturing, BioNTech AG, Mainz, Germany, [7]Management, BioNTech IMFS, Idar-Oberstein, Germany, [8]Biomarker Development, TRON gGmbH, Mainz, Germany, [9]Department of Oncology, University Hospital Uppsala Akademiska Sjukhuset, Uppsala, Sweden, [10]URPP Translational Cancer Research, University of Zurich, Zurich, Switzerland, [11]Klinik und Poliklinik für Geburtshilfe und Frauengesundheit, Johannes Gutenberg-Universität Mainz, Mainz, Germany, [12]Division Gynecologic Oncology/National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany, [13]Department of Immunology, Uppsala University, Uppsala, Sweden, [14]Department of Immunology-Physiology, University Hospital Brussels, Brussels, Belgium, [15]Gustave Roussy Institut de Cancérologie, Villejuif, France, [16]Management, Cluster for Individualized Immune Intervention, Mainz, Germany, [17]Management, BioNTech AG, Mainz, Germany

Background: Treatment of triple negative breast cancer (TNBC) is hampered by lack of established therapeutic targets like hormone receptors or HER-2. Surgery, chemotherapy and radiotherapy are the standard of care yet cure rates in patients with TNBC remain inferior compared to other BC subtypes. Approaches tailored to the patient's individual tumor signature may lead to improvement. The "Mutanome Engineered RNA Immuno-Therapy (MERIT)" consortium is validating an innovative individualized mRNA-based vaccine for TNBC treatment. MERIT is a collaboration of 5 European partners (academia and industry) dedicated to realize a personalized approach for TNBC treatment. The consortium set up a clinical workflow covering drug development from target discovery and validation to GMP manufacturing and drug release for each individual patient (MUTANOME). Moreover, the consortium established a pre-synthesized mRNA vaccine warehouse containing the most frequently shared tumor-associated antigens (TAA) in TNBC for drug supply (WAREHOUSE).

Trial design: A phase I trial in 2 European countries assesses the feasibility, safety and biological efficacy of this personalized immunotherapy. TNBC patients (pT1cN0M0 – T_xN_xM0) after surgery and (neo-)adjuvant chemotherapy will be allocated to one of two study arms. Patients in ARM1 receive 8 WAREHOUSE vaccinations with personalized TAA combinations corresponding to the patient tumor's antigen-expression profile. Patients in ARM2 are first treated with the WAREHOUSE approach followed by 8 vaccination cycles of an on-demand manufactured MUTANOME vaccine encoding the unique mutation signature of the individual patient identified by NGS. The mRNAs are administered intravenously as a RNA-lipoplex formulation which protects RNA from degradation, activates innate immunity, transfects APCs and consequently induces highly potent antigen-specific T-cell responses. Three clinical sites are open for recruitment; >12 patients were screened and vaccinations with WAREHOUSE or MUTANOME RNAs have started. We give insights into features of the established process and present first stratification data. MERIT was funded by the EU Commission's FP7 and is led by BioNTech AG.

Clinical trial identification: EudraCT: 2014-002274-37.

Legal entity responsible for the study: BioNTech AG.

Funding: European Commission's FP7; BioNTech AG.

Disclosure: L. Heesen, K. Frenzel, S. Bolte, V. Bukur, E. Derhovanessian, S. Kreiter, A. Kuhn: Employment: BioNTech. M. Diken: Patent ownership, patent applications, employment: BioNTech AG. K. Kühlcke: Employment: BioNTech IMFS. T. Sjöblom: Founder, board member, shareholder: ExScale Biopecimen Solutions. A. Ö. Türeci: Co-founder: Ganymed Pharmaceuticals GmbH. U. Sahin: Patent ownership, patent applications, stock owner, management board member, co-founder: BioNTech AG; Co-founder, chair: TRON gGmbH; Membership on advisory board, co-founder: Ganymed Pharmaceuticals GmbH. All other authors have declared no conflicts of interest.

271TiP Preoperative pembrolizumab (Pembro) with radiation therapy (RT) in patients with operable triple-negative breast cancer (TNBC)

H.L. McArthur[1], R. Basho[1], S. Shiao[1], D. Park[1], C. Dang[1], S. Karlan[1], S. Knott[1], M. Mita[1], C. Dilauro Abaya[1], A.E. Giuliano[1], F. Dadmanesh[1], A. Ho[2]

[1]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [2]Harvard University, Massachusetts General Hospital, Boston, MA, USA

Background: Radiation therapy (RT) induces immune-mediated cell death. If administered pre-operatively, RT could also generate a rich supply of tumor antigens. The addition of PD-1 mediated checkpoint blockade to pre-operative RT could thus, generate robust anti-tumor immune responses, induce long-term tumor-specific memory, and ultimately, improve cure rates. This study aims to establish the safety of pre-operative pembrolizumab (pembro)-mediated immune modulation with a RT "boost" equivalent in patients with operable triple negative breast cancer (TNBC) for whom lumpectomy and adjuvant RT are planned (NCT03366844). Serial research biopsies will permit interrogation of conventional biomarkers including tumor infiltrating lymphocytes (TILs) and novel immune correlates as potential predictors of response to pembro alone versus pembro with RT.

Trial design: Women with operable, primary TNBC >2cm for whom breast-conserving therapy is planned are enrolled in this single-institution pilot study. Study treatment consists of 1 cycle of pre-operative pembro (200 mg IV) alone, followed 3 weeks later by a RT boost (24 Gy/3 fractions) to the primary breast tumor concurrently with pembro (+/- 5 days). Curative-intent, standard-of-care, neoadjuvant chemotherapy or breast-conserving surgery is then undertaken within 8 weeks of study enrollment (i.e. within 5 weeks of pembro #2). Adjuvant RT is administered per standard-of-care after surgery, but without a boost dose. Research blood and fresh tumor biopsies are obtained at baseline and after cycles 1 and 2 of pembro. Correlative analysis will include single-cell RNA sequencing of the tumor immune infiltrate and multispectral immunohistochemistry. Co-primary endpoints are: 1) safety/tolerability, as defined by the number of patients who do not necessitate a delay in standard-of-care chemotherapy or surgery and 2) change in TIL score. Secondary endpoints include safety/toxicity up to 19 weeks after study enrollment and disease-free survival.

Legal entity responsible for the study: Heather McArthur.

Funding: Has not received any funding.

Disclosure: H.L. McArthur: Advisory boards: Amgen, Celgene, Immunomedics, Merck, OBI Pharma, Pfizer, Puma, Spectrum Pharmaceuticals, Syndax Pharmaceuticals, Roche, Peregrine, Calithera, Eli Lilly, TapImmune; Research support: Bristol-Myers Squibb, Eli Lilly, MedImmune, LLC/AstraZeneca, Merck. All other authors have declared no conflicts of interest.

272TiP Development of mPRO Mamma mobile application and its impact on the quality of life and health resource usage in patients with early stage and locally advanced breast cancer receiving chemotherapy

T. Gortnar[1], C. Grasic Kuhar[2], E. Drmota[1], T. Kovač[3], M. Kukar[3]

[1]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, [2]Department of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia, [3]Faculty of Computer and Information Science, University of Ljubljana, Ljubljana, Slovenia

Background: Many possible adverse effects, from mild to life threatening, accompany the systemic treatment of cancer patients. Recognition and appropriate action is essential for optimal quality of life of patients. Consequently, patient-reported outcomes have become essential in clinical oncology. The purpose of this study is to involve the patients in ongoing monitoring, recording, and resolution of adverse effects resulting from chemotherapy via a self-developed smartphone application. We aim to assess the effect of this mobile application on improving symptom management and optimising health care usage, thus positively affecting the quality of life of our patients.

Trial design: We plan to develop a mobile application mPRO Mamma, which includes: symptom reporting module, useful measures and tips for managing adverse events based on intensity of symptoms, cancer-specific educational materials and an option to share collected data with the oncologist. Between December 2017 and June 2018, we plan to enrol 90 patients with early-stage or locally advanced breast cancer who own an Android-based smartphone and are proficient in using mobile applications in the open trial prior to them starting chemotherapy. Pending completion of mPRO Mamma mobile app development, half of the patients will be assigned to the control group. Upon the release of mPRO Mamma, the other half of the patients will be assigned to the experimental group and given access to the app. The primary objective is to determine the effect of using mPRO Mamma on the quality of life, measured by self-report using EORTC QLQ - BR23 and EORTC QLQ-C30 (version 3.0). Assessment will be performed before the first cycle, after 1 week, at the end of the first cycle, and at the end of chemotherapy. The quality of life index scores in each group will be compared to baseline scores. The secondary objectives are to assess the usage of health resources and to build a database of incidences of adverse events related to chemotherapy for breast cancer.

Clinical trial identification: EudraCT: 2018-001869-16.

Legal entity responsible for the study: Institute of Oncology Ljubljana, Slovenia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii87–viii89, 2018
doi:10.1093/annonc/mdy271

BREAST CANCER, LOCALLY ADVANCED

274P CD8+, CD4+ and FOXP3+ cell profiles and their change after neoadjuvant chemotherapy in patients with triple negative breast cancer

N.O. Verovkina[1], S. Lyalkin[1], L.A. Syvak[2], A. Askolskyi[2], N. Majdanevych[2],

[1]Research Department, Chemotherapy of Solid Tumors, National Cancer Institute of the MPH Ukraine, Kiev, Ukraine, [2]Chemotherapy of Solid Tumors, National Cancer Institute, Kiev, Ukraine

Background: Neoadjuvant therapy for breast cancer has been increasingly used in recent years as first-line treatments for breast cancer. A high lymphocytic infiltration is known to correlate with response to neoadjuvant chemotherapy and prognosis, however little attention has been paid to changes in CD8+, CD4+, FOXP3+ immune call profiles during perioperative chemotherapy.

Methods: Treatment results of 43 patients with TNBC stages IIB-IIIB homogeneously treated with neoadjuvant chemotherapy were analyzed. We studied the baseline and post-treatment FOXP3+, CD4+, CD8+ tumor-infiltrating immune cells by immunohistochemistry. Therapeutic pathomorphism was evaluated in terms of the residual tumor burden identification (RCB) (using Miller-Payne classification). Variables distribution was scored using ANOVA test. Survival probabilities were estimated by the Kaplan-Meir method. Hazard ratios and their 95% confidence interval were calculated with the Cox proportional hazards model.

Results: Pathological complete response (pCR) to neoadjuvant chemotherapy was identified in 12% of patients. In group without pCR high baseline levels of the stromal CD4+ cells were identified in 39,4% of patients, peritumoral CD4+ cells – in 44,7%; high levels of stromal CD8+ cells were identified in 28% and peritumoral CD8+ – in 52% of patients; and high levels of FOXP3+ were identified 47,3% of patients. The levels of CD8+ and FOP3+ cells decreased during treatment in 13% of patients. The levels of peritumoral CD4+ cells deceased during treatment in 34, % of patient, whereas levels of stromal CD4+ increased during treatment in 10,6% of patients. We found that in the population with residual disease after neoadjuvant chemotherapy the high baseline levels of peritumoral CD4+ immune cells were strongly associated with adverse outcome (HR 3,33, CI 1,29 – 8,58; p = 0,013).

Conclusions: The high baseline levels of peritumoral CD4+ lymphocytes in triple negative breast cancer tumor failing to achieve pCR were associated with adverse outcome. Further studies are required for identifying patients who are likely to benefit from immunotherapeutic adjuvants to conventional treatment approaches.

Legal entity responsible for the study: National Cancer Institute, Ukraine, Kiev.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

275P Multiplex immunoassays analysis of plasma biomarker levels and response to neoadjuvant chemotherapy for locally advanced breast cancer

J.H. Cho[1], K. Park[2], E. Lee[2], Y. Kim[1], S. Park[1], S.E. Yoon[1], K.K. Lee[1], J.Y. Hur[1], S.K. Lee[3], J.E. Lee[3], S.W. Kim[3], S.J. Nam[3], J. Yu[3], J-Y. Kim[1], H.H. Jung[4], Y.H. Park[1]

[1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Samsung Genome Institute, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [3]Division of Breast Surgery, Department of Surgery, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [4]Biomedical Research Institute, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: Neoadjuvant chemotherapy (NAC) has become as the preferred initial therapy for locally advanced breast cancer (LABC) patients. A pathologic complete response (pCR) following NAC correlates strongly with both prolonged disease-free survival and overall survival especially for patients with HER2+ or triple negative breast cancer (TNBC). A lot of modalities and molecular markers for assessing chemotherapy response have been evaluated; however, they have demonstrated only limited predictive value.

Methods: Plasma samples have been collected from 167 patients diagnosed with LABC and received NAC from month, year to month, year prospectively. Samples were collected three times from each patient, prior to NAC (pre-treatment), prior to second cycle of NAC (on-treatment), and after breast surgery (post-treatment). Samples were assayed by multiplex immunoassays for 45 biomarkers. Plasma biomarker levels using Cytokine/Chemokine/Growth Factor 45-Plex Human ProcartaPlex™ Panel were compared with pathologic treatment responses. pCR was defined as the absence of residual tumor both in breast and axillary lymph nodes. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2014-11-015-017).

Results: A median age at diagnosis of the 167 patients was 42 (range, 23-68 years). Most of the patients were treated with anthracycline and taxane-based regimen including adriamycin with cyclophosphamide plus docetaxel (AC-T), or AC-T plus trastuzumab. The patients were divided into the following four groups: HR+/HER2- (n = 46, 28%), HR+/HER2 + (n = 26, 16%), HR-/HER2 + (n = 32, 19%), and TNBC (n = 63, 38%). Thirty four patients (20%) achieving a pCR were compared with 133 patients (80%) demonstrating no pCR. Several groups of biomarker expression, BDNF, bNGF, HGF, IFN-gamma, IL-18, IP-10, MCP-1, RANTES, and SCF, were significantly different among pre-treatment, on-treatment and post-treatment. Multivariate analysis on pCR showed that analysis using the multiplex panel has predictive power.

Conclusions: Plasma biomarkers including immune-cytokine may have a role to predict treatment response in the neoadjuvant setting.

Legal entity responsible for the study: Samsung Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

276P Prognostic role of changes in neutrophil-to-lymphocyte ratio, tumor-infiltrating lymphocyte with programmed death ligand-1 in triple-negative breast cancer

E.K. Joung[1], J.E. Lee[2]

[1]Medical Oncology, Incheon St. Mary's Hospital, The Catholic University of Korea, Incheon, Republic of Korea, [2]Medical Oncology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea

Background: Neutrophil-to-lymphocyte ratio (NLR), tumor-infiltrating lymphocyte (TIL) and programmed death-ligand 1 (PD-L1) expression is known to be associated with immunogenicity and prognosis of breast cancer. We analyzed baseline NLR and its clinical association in triple-negative breast cancer (TNBC). The changes of NLR, TIL and PD-L1 during neoadjuvant chemotherapy (NAC) and their association to recurrence was analyzed.

Methods: Between Jan 2008 to Dec 2015, 358 TNBC patients were analyzed. NLR was based on initial complete blood count (CBC). Fifty paired NLR (initial diagnosis, after completion of NAC) and 34 paired tissues (initial diagnosis, surgical specimen) were collected. The changes of TIL, CD4, CD8, forkhead box P3 (FOXP3) and PD-L1 expression were assessed with immunohistochemical stain. The relationship of prior markers and tumor recurrence was analyzed.

Results: Low NLR (NLR$\leq$3.16) was associated to superior survival [overall survival; 41.83 vs. 36.5 months, P = 0.002; disease-free survival (DFS) 37.85 vs. 32.14 months, P = 0.032]. After NAC, patients with radical NLR changes (NLR change $<$ -30% or $>$ 100%) showed inferior DFS (38.37 vs. 22.37 months, P = 0.015). Same or increased TIL after NAC showed trends for superior DFS (80.0 vs. 46.0 months, P = 0.366). Positive PD-L1 ($\geq$1%) in tumor cells at baseline was associated to superior DFS (97.45 vs. 33.02 months, P = 0.031), and positive tumor PD-L1 at post-NAC tissues showed trends for superior DFS (86.43 vs. 38.76 months, P = 0.056).

Conclusions: In TNBC patients, low NLR might be associated with superior survival. Modest changes of NLR or increased TIL after NAC may reflect good prognosis. Positive tumor PD-L1 was associated with superior DFS in our study.

Legal entity responsible for the study: Seoul St. Mary's Hospital, Incheon St. Mary's Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

277P Expression of Sp17 and its association with clinicopathological parameters of breast cancer

Y-T. Zhou

Breast Department, West China Hospital, Sichuan University, Chengdu, China

Background: Sperm protein 17 (Sp17) was found to be only expressed in breast cancer and not the normal breast tissue. Although Sp17 antibody can effectively inhibit the growth of human cancer cells, suggesting a potential therapeutic target, the role of Sp17 in tumor remains unclear. Hence, we examined the expression status of Sp17 in breast cancer and analyzed the correlation between Sp17 expression and clinicopathological parameters of breast cancer. We then proceeded to assess whether the expression of Sp17 has any effect on patient prognosis.

Methods: Quantitative real-time PCR and immunohistochemistry were conducted to test expression rate of Sp17 mRNA and protein in breast cancer samples, respectively.

Clinicopathological parameters of each patient were collected by reviewing medical records. Reliable follow-up information was obtained via phone call. Kaplan–Meier regression was conducted for survival analysis. Univariate and multivariate analyses were used to identify the variables associated with Sp17 expression.

Results: We studied 100 primary breast cancer and 20 normal breast specimens. Sp17 was expressed in 27% of breast cancer samples. The difference between expression and non-expression of Sp17 was statistically significant in disease-free survival and overall survival. Lymph node metastasis and molecular subtyping were independent factors associated with Sp17 expression.

Conclusions: Our findings suggest a role for Sp17 in tumor metastasis and aggressiveness. Whether Sp17 can be used as a prognostic marker for breast cancer will require a study of a larger sample size.

Legal entity responsible for the study: The Ethics Committee of the Sichuan University.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

278P Intratumoral heterogeneity on dedicated breast positron emission tomography before chemotherapy predicts the outcome of neoadjuvant chemotherapy in breast cancer

N. Masumoto[1], T. Kadoya[2], E. Suzuki[2], S. Sueoka[2], N. Goda[2], S. Sasada[3], A. Emi[2], R. Haruta[2], T. Kataoka[2], M. Okada[1]

[1]Surgical Oncology, Hiroshima University, Hiroshima, Japan, [2]Breast Surgery, Hiroshima University Hospital, Hiroshima, Japan, [3]Surgical Oncology Hiroshima University, Hiroshima, Japan

Background: Dedicated breast positron emission tomography (DbPET) can detect intratumoral heterogeneity using ^{18}F-fluorodeoxyglucose (FDG). We have proved that intratumoral heterogeneous distribution of FDG on DbPET was significantly related with high nuclear grade and high Ki-67 proliferation index (Breast Cancer Res Treat 2018; 171:315–23). We aimed to evaluate whether intratumoral heterogeneous distribution of FDG on DbPET can predict the effects of neoadjuvant chemotherapy (NAC) on breast cancer.

Methods: We evaluated 58 consecutive patients with breast cancer who underwent DbPET before NAC concurrently between August 2016 and March 2018. The relationships between the pathological response for NAC and the maximum standard uptake values (SUVmax) of DbPET, including estrogen receptor (ER) and human epidermal growth factor receptor type-2 (HER2) statuses, and the intratumoral heterogeneous distribution of FDG on DbPET, were evaluated.

Results: Breast cancer with intratumoral heterogeneous distribution of FDG on DbPET showed a tendency to be related with pathological complete response (pCR) (Table). The SUVmax of DbPET showed an increasing tendency with intratumoral heterogeneous distribution. ER positive-breast cancer with intratumoral heterogeneous distribution showed a tendency to be related with pCR.

Table: 278P Relation between biological factors and pathological response

	pCR	Non-pCR	p
Grade			0.17
1–2	3	10	
3	20	25	
Ki-67			0.35
< 20%	1	4	
≥ 20%	22	31	
ER		0.07	
positive	15	24	
negative	8	11	
HER2		0.06	
positive	13	11	
negative	10	24	
DbPET, intratumoral distribution		0.23	
Heterogeneity	19	24	
Homogeneity	4	11	

Conclusions: The SUVmax of DbPET associates with intratumoral heterogeneous distribution. In addition, intratumoral heterogeneity on DbPET provides predictive value for achieving pCR on ER positive-breast cancer and might inform therapeutic decisions.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

279P Results from NRG oncology/NSABP protocol DMP-1: Physician counseling

C. Holmberg[1], H. Bandos[2], W. McCaskill-Stevens[3], D.L. Wickerham[4], T. Battaglia[5], T.B. Bevers[6], A. Fagerlin[7]

[1]Social Medicine and Epidemiology, Institute of Social Medicine and Epidemiology, Medical School Brandenburg Theodor Fontane Brandenburg/Havel, Berlin, Germany, [2]Biostatistics, NRG Oncology, Pittsburgh, PA, USA, [3]Cancer Prevention, National Cancer Institute Div. Cancer Treatment, Rockville, MD, USA, [4]Oncology, NRG Oncology/NSABP, The Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA, [5]Medicine, Women's Health Unit, Section of General Internal Medicine, Boston, MA, USA, [6]Clinical Cancer Prevention, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA, [7]Population Health, University of Utah School of Medicine/VA Salt Lake City, University of Michigan, Ann Arbor Center for Clinical Management, Salt Lake City, UT, USA

Background: Although selective estrogen receptor modulators (SERMs) reduce the risk of developing breast cancer (BC) in women at increased risk of the disease, there are also risks to consider. Guidelines suggest that such women should be counseled on risk-reducing options including SERMs. However, overall uptake is low. Previous results of DMP-1 showed that the health care provider's (HCP) recommendation plays an important role in a woman's decision to use a SERM. In this secondary analysis we aimed to better understand the counseling process of HCPs in the clinical care setting.

Methods: Women (N = 1,023) and their HCP discussed SERM use for BC risk reduction and were asked about the counseling, including risks and benefits presented and whether the HCP recommended SERM use. HCPs were also asked to report on the reasons for their recommendation and if the patient was likely to take a SERM or not. We describe the counseling and evaluate the agreement between the HCPs' and women's responses.

Results: HCPs reported on 1,022 counseling sessions. Benefits of SERMs in BC risk reduction were discussed in 96% of consultations; the risk of thromboembolism, endometrial cancer, and menopausal symptoms was discussed in > 86%; the risk of cataracts and decrease in libido in < 58%. Five HCPs reported no SERM discussion and were excluded. 66% of HCPs based their recommendation of SERM use on the Gail model risk score. Data for 895 participants were available to evaluate agreement. There was a modest agreement between the women's and the HCPs' statements on SERM recommendation (kappa=0.50), with fair agreement on the strength of the recommendation (weighted kappa=0.22) and substantial agreement between a woman's decision and the HCP's assumption of what his/her patient would do (kappa=0.65).

Conclusions: Most severe medical risks associated with SERM use were discussed during the counseling. The fairly low percentage of discussions about potential sexual consequences was comparable to that of other studies. Overall, there was fair to moderate agreement between HCPs and women's perceptions of the counseling. Of note, HCPs had a good sense of what treatment the counseled women would choose. Support: U10CA180868, -180822; UG1-CA189867.

Clinical trial identification: NRG Oncology/NSABP DMP-1; NCT01399359; Opened to accrual: 8-1-11.

Legal entity responsible for the study: NRG Oncology.

Funding: NRG Oncology via NIH Grants: U10CA180868, -180822; UG1-CA189867.

Disclosure: All authors have declared no conflicts of interest.

280P Neoadjuvant eribulin plus carboplatin vs. paclitaxel plus carboplatin in patients with triple-negative breast cancer (TNBC)

L. Gigolaeva[1], P. Krivorotko[1], S. Khadzhimatova[1], E. Zhiltsova[1], S. Yerechshenko[1], M. Nikitina[1], V. Ni[1], A. Emelyanov[1], E.N. Imyanitov[2], A.P. Sokolenko[2], T. Tabagua[1]

[1]Breast Tumors Department, Petrov's National Medical Research Center for Oncology, St. Petersburg, Russian Federation, [2]Department of Tumor Growth Biology, Petrov's National Medical Research Center for Oncology, St. Petersburg, Russian Federation

Background: Eribulin is a novel microtubule poison, which has certain advantages as compared to taxanes in some laboratory experiments and shows clinical efficacy in breast cancer patients after failure of taxane and anthracycline treatment. Promising activity of neoadjuvant eribulin plus carboplatin combination was shown in previous TNBC studies [Kaklamani et al. Breast Cancer Res Treat, 2015]. This investigation aimed to directly compare the efficacy of neoadjuvant eribulin/carboplatin vs. paclitaxel/carboplatin doublets in TNBC patients.

Methods: 61 TNBC patients (median age 45, range 31-76) were randomized to receive carboplatin AUC6 with either eribulin (1.1 mg/m^2 on days 1 and 8, every three weeks) or paclitaxel (80 mg/m^2 on days 1 and 8, every three weeks). Each patient was treated with four cycles of neoadjuvant therapy followed by surgery and four cycles of adjuvant FAC (5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2). After adjuvant chemotherapy, patients with breast-conserving surgery or with positive lymph nodes also received radiation treatment.

Results: The rates of clinical complete responses were similar in both cohorts (eribulin/carboplatin: 12/24 (50%); paclitaxel/carboplatin: 19/37 (51%)). Pathologic complete responses (pCR) were numerically less frequent in patients receiving eribulin [9/24 (38%) vs. 20/37 (54%)], although the difference was below statistical significance (p = 0.2). Five patients were carriers of deleterious BRCA1 alleles; pCRs were observed

in 2/3 (67%) and 2/2 (100%) women in eribulin and paclitaxel arms, respectively. 56 patients had a follow-up above 12 months at the time of data analysis. 4/24 (17%) disease recurrences were documented in the eribulin arm, while only 1/32 (3%) TNBC relapse was noticed for paclitaxel ($p = 0.15$).

Conclusions: Eribulin plus carboplatin combination does not outperform, in terms of pathomorphological response to treatment, paclitaxel plus carboplatin doublet while given as a neoadjuvant treatment for triple-negative breast cancer.

Legal entity responsible for the study: Petrov's National Medical Research Center for Oncology.

Funding: Russian Science Foundation [grant number 14-25-00111].

Disclosure: All authors have declared no conflicts of interest.

281TiP A phase Ib/II study of durvalumab combined with dose-dense EC in neoadjuvant setting for patients with locally advanced luminal B HER2(-) or triple negative breast cancers (B-IMMUNE)

A. Devaux[1], J-L. Canon[2], F.P. Duhoux[3], P. Delrée[4], C. Galant[5], P.G. Coulie[1], I. Bar[4], M. Constant[4], S. Haussy[4], O. Bricard[1], K. Missault[1], M. Berlière[6], T. Willems[7], J. Carrasco[2]

[1]GECE Unit, De Duve Institute, UCL, Brussels, Belgium, [2]Oncology, Grand Hopital de Charleroi Site Notre Dame, Charleroi, Belgium, [3]Medical Oncology, King Albert II Cancer Institute, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [4]Laboratoire d'Oncologie Translationnelle, Grand Hopital de Charleroi/Institut de Pathologie et Génétique, Gosselies, Belgium, [5]Pathology, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [6]Gynecology, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [7]Gynecology, Grand Hopital de Charleroi Site Notre Dame, Charleroi, Belgium

Background: Most patients with advanced breast cancer (BC) do not respond to immunotherapy with immunostimulating antibodies. Breast tumours are considered poorly antigenic due to a low mutational load, yet they contain tumour-infiltrating lymphocytes (TILs). As continuous immune pressure selects tumours that escape immune destruction, there is growing interest for the use of immunostimulatory antibodies for early-stage cancers. Based on data suggesting that anthracyclines increase tumour immunogenicity, we initiated a phase Ib/II trial to study the safety and efficacy of the anti-PD-L1 antibody durvalumab combined to epirubicin in the neoadjuvant setting for localized BC.

Trial design: B-IMMUNE study is a multicentric prospective trial including luminal B HER2(-) and triple negative BC (TNBC) patients. The study includes two parts. First a phase Ib with a 3 + 3 design whose primary objective is to evaluate the safety of an increasing number of durvalumab infusions associated to dose-dense Epirubicin-Cyclophosphamide (EC) after weekly paclitaxel for 12 weeks in the neoadjuvant setting. Then, if the durvalumab-EC combination is safe, a phase II will be initiated with an open-label 4:1 randomization in favour of the experimental durvalumab arm. Its primary objective is to evaluate clinical efficacy based on the complete pathological response rate (pCR) compared to historical controls (15% for luminal B HER2(-) BC and 30% for TNBC). The phase II will include 24 luminal B HER2(-) BC patients and 22 TNBC patients, allowing to detect pCR rate improvements of 40% and 60%, respectively ($\alpha \leq 0.1$ and $\beta \leq 0.1$). Exploratory objectives include the identification of predictive biomarkers for anti-PD-L1 efficacy with a focus on the TCR repertoires of tumour-infiltrating T cells collected before and after durvalumab. Translational research will evaluate the presence of tumour-specific CD8 T cells among TILs and the influence of durvalumab on this population using the control arm as a reference.

Clinical trial identification: NTC03356860, ONCOGHdC2015_01, November 29, 2017.

Legal entity responsible for the study: Grand Hôpital de Charleroi (GHdC).

Funding: AstraZeneca, Télévie (FNRS).

Disclosure: J. Carrasco: Research grant: AstraZeneca. All other authors have declared no conflicts of interest.

282TiP Real-world effectiveness of ribociclib + aromatase inhibitor, or endocrine monotherapy, or chemotherapy as first-line treatment in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer: The RIBANNA study

P.A. Fasching[1], T. Decker[2], G. Guderian[3], J. Heim[4], C. Jackisch[5], H-J. Lueck[6], D. Lüftner[7], F. Marmé[8], T. Reimer[9], A. Woeckel[10]

[1]Comprehensive Cancer Centrer Erlangen-EMN, Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany, [2]Onkologie, Ravensburg, Germany, [3]BU Oncology, Novartis Pharma Germany, Nuremberg, Germany, [4]BU Oncology, Novartis Pharma GmbH, Nuremberg, Germany, [5]Obstetrics and Gynecology, Sana Klinikum, Offenbach, Germany, [6]Gynökologisch-Onkologische Schwerpunktpraxis, Hannover, Germany, [7]Hematology and Oncology, Charité University Hospital, Berlin, Germany, [8]National Center for Tumor Diseases and Department of Obstetrics and Gynecology, University Hospital Heidelberg, Heidelberg, Germany, [9]Klinikum Südstadt, University of Rostock, Rostock, Germany, [10]Gynecology and Obstetrics, University Hospital Wuerzburg, Wuerzburg, Germany

Background: In the double blind, placebo-controlled phase III MONALEESA-2 trial, the selective CDK4/6 inhibitor ribociclib in combination with letrozole significantly prolonged progression free survival (PFS) in patients who were treatment-naïve for HR+/HER2- advanced breast cancer (aBC). In 2017, Ribociclib was approved in combination with an aromatase inhibitor (AI) for the treatment of HR+/HER2- aBC (locally advanced or metastatic). However, real-world evidence for the effectiveness, safety and tolerability of ribociclib+AI in routine clinical practice is needed to further support its use.

Trial design: RIBANNA is a non-interventional study (NIS) running in Germany since Oct 2017. Up to 400 German sites are expected to enroll 3020 postmenopausal patients receiving ribociclib+AI, or endocrine monotherapy, or chemotherapy as first-line treatment for HR+/HER2- aBC. Data will be collected from clinical practice on the effectiveness, safety, tolerability, and duration of therapy, including impact on quality of life (QoL) in all three cohorts prescribed in line with the respective German prescribing guidelines. These data and the corresponding outcomes will be described for the three different cohorts. Further lines of treatment will also be documented in RIBANNA to gain insight into the outcome of sequential therapy. For this purpose, patients will be documented for up to 7 years in total. In addition, RIBANNA will collect information on QoL using validated patient reported outcome measures to assess the impact of routine ribociclib+AI treatment, endocrine monotherapy or chemotherapy. The RIBANNA study will provide the first real-world evidence regarding the treatment of HR+/HER2- aBC/mBC with the novel CDK4/6 inhibitor ribociclib, including insights into treatment regimen, sequence of therapies and impact on QoL.

Clinical trial identification: CLEE011ADE03.

Editorial acknowledgement: Editorial assistance was provided by Product Lifecycle Services.

Legal entity responsible for the study: Novartis Pharma GmbH.

Funding: Novartis Phrama GmbH.

Disclosure: P.A. Fasching: Consulting: Amgen, Roche, Novartis, Pfizer, Roche, Celgene; Fees: Amgen, Roche, Novartis, Pfizer, Roche, Celgene; Research funding: Novartis, Pfizer, Celgene. T. Decker: Consulting: Novartis; Support for travel fees: Novartis. J. Heim: Employee: Novartis Pharma GmbH. C. Jackisch: Employee: Sana Klinikum Offenbach; Consulting: Roche Pharma AG, Genomic Health; Research funding: Novartis Pharma, Roche, AstraZeneca, Genomic Health. H-J. Lueck: Consulting: Roche, Tesaro, Novartis, Astrazeneca, Lilly, Pfizer; Fees: Pfizer, Astrazeneca, Tesaro, Novartis, Roche. D. Lüftner: Consulting: Novartis, Pfizer, Eli Lilly, Celgene, Loreal, AstraZeneca; Fees: Novartis, Pfizer, Eli Lilly, Celgene, Loreal, AstraZeneca. F. Marmé: Consulting: Novartis, Pfizer, AstraZeneca, Roche, Amgen, Celgene; Fees: Novartis, Pfizer, AstraZeneca, Roche, Amgen, Genomic Health, PharmaMar, Celgene, MSD. T. Reimer: Consultant: Department of Obstetrics and Gynecology, University of Rostock, Germany; Fees: Roche, Novartis, Amgen, Pfizer, AstraZeneca. A. Woeckel: Clinic Director; Fees: GSK, Pfizer, Novartis, Amgen, Jannsen-Cilag, Celgene, Hexal, Roche; Research funding: Roche.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii90–viii121, 2018
doi:10.1093/annonc/mdy272

BREAST CANCER, METASTATIC

284O Primary results of the first nationwide molecular screening program in Spain for patients with advanced breast cancer (AGATA SOLTI-1301 study)

S. Pernas[1], P. Villagrasa[2], A. Vivancos[3], M. Scaltriti[4], J. Rodon[5], O. Burgues[6], P.G. Nuciforo[7], J. Canes[2], M. Dueñas[8], M. Vidal[9], A. Lluch[10], A. Perelló[11], A. Llombart[12], J. Dorca[13], Á. Montaño[14], M. Oliveira[5], G. Ribas[15], I. Rapado[16], A. Prat[9], E.M. Ciruelos[17]

[1]Medical Oncology, Institut Català d'Oncologia-Hospitalet, Hospitalet de Llobregat, Spain, [2]Scientific Department, SOLTI Breast Cancer Research Group, Barcelona, Spain, [3]Genomics, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [5]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [6]Pathology Department, Hospital Clínico Universitario de Valencia, Valencia, Spain, [7]Molecular Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [8]Oncology, CIEMAT, Madrid, Spain, [9]Medical Oncology, Hospital Clínic i Provincial de Barcelona, Barcelona, Spain, [10]Medical Oncology, Hospital Clínico Universitario de Valencia / INCLIVA / CIBERONC, Valencia, Spain, [11]Medical Oncology, Hospital Son Espases, Palma de Mallorca, Spain, [12]Medical Oncology, Hospital Universitario Arnau Vilanova de Lleida, Lleida, Spain, [13]Medical Oncology, Institut Català d'Oncologia-Girona, Girona, Spain, [14]Medical Oncology, Hospital Virgen del Rocío, Seville, Spain, [15]Genomics, Hospital Clínico Universitario de Valencia / INCLIVA / CIBERONC, Valencia, Spain, [16]Genomics, University Hospital 12 de Octubre, Madrid, Spain, [17]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain

290O Patient-reported outcomes (PROs) in advanced breast cancer (ABC) treated with ribociclib + fulvestrant: Results from MONALEESA-3

P.A. Fasching[1], F.J. Esteva[2], X. Pivot[3], A. Nusch[4], J.T. Beck[5], A. Chan[6], A. Pieris-Gunatilaka[7], Y. Wang[8], B. Lanoue[9], D. Chandiwana[9], P. Neven[10]

[1]Department of Gynecology and Obstetrics, Erlangen University Hospital, Erlangen, Germany, [2]Division of Hematology and Medical Oncology, NYU Langone Health, New York, NY, USA, [3]Department of Medical Oncology, Institut Régional du Cancer, Strasbourg, France, [4]Department of Oncology, Practice for Haematology and Internal Oncology, Velbert, Germany, [5]Department of Medical Oncology and Hematology, Highlands Oncology Group, Fayetteville, AR, USA, [6]Breast Cancer Research Center – WA, Nedlands, Australia, [7]Medical Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [8]Oncology, Novartis Pharma AG, Basel, Switzerland, [9]Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [10]Gynaecology and Obstetrics, University Hospitals Leuven, Leuven, Belgium

291O **Ribociclib (RIB) + tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) in premenopausal patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC): MONALEESA-7 patient-reported outcomes (PROs)**

N. Harbeck[1], R. Villanueva[2], F. Franke[3], G. Babu[4], P. Wheatley-Price[5], Y-H. Im[6], K. Altundag[7], B. Lanoue[8], J. Alam[8], D. Chandiwana[8], M. Colleoni[9]

[1]*Breast Center, Ludwig Maximilians University - Grosshadern, Munich, Germany,* [2]*Hospital de Sant Joan Despí Moisès Broggi, Institut Català d'Oncologia, Barcelona, Spain,* [3]*CACON, Hospital de Caridade de Ijuí, Ijuí, Brazil,* [4]*Kidwai Memorial Institute of Oncology, HCG Curie Centre of Oncology, Bangalore, India,* [5]*University of Ottawa, Ottowa, ON, Canada,* [6]*Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea,* [7]*Department of Medical Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey,* [8]*Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA,* [9]*Division of Medical Senology, Istituto Europeo di Oncologia, Milan, Italy*

292O **Patient-reported outcomes (PRO) in patients (pts) with advanced breast cancer and a germline BRCA1/2 mutation (gBRCAm) receiving talazoparib (TALA) vs physician's choice chemotherapy treatment (PCT): A focus on the EMBRACA triple negative (TNBC) subpopulation**

H.S. Rugo[1], R. Quek[2], J. Ettl[3], S.A. Hurvitz[4], H. Bhattacharyya[2], A.L. Hannah[5], J.K. Litton[6]

[1]*Breast Cancer Center, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA,* [2]*Health Economics, Pfizer, Inc., San Francisco, CA, USA,* [3]*Obs Gyn, Technische Universität München, Munich, Germany,* [4]*Hematology/Oncology, University of California, Los Angeles, Santa Monica, CA, USA,* [5]*Oncology, Pfizer, Inc., San Francisco, CA, USA,* [6]*Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

285PD **Balixafortide (a novel CXCR4 inhibitor) and eribulin in HER2-neg metastatic breast cancer (MBC) patients (pts): A phase I trial**

J. Cortes Castan[1], M. Martín[2], S. Pernas Simon[3], P. Gomez Pardo[4], S. Lopez-Tarruella[2], M. Gil Martin[3], L.M. Manso[5], E.M. Ciruelos[6], J.A. Perez Fidalgo[7], C. Hernando[8], F. Ademuyiwa[9], K. Weilbaecher[9], I.A. Mayer[10], T. Pluard[11], M. Martinez Garcia[12], L.T. Vahdat[13], A. Wach[14], D. Barker[14], B. Romagnoli[14], P.A. Kaufman[15]

[1]*Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain,* [2]*Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain,* [3]*Departamento de Oncología Médica, Institut Català d'Oncologia L'Hospitalet-Barcelona, Barcelona, Spain,* [4]*Servicio Oncología Médica, Vall d'Hebron University Hospital, Barcelona, Spain,* [5]*Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain,* [6]*Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain,* [7]*Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain,* [8]*Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain,* [9]*Department of Hematology and Oncology, Washington University, St Louis, MO, USA,* [10]*Breast Cancer Research Program, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA,* [11]*KC School of Medicine, St Luke's Cancer Institute, Kansas City, MO, USA,* [12]*Servicio de Oncología, University Hospital del Mar, Barcelona, Spain,* [13]*Division of Hematology & Medical Oncology, Weill Medical College, New York, NY, USA,* [14]*Clinical Development, Polyphor AG, Allschwil, Switzerland,* [15]*Hematology/Oncology, Norris Cotton Cancer Center Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA*

287PD **Oral paclitaxel and HM30181A demonstrate clinical activity in metastatic breast cancer (MBC) patients**

M-S. Dai[1], T-Y. Chao[2], T-C. Chao[3], C-F. Chiu[4], Y-S. Lu[5], H-S. Shiah[6], Y-Y. Wu[1], G. Gerald Fetterly[7], N. Hung[8], D.L. Cutler[7], R. Kwan[7], D. Douglas Kramer[7], W-K. Chan[7], T. Hung[9]

[1]Hematology/Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, [2]Division of Hematology-Oncology, Taipei Medical University - Shuang Ho Hospital, New Taipei, Taiwan, [3]Medical Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, [4]Hematology/Oncology, China Medical University Hospital, Tai-Chung, Taiwan, [5]Hematology/Oncology, National Taiwan University Hospital, Taipei, Taiwan, [6]Hematology/Oncology, Taipei Medical University Hospital, Taipei, Taiwan, [7]Athenex, New York, NY, USA, [8]University of Otago, Dunedin, New Zealand, [9]Zenith Technology Corporation Limited, Dunedin, New Zealand

286PD **Post-treatment biopsies show evidence of cell cycle arrest and immune cell infiltration into tumors of ladiratuzumab vedotin-treated advanced breast cancer patients**

J. Specht[1], L. Pusztai[2], A. Forero-Torres[3], M. Mita[4], A. Weise[5], I. Krop[6], A. Grosse-Wilde[7], Z. Wang[8], M. Li[7], S. Hengel[9], P. Garfin[10], G. Means[7], M. Onsum[7], S. Modi[11]

[1]Seattle Cancer Care Alliance, University of Washington, Seattle, WA, USA, [2]Yale Cancer Cener, Yale School of Medicine, New Haven, CT, USA, [3]Division of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL, USA, [4]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [5]Medical Oncology, Karmonas Cancer Institute, Detroit, MI, USA, [6]Breast Oncology Center, Dana Farber Cancer Institute, Boston, MA, USA, [7]Diagnostics and Biomarkers, Seattle Genetics, Bothell, WA, USA, [8]Bioinformatics, Seattle Genetics, Bothell, WA, USA, [9]Quantitative Pharmacology and Disposition, Seattle Genetics, Bothell, WA, USA, [10]Clinical Research, Seattle Genetics, Bothell, WA, USA, [11]Division of Solid Tumor Oncology, Memorial Sloan-Kettering Cancer Center, New York City, NY, USA

288PD PERNETTA: A non-comparative randomized open label phase II trial of pertuzumab (P) + trastuzumab (T) with or without chemotherapy both followed by T-DM1 in case of progression, in patients with HER2-positive metastatic breast cancer (MBC): (SAKK 22/10 / UNICANCER UC-0140/1207)

J. Huober[1], P. Weder[2], C. Veyret[3], B. Thürlimann[2], A. Xyrafas[4], L. Vanlemmens[5], S. Guiu[6], E. Brain[7], J. Grenier[8], F. Dalenc[9], C. Levy[10], A.M. Savoye[11], A. Müller[12], V. Membrez-Antonioli[13], M.A. Gerard[14], J. Lemonnier[15], H. Hawle[16], E. Boven[17], H. Bonnefoi[18]

[1]Breast Center, University Hospital Ulm, Ulm, Germany, [2]Breast Center, Cantonal Hospital St. Gallen, St. Gallen, Switzerland, [3]Medical Oncology, Centre Henri Becquerel, Rouen, France, [4]Statistics, SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland, [5]Medical Oncology, Centre Oscar Lambret, Lille, France, [6]Medical Oncology, Reginal Cancer Institute, Montpellier, France, [7]Department of Medical Oncology, Institut Curie, Paris & Saint-Cloud, France, [8]Medical Oncology, Institut Ste Catherine, Avignon, France, [9]Medical Oncology, Centre Claudius-Regaud, Toulouse, France, [10]Medical Oncology, Centre Francois Baclesse, Caen, France, [11]Medical Oncology, Institut Jean Godinot, Reims, France, [12]Department of Medical Oncology, Kantonsspital Winterthur, Winterthur, Switzerland, [13]Medical Oncology, Hospital of Valais, Sion, Switzerland, [14]Clinical Research Center, SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland, [15]R&D, UNICANCER, Paris, France, [16]Clinical Research, SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland, [17]Medical Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [18]Medical Oncology, Institute Bergonié, Bordeaux, France

289PD Lucitanib for the treatment of HR+ HER2- metastatic breast cancer (MBC) patients (pts): Results from the multicohort phase II FINESSE trial

R. Hui[1], A. Pearson[2], J. Cortes Castan[3], C. Campbell[4], C. Poirot[5], H.A. Azim Jr.[6], D. Fumagalli[7], M. Lambertini[8], F. Daly[4], A. Arahmani[7], J. Perez-Garcia[9], P.G. Aftimos[10], P. Bedard[11], L. Xuereb[5], S. Loibl[12], S. Loi[13], M-J. Pierrat[5], N.C. Turner[14], F. André[15], G. Curigliano[16]

[1]Department of Medical Oncology, Westmead Hospital and the University of Sydney, Sydney, Australia, [2]The Breast Cancer Now Research Centre, The Institute of Cancer Research, London, UK, [3]IOB Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Frontier Science Scotland, Kingussie, UK, [5]Institut de Recherches Internationales Servier, Suresnes, France, [6]Internal Medicine, American University of Beirut, Beirut, Lebanon, [7]Scientific Department, Breast International Group, Brussels, Belgium, [8]Department of Medecine, Institute Jules Bordet, Brussels, Belgium, [9]Department of Oncology, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [10]Medical Oncology, Institut Jules Bordet, Brussels, Belgium, [11]Medical Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [12]GBG, German Breast Group Forschungs GmbH, Neu-Isenburg, Germany, [13]Translational Breast Cancer Genomics Lab, Division of Research, Peter MacCallum Cancer Center, Melbourne, Australia, [14]Toby Robins Breast Cancer Research Centre, Royal Marsden Hospital and Institute of Cancer Research, London, UK, [15]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [16]Early Drug Development for Innovative Therapies Division, Istituto Europeo di Oncologia, Milan, Italy

295P Exploratory biomarker analysis in patients treated with vinorelbine plus everolimus or vinorelbine monotherapy as second-line treatment for HER2-negative advanced breast cancer: Final results from the randomized phase II trial VicTORia

T. Decker[1], A. Mündlein[2], N. Marschner[3], A. Welt[4], T. Riedt[5], V. Hagen[6], J. Rauh[7], D. Klein[8], K. Potthoff[5], P. Jähnig[9], H. Schröder[10], S. Hegewisch-Becker[11], C. Lerchenmüller[12]

[1]Gemeinschaftspraxis für Hämatologie und Onkologie, Onkologie Ravensburg, Ravensburg, Germany, [2]Labor, VIVIT Molekularbiologisches Labor, Dornbirn, Austria, [3]Medical Oncology, Praxis für Interdisziplinaere Onkologie, Freiburg, Germany, [4]Klinik f. Innere Medizin/ Tumorforschung, Universitätsklinikum Essen (AöR), Essen, Germany, [5]Clinical Operations, IOMEDICO AG, Freiburg, Germany, [6]Onko Zentrum, St.-Johannes-Hospital Dortmund, Dortmund, Germany, [7]Praxis, GIM - Gemeinschaftspraxis Innere Medizin, Witten, Germany, [8]Medical Team, IOMEDICO AG, Freiburg, Germany, [9]Statistik, ICRC Weyer GmbH, Berlin, Germany, [10]Clinical Operations, AIO-Studien-gGmbH, Berlin, Germany, [11]HOPE, Hämatologisch-Onkologische Praxis Eppendorf, Hamburg, Germany, [12]Praxis, Hämatologisch-Onkologische Gemeinschaftspraxis, Münster, Germany

Background: The purpose of the VicTORia trial was to evaluate efficacy and safety of the combined treatment of everolimus (EVE) and vinorelbine (VIN) compared to VIN monotherapy as second-line treatment for HER2-negative advanced breast cancer. The study was accompanied by an exploratory analysis of phosphoinositide 3 kinase subunit (PIK3CA) as potential predicitve marker for response.

Methods: Patients were randomized 1:1 to receive i.v. VIN at a dose of 25 mg/m2 on days 1, 8 and 15 q3w plus 5 mg EVE once daily or i.v. VIN at a dose of 25 mg/m2 on days 1, 8 and 15 q3w. The primary objective was progression-free survival (PFS). Safety and tolerability, overall survival (OS) and overall response rates were secondary objectives. The mutational status of PIK3CA was determined at baseline from plasma samples.The study was initially planned to enroll 166 patients.

Results: Between December 2011 and February 2016 138 patients were enrolled from 32 sites across Germany. Of 69 patients randomized to receive VIN plus EVE, 68 received treatment and 65 of 69 patients randomized to VIN monotherapy received treatment. Baseline characteristics were balanced. Median age was 63 and 62 years, ECOG 0-1 98.5% and 90.7%, postmenopausal status 79.4% and 80.0%, and visceral metastases 89.7% and 87.7%, respectively. Median PFS was 4.01 months [95% CI, 2.40-6.09] for the combination vs. 4.08 months [95% CI, 2.80-5.33] for VIN monotherapy (HR = 1.05 [0.730-1.512], log rank p = 0.7908). The median OS was not statistically different between treatment arms (VIN+EVE: 16.25 months [95% CI, 11.38-18.95] vs. VIN: 13.78 months [95% CI, 10.23-19.05]), log rank p = 0.9361). PIK3CA mutational status was neither associated with PFS nor with OS in the total patient cohort, in patients treated with VIN+EVE and in patients treated with VIN monotherapy, respectively.

Conclusions: The addition of EVE to VIN was not associated with a benefit in PFS. Overall survival also did not significantly differ between treatment arms. No correlation between PIK3CA mutation status and outcome was detected.

Clinical trial identification: EudraCT: 2011-001024-38.

Legal entity responsible for the study: AIO-Studien-gGmbH.

Funding: Novartis.

Disclosure: T. Decker: Advisory role or expert testimony: Novartis; Advisory boards, other financial relationships, travel expenses: Novartis. N. Marschner: Advisory role or expert testimony: Novartis; Advisory boards, honoraria: Novartis; Other financial relationships, travel expenses: Novartis. A. Welt: Advisory role or expert testimony: Novartis; Advisory boards, financing of scientific research: Novartis. J. Rauh: Other financial relationships: Honoraria for documentation in clinical studies: Novartis. All other authors have declared no conflicts of interest.

296P Applicability of the lung immune prognostic index (LIPI) to metastatic triple negative breast cancer (mTNBC) patients treated with immune checkpoint targeted monoclonal antibodies (ICT mAbs)

A. Vozy[1], A. Simonaggio[1], E. Auclin[2], L. Mezquita[3], C. Baldini[1], P. Martin-Romano[1], B. Pistilli[4], A. Gazzah[1], R. Bahleda[1], V. Ribrag[1], S. Postel-Vinay[1], S. Champiat[1], J-C. Soria[5], F. André[6], C. Massard[7], B. Besse[8], S. Delaloge[4], A. Varga[1]

[1]DITEP, Gustave Roussy Institut de Cancérologie, Villejuif, France, [2]Oncology, Hopital European George Pompidou, Paris, France, [3]Department of Cancer Medicine, Gustave Roussy Institut de Cancérologie, Villejuif, France, [4]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [5]DITEP, Medimmune, Gaithersburg, MD, USA, [6]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [7]DITEP, Gustave Roussy Institut de Cancérologie, Villejuif, France, [8]Department of Cancer Medicine, Gustave Roussy Institut de Cancérologie, Villejuif, France

Background: Tumor-infiltrating lymphocytes are prognostic and predictive in TNBC. However, the level of activity of Immune Checkpoint Targeted Monoclonal Antibodies (ICT mAbs) remains low in this indication and biomarkers are needed to select for patients who could benefit from these treatments. Pretreatment LIPI, based on derived NLR (dNLR = neutrophils/[leucocytes-neutrophils]) and lactate dehydrogenase (LDH) assessment has been associated with outcomes for ICT mAbs in advanced NSCLC patients. We tested whether LIPI has the same impact on mTNBC patients' outcome.

Methods: Biological and clinical data were retrospectively collected from mTNBC patients treated with ICT mAbs between Jan 2014 & Apr 2018 in our Drug Development Department. Three LIPI risk groups were studied: good (dNLR<3 & LDH<upper limit of normal (ULN)), intermediate (dNLR>3 or LDH>ULN), poor (dNLR>3 & LDH>ULN). The primary endpoint was progression-free survival (PFS) and the secondary endpoint was overall survival (OS).

Results: Forty-two patients were included with a median age of 45, 48% were ECOG 0 and the median prior chemotherapy lines was 3. Twenty-one percent of patients received a PD1/PD-L1 inhibitor as monotherapy, 79% had ICT mAbs combination. The median PFS and OS under ICT mAbs was 1.35 months (IC 95% 1.27; 2.93) and 13.5 months (5.9; not reached) respectively according to RECIST v1.1. LIPI classified 18 patients as good (43%), 18 patients (43%) as intermediate and 6 patients (14%) as poor risk group. Median PFS was 2.65, 1.32 and 0.85 months for good (GP), intermediate (IP) and poor prognosis (PP) respectively (P = 0.002). Median OS was 18.10 months for GP, 9.8 months for IP and 1.6 months PP (P = <0.0001). Metastatic cutaneous lesions were also associated with poor PFS with ICT mAbs in our cohort, HR 3.189, P = 0.0028. The PDL1 status does not seem to influence LIPI risk groups.

Conclusions: Applying baseline LIPI in mTNBC patients is feasible and is correlated with ICT mAbs outcomes for this population. A larger retrospective validation cohort is being evaluated and more data will be available for the ESMO presentation.

Legal entity responsible for the study: Varga Andréa.

Funding: Has not received any funding.

Disclosure: J-C. Soria: Full time employee: MedImmune AstraZeneca since September 2017. C. Massard: Amgen, Astellas, Astra Zeneca, Bayer, Celgene, Genentech, Ipsen, Janssen, Lilly, Novartis, Pfizer, Roche, Sanofi, Orion. B. Besse: AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Servier, Onxeo, OncoMed, Inivata, OSE Pharma, Loxo. All other authors have declared no conflicts of interest.

297P Peripheral blood mononuclear cell biomarkers predict response to immune checkpoint inhibitor therapy in metastatic breast cancer

Y. Yuan[1], W. Hou[2], S. Padam[1], P. Frankel[3], M.S. Sedrak[1], J. Portnow[1], J. Mortimer[1], C. Yeon[1], A. Hurria[1], A. Tang[1], N. Martinez[1], P. Lee[2]

[1]Medical Oncology, City of Hope, Duarte, CA, USA, [2]Immunology, City of Hope, Duarte, CA, USA, [3]Biostatistics, City of Hope, Duarte, CA, USA

Background: The role of immune checkpoint PD-1/PD-L1 inhibitor (ICI) in breast cancer (BC) is being investigated in clinical trials. Preclinical evidence strongly supports the synergistic effects of CDK4/6 inhibitor and ICI. A phase II trial is testing the safety and efficacy of the combination of letrozole, palbociclib and pembrolizumab in patients with hormone receptor positive (HR+) BC (NCT02778685). Currently, there is no well-defined circulating biomarker to predict response to ICI.

Methods: Peripheral blood mononuclear cells (PBMC) were collected at day 1 of cycles 1 (pre-treatment), 2, 4, 6 and 8. The comprehensive characterization of 14 innate cell types, 7 adaptive T-cells, and 16 exhaustion-related T-cells was performed using 15-color flow cytometry. Core biopsies were taken at baseline and optionally on-study to assess immune cell subsets.

Results: Preliminary analysis included nine patients with the following responses by RECIST 1.1: 1 complete response, 4 partial responses, 2 stable disease, and 2 progression of disease. Analysis showed correlation of clinical response to high baseline levels of γδ T-cells (r = 0.74, p = 0.02) and exhausted T-cells: $CD4^+PD\text{-}1^+KLRG1^+$ (r = 0.74, p = 0.02), $CD4^+PD\text{-}1^+CD160^+$ (r = 0.71, p = 0.02), and $CD4^+PD\text{-}1^+TIM3^+$ (r = 0.71, p = 0.03). Most patients showed a decrease in the number of $CD33^{hi}$ myeloid-derived suppressor cells (p = 0.04) and $CD4^+PD\text{-}1^+TIGIT^+$ exhausted T-cells (p = 0.04) in peripheral blood at C2D1. Strong indicators of clinical response included increased $CD33^{low}$ myeloid-derived suppressor cells (r = 0.70, p = 0.04) and decreased type-1 CD8+ T-cells (r = 0.81, p = 0.009) at C4D1.

Conclusions: High pre-treatment peripheral blood exhausted CD4+ T-cells is associated with clinical response to ICI in HR+BC. Further analysis including tumor tissue immune profiling is currently ongoing to verify these findings.

Clinical trial identification: NCT02778685.

Legal entity responsible for the study: City of Hope.

Funding: City of Hope, Merck, Pfizer.

Disclosure: Y. Yuan: Industry funded research: Pfizer, Merck, Puma, GTX, Novartis, Eisai; Advisory board: Puma, Novartis, Eisai; Speaker Bureau: Eisai. All other authors have declared no conflicts of interest.

298P Circulating exosomal microRNA profiling to depict mechanisms of chemotherapy resistance among triple negative breast cancer

Y. He[1], T. Jinhai[2]

[1]Department of General Surgery, Jiangsu Province Hospital, Nanjing, China, [2]Department of General Surgery, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Background: Chemotherapeutic resistance leads to high mortality among triple negative breast cancer (TNBC) patients and underlying mechanisms are poorly understood. Exosomes have become new area of interest for liquid biopsy. MicroRNAs (miRNAs), as the most important inclusions in exosomes, are ideal candidate biomarkers and therapeutic targets.

Methods: We isolated exosomes and analyzed exosome-carried miRNA signatures in several TNBC cells lines sensitive or resistant to adariamycin, docetaxel or cisplatin. The resistance transfer capacity was determined by flow cytometry after sensitive cells incubated 48 hours with exosomes from drug-resistant cells. Locked nucleic acid probes and enzyme-labeled fluorescence (LNA-ELF-FISH) was performed to detect exosomal miRNA molecule transfer. Animal mode was constructed to evaluate treatment feasibility using miRNA-modified exosomes. Serum exosomes from 40 TNBC stage IV patients who underwent chemotherapy before or after progressive disease (PD) status were isolated to analyze miRNA profiling for potential biomarker identification.

Results: We successfully isolated and identified exosomes from several drugsensitive and resistant TNBC cell lines and patients. Exosomal miR-222, miR-4443, miR-100, miR-17, miR-210 were found significantly upregulated from chemotherapy-resistant cells. Incubation of exosomes from the resistant cells with the sensitive cells resulted in increasing resistant capacity among sensitive cells. Exosomal miRNA molecule transfer was detected using LNA-ELF-FISH. Transfection of synthesized miRNAs competitors into exosomes increased drug sensitivity in vivo. Exosomal miR-222, miR-4443, miR-100, miR-17, miR-210 were also found upregulated significantly from serums of patients after PD status. These five miRNAs were able to differentiate patients with PD status from those with CR or PR status with at least 89% accuracy.

Conclusions: Exosomes from chemotherapy-resistant TNBC cells could transfer drug resistance to sensitive cells via exosomal miRNAs. A circulating exosomal microRNA profiling was estabilished for potential biomarkers and therapeutic target identification.

Legal entity responsible for the study: Jinhai Tang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

299P The prevalence of PIK3CA mutations in HR+/HER2– metastatic breast cancer (BELLE2, BELLE3 and BOLERO2 clinical trials)

K. Wan[1], Y.A. Wang[2], M. Kaper[3], M. Fritzemeier[4], N. Babbar[5]

[1]Biostatistics, Novartis Pharma AG, Basel, Switzerland, [2]Biostatistics, Novartis Institutes for BioMedical Research, Cambridge, MA, USA, [3]Biostatistics, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [4]Oncology Precision Medicine, Novartis Institutes for BioMedical Research, Cambridge, MA, USA, [5]Oncology Precision Medicine, Novartis, East Hanover, NJ, USA

Background: Breast cancer (BC) is the most common form of malignant tumor in women worldwide. 60-70% of BC are hormone receptor-positive (HR+), HER2-negative (HER2–). The purpose of this analysis was to enhance understanding on the epidemiology for women with PIK3CA-mutant HR+/HER2– metastatic breast cancer (mBC).

Methods: PIK3CA mutations were tested from tumor biopsy (N = 1617) and circulating tumor DNA (ctDNA) (N = 1466) from patients enrolled into BOLERO-2, BELLE-2 and BELLE-3, which are three randomized Phase III studies in HR+/HER2– mBC. Various PIK3CA mutation testing methods were applied, including Next-Generation Sequencing (NGS) and Polymerase Chain Reaction (PCR) for tumor biopsies, as well as BEAMing and droplet digital PCR for ctDNA samples.

Results: Prevalence of the PIK3CA mutations among tissue biopsies ranged from 34.1% to 41.1% while prevalence of the PIK3CA mutations among liquid biopsies ranged from 27.5% to 43.3%. Besides gene-level analysis, the PIK3CA prevalence by hot spots and by exons was examined as well. Further, subgroup analysis of PIK3CA prevalence had been conducted based on patient cohort (2L vs 3L), mutation testing methods, ethnicity, biopsy source (primary tissue vs metastatic) and previous treatment.

Conclusions: PIK3CA mutations (specifically hotspots H1047R, E545K and E542K) frequently occur in HR+/HER2– mBC. The prevalence of PIK3CA mutations are in a relatively narrow range across the three randomized Phase III studies in HR+/HER2– mBC regardless of tissue types and testing methods.

Legal entity responsible for the study: Novartis Pharma.

Funding: Novartis Pharma.

Disclosure: K. Wan: Employment: Novartis Pharma AG; Stock options: Novartis. Y.A. Wang, N. Babbar, M. Kaper, M. Fritzemeier: Employment: Novartis Pharmaceutical Corporation; Stock options: Novartis.

300P Differential molecular signature in patients from African origin with triple-negative breast cancer

A.T. Matias[1], A. Jacinta-Fernandes[2], R. Magno[2], J. Xavier[2], M.G. Cabral[1], A. Jacinto[1], A.T. Maia[2], S. Braga[1]

[1]CEDOC, Nova Medical School, Lisbon, Portugal, [2]Department of Biomedical Sciences and Medicine (DCBM), Centre for Biomedical Research (CBMR), Algarve Biomedical Center (ABC), University of Algarve, Campus de Gambelas, Faro, Portugal

Background: Breast cancer (BC) is more aggressive in pre-menopausal women of Black race (BW). These women usually have worse prognosis and higher mortality rate when compared with patients of other races, even when socioeconomic factors are accounted for. Triple-negative BC (TNBC), the most aggressive and less treatable BC, due to the lack of therapeutic targets, such as oestrogen and progesterone receptor or HER2, is more frequently diagnosed in these young BW.

Methods: To identify the driving biological factors of this racial disparity we performed a comprehensive differential gene expression (DGE) analysis using the R package edgeR and RNA-sequencing BC data from The Cancer Genome Atlas, which has specifically USA data. In a total of 1097 BC patients, 183 are BW, 32 with TNBC (17.5% of all BW); 757 are White, 69 with TNBC (9.1%); and 61 are Asian, 8 with TNBC (13.1%).

Results: DGE between BW with TNBC and TNBC patients of other races revealed 251 up- and 269 downregulated genes (adjusted p-value ≤ 0.05, $|\log_2(\text{Fold Change})| \geq 1$, applied in all the analysis). To remove genes associated with race alone and not with TNBC in BW per se, we performed a DGE analysis between all non-TNBC cases in BW and all non-TNBCs in the other races, resulting in 315 up- and 139 downregulated genes in non-TNBCs of BW. Common genes between the two analyses were identified and extracted from the first list, resulting in 198 up- and 250 downregulated genes exclusively differentially expressed in TNBC of BW. Our candidates include genes related to insulin-resistance and obesity (e.g. FBXO2 [p-adj = 2.07E-04, $\log_2$FC = 1.58], POU2AF1 [p-adj = 1.80E-03, $\log_2$FC = 1.43]), and epithelial-mesenchymal transition and metastasis (e.g. FOXF2 [p-adj = 9.51E-05, $\log_2$FC = 1.39], NOTCH3 [p-adj = 9.51E-05, $\log_2$FC = 1.35]). These genes are being validated using formalin-fixed paraffin-embedded TNBC tissues from BW, collected from different Portuguese hospitals and from a Mozambican hospital, where tumour tissue is compared to normal adjacent tissue by qRT-PCR, immunohistochemistry and Western blot.

Conclusions: Our work will unveil the molecular signature(s) that characterise and define molecularly TNBC in BW and, ultimately, will guide the development of new therapeutics for this unmet medical problem.

Legal entity responsible for the study: CEDOC, Nova Medical School, Lisbon, Portugal.

Funding: Fundação para a Ciência e Tecnologia (PD/BD/114053/2015); iNOVA4Health (UID/Multi/04462/2013 – LISBOA-01-0145-FEDER-007344).

Disclosure: All authors have declared no conflicts of interest.

301P Analysis of the JAK2 gene in triple-negative breast cancer (TNBC)

L. Stanek[1], P. Tesarova[2], M. Vocka[2], L. Petruzelka[2]

[1]Department of Oncology, First Faculty of Medicine of Charles University in Prague, Prague, Czech Republic, [2]Department of Oncology, General Faculty Hospital, VFN Charles University, Prague, Czech Republic

Background: The JAK2 gene is located on chromosome 9p24.1, its product is a tyrosine kinase protein that plays a role in signal transduction between membrane receptors for growth factors and intracellular signaling molecules and is also involved in cytokine signaling. Mutation V617F of JAK2 (Janus kinase 2) causes violation of autoinhibiting activity and promotes malignant transformation and proliferation. Recent studies, however, indicate a possible amplification of somatic chromosome 9p24.1 region encoding the JAK2 in triple-negative breast cancer (TNBC) in connection with a poorer prognosis and shorter survival.

Methods: The aim of our pilot study was to perform a cytogenetic and molecular biological analysis of the JAK2 gene in a cohort of 40 patients diagnosed and confirmed with TNBC. The FISH method was used to analyze numerical changes and translocations, including the detection of possible merger partners. In the next step mutation analysis was by PCR and direct sequencing performed.

Results: On the basis of cytogenetic and molecular changes of the JAK2 gene, it can be stated that the numerical, structural and molecular changes occur in TNBC at a high frequency. In addition to amplification which is a potential predictor of ruxolotinib inhibition, a number of numerical and structural changes (including point mutations) of the gene was detected (amplification detected in 25% of cases, polysomy detected in 15% of cases, monosomy detected in 5% of cases, break detection in 10% of cases, amplification/break detected in 10% of cases). Mutational analysis showed the presence of the V617F mutation in 15% of cases where there was normal cytogenetics.

Conclusions: These changes may potentially cause worse response to treatment with an inhibitor and will require us to focus attention in this direction.

Legal entity responsible for the study: First Faculty of Medicine.

Funding: This work was supported by the Charles University research program PROGRESQ 28 (Oncology).

Disclosure: All authors have declared no conflicts of interest.

302P A risk score integrating lymphocytes ratios (LRs) and lactate dehydrogenase (LDH) levels to predict prognosis in metastatic breast cancer (MBC) patients

G. Pelizzari[1], L. Gerratana[1], D. Basile[1], S. Zago[2], M.G. Vitale[1], M. Bartoletti[1], C. Lisanti[1], V. Fanotto[1], C. Corvaja[1], L. Bortot[1], A. Liguori[3], M. Cinausero[1], S. Russo[4], C. Andreetta[4], M. Bonotto[4], M. Mansutti[4], A.M. Minisini[4], F. Curcio[5], G. Fasola[4], F. Puglisi[6]

[1]Department of Medicine (DAME), University of Udine, Udine, Italy, [2]Clinical Pathology, Hospital "Santa Maria degli Angeli", Pordenone, Italy, [3]Medical Oncology Unit, Department of Human Pathology "G. Barresi", AOU Policlinico G. Martino Università di Messina, Messina, Italy, [4]Department of Oncology, ASUIUD Santa Maria della Misericordia, Udine, Italy, [5]Clinical Pathology Institute, ASUIUD Santa Maria della Misericordia, Udine, Italy, [6]University of Udine - Udine, Italy, Department of Medical Oncology and Cancer Prevention, CRO National Cancer Institute, Aviano, Italy

Background: Monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR) and LDH levels have been associated with worse prognosis in several malignancies, including MBC. This study aimed at exploring the prognostic impact of a novel risk score, integrating baseline LRs and LDH levels in MBC patients (pts).

Methods: This retrospective study analyzed 396 consecutive pts with a diagnosis of MBC, treated between 2007 and 2017 at the Oncology Department of Udine (Italy). MLR and NLR cut-offs were previously obtained through ROC analysis using propensity score-matched healthy controls (Gerratana et al 2018). The LDH cut-off value (480 U/L) was chosen according to the local laboratory upper reference limit. Based on these data, an integrated LRs-LDH score (LLS) was calculated ranging from 0 (LRs and LDH low), through 1 (LRs or LDH high), to 2 (both LRs and LDH high). The prognostic impact of baseline LLS was investigated through Cox regression, and differences in survival were tested by log-rank test.

Results: After a median follow-up of 52.8 months, median overall survival (OS) was 30.9 months and median progression free survival (PFS) was 9.2 months. Pts with baseline elevated MLR, NLR or LDH were 64.2% (251/391), 70.8% (277/391), and 31.5% (70/222), respectively. The 78.8% (308/391) of pts had elevated LRs (MLR, NLR or both). Considering subgroup analysis, no interaction was seen between LDH and LRs. By multivariate analysis, after adjustment for molecular profiles, performance status, number of metastatic sites, central nervous system and liver involvement, a worse prognosis in terms of OS was seen for pts with elevated levels of both LRs and LDH (LLS 2: HR 2.41, 95% CI: 1.31-4.37, p=.003), compared to pts with normal LRs and LDH (LLS 0). Notably, significant differences in OS were observed according to the LLS (LLS 2: median OS 19.2 months, LLS 1: median OS 43.9 months, LLS 0: median OS 54.9 months; p<.0001).

Conclusions: Baseline LLS is able to predict survival in pts with MBC and provides independent prognostic information. Prospective studies are needed to validate this novel score and to explore how it may affect different treatment strategies.

Legal entity responsible for the study: University of Udine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

303P EMBRACA: Comparison of efficacy and safety of talazoparib (TALA) and physician's choice of therapy (PCT) in patients (pts) with advanced breast cancer (aBC), a germline BRCA1/2 mutation (gBRCAm), and prior platinum treatment

M. Martín[1], W. Eiermann[2], H.S. Rugo[3], J. Ettl[4], S.A. Hurvitz[5], A. Gonçalves[6], R. Yerushalmi[7], D. Markova[8], I.C. Tudor[8], J.L. Blum[9], A.L. Hannah[10], J.K. Litton[11]

[1]Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain, [2]Chest Surgery, Interdisziplinäres Onkologisches Zentrum München, Munich, Germany, [3]Breast Cancer Center, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [4]Obstetrics and Gynecology, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany, [5]Hematology/Oncology, University of California, Los Angeles, CA, USA, [6]Medical Oncology, Institut Paoli-Calmettes, Marseille, France, [7]Medical Oncology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, [8]Biostatistics, Pfizer, Inc., San Francisco, CA, USA, [9]Medical Oncology, Baylor Sammons Cancer Center, Dallas, TX, USA, [10]Medical Oncology, Pfizer, Inc., San Francisco, CA, USA, [11]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: TALA is a dual-mechanism PARP inhibitor that prevents DNA damage repair by trapping PARP on DNA, resulting in cell death in BRCA1/2-mutated cells.

Methods: EMBRACA is an open-label, randomised, 2-arm phase 3 trial in which efficacy and safety of TALA (1 mg/day) is compared with standard single-agent PCT (capecitabine, eribulin, gemcitabine, or vinorelbine) in pts with aBC and gBRCAm. In this analysis clinical outcomes were assessed in 2 subgroups of pts who had either received prior platinum (PP) or had no prior platinum (NPP) treatment.

Results: Of 431 pts randomised, 76 had PP in any setting (46 TALA; 30 PCT) and 355 were NPP (241 TALA; 114 PCT). Mean (SD) age was 46.4 (11.15) years. Pts in all groups had received a median of 1 prior cytotoxic regimen for aBC. TALA demonstrated a statistically significant improvement in both objective response rate (odds ratio [OR] [95% CI]: PP 3.16 [0.88-15.67], P=.0456; NPP 5.36 [2.89-9.89], P<.0001) and progression-free survival (hazard ratio [95% CI]: PP 0.76 [0.40-1.45], P=.41; NPP 0.52 [0.39-0.71], P<.0001) compared with PCT. Mean (SD) duration of TALA therapy was 7.2 (6.52) mo (PP) and 8.7 (7.09) mo (NPP), with 15% (PP) and 19% (NPP) of pts receiving TALA for ≥12 mo. Median duration of response (DOR) to TALA was longest in NPP pts (5.4 mo), followed by PP pts (4.2 mo); pts receiving PCT had a DOR of approximately 3.0 mo regardless of prior platinum status. Pts on TALA achieved a clinical benefit rate at 24 weeks (PP 59%; NPP 71%) with OR significantly favouring TALA over PCT in both groups. Of pts receiving TALA, nausea was the most common adverse event (AE) in PP pts (59%) and anaemia in NPP pts (53%). Serious AEs occurred in both PP (33%) and NPP pts (32%) taking TALA.

Conclusions: In pts with advanced gBRCAm breast cancer, TALA demonstrated statistically significant improvements in clinical outcomes for both PP and NPP subgroups compared with PCT. Although TALA treatment benefitted both groups, the benefit was greater if TALA was used before platinum therapy.

Clinical trial identification: NCT01945775.

Editorial acknowledgement: Editorial and medical writing support funded by Pfizer Inc. were provided by Edwin Thrower, PhD, Mary Kacillas and Paula Stuckart of Ashfield Healthcare Communications, Middletown, Connecticut.

Legal entity responsible for the study: Pfizer, Inc.

Funding: This study was sponsored by Medivation LLC, a Pfizer company.

Disclosure: M. Martín: Consulting fees: Pfizer; Fees for non-CME services received directly from commercial interests or their agents: Pfizer. H.S. Rugo: Fees for contracted research to the University of California: Eisai, Genentech, GSK, Lilly, Macrogenics, Merck, Novartis, OBI Pharma, Pfizer, Plexxikon; Travel: Lilly, Mylan, Puma. J. Ettl: Consulting fees: Novartis, Pfizer, Roche, Eisai; Contracted research: Celgene; Honoraria: Pfizer, Roche, Teva, and Pierre Fabre. S.A. Hurvitz: Contracted research: Amgen, Bayer, BioMarin, BI, Cascadian Therapeutics, Dignitana, Genentech/Roche, GSK, Lilly, Medivation, Merrimack, Novartis, OBI Pharma, Pfizer, Puma Biotechnology, Sanofi; Travel: Bayer, Lilly, Novartis, and OBI Pharma. D. Markova, I.C. Tudor: Employee: Pfizer, Inc. J.L. Blum: Consulting fees: Pfizer. A.L. Hannah: Consulting fees: Basilea, Medivation/Pfizerand Nektar; Ownership interest: NeoGenomics Laboratories. J.K. Litton: Institutional-contracted research: Pfizer, Novartis, EMD-Serono, AstraZeneca, GlaxoSmithKline, Genentech; Advisory board participation: AstraZeneca and Pfizer, both uncompensated. All other authors have declared no conflicts of interest.

304P EMBRACA: Efficacy and safety in comparing talazoparib (TALA) with physician's choice of therapy (PCT) in patients (pts) with advanced breast cancer (aBC) and a germline BRCA mutation (gBRCAm); BRCA1/BRCA2 subgroup analysis

A. Gonçalves[1], W. Eiermann[2], H.S. Rugo[3], J. Ettl[4], S.A. Hurvitz[5], R. Yerushalmi[6], M. Martín[7], M. Al-Adhami[8], I.C. Tudor[9], J.L. Blum[10], A.L. Hannah[11], J.K. Litton[12]

[1]Medical Oncology, Institut Paoli-Calmettes, Marseille, France, [2]Chest Surgery, Interdisziplinäres Onkologisches Zentrum München, Munich, Germany, [3]Breast Cancer Center, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [4]Obstetrics and Gynecology, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany, [5]Hematology/Oncology, University of California, Los Angeles, CA, USA, [6]Medical Oncology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, [7]Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain, [8]Biostatistics, Pfizer Inc., Groton, CT, USA, [9]Biostatistics, Pfizer, Inc., San Francisco, CA, USA, [10]Medical Oncology, Baylor Sammons Cancer Center, Dallas, TX, USA, [11]Medical Oncology, Pfizer, Inc., San Francisco, CA, USA, [12]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: TALA is a dual-mechanism PARP inhibitor that traps PARP on DNA, prevents DNA damage repair, and causes cell death in BRCA1/2-mutated cells.

Methods: EMBRACA is an open-label, randomized, 2-arm phase 3 trial comparing the efficacy and safety of TALA (1 mg/day) with standard single-agent PCT (capecitabine, eribulin, gemcitabine, or vinorelbine) in pts with aBC and a gBRCAm). In this analysis clinical outcomes were assessed in BRCA1 and BRCA2 subgroups.

Results: Of 431 pts randomized, 196 were BRCA1 (133 TALA; 63 PCT), 235 were BRCA2 (154 TALA; 81 PCT). Mean (SD) age was 45.4 (11.66) years (BRCA1) and 50.4 (11.45) years (BRCA2). Pts in all groups had received a median of 1 prior cytotoxic regimen for aBC. TALA demonstrated a statistically significant improvement in both objective response rate (odds ratio [OR] [95% CI] BRCA1 7.01 [2.99-19.54]; BRCA2 4.15 [1.90-8.52]; both P<.0001) and progression-free survival (hazard ratio [95% CI] BRCA1 0.59 [0.39-0.90]; BRCA2 0.47 [0.32-0.70]) in BRCA1 and BRCA2 subgroups compared with PCT. Mean (SD) duration of TALA therapy was 7.5 (7.07) mo (BRCA1) and 9.2 (6.88) mo (BRCA2), with 15% (BRCA1) and 22% (BRCA2) of pts receiving TALA for ≥12 mo. Median duration of response (DOR) to TALA was longest in BRCA2 pts (6.3 mo), followed by BRCA1 pts (4.2 mo); BRCA1 and BRCA2 pts receiving PCT had a DOR of approximately 3.0 mo. Pts on TALA achieved a clinical benefit rate at 24 weeks (BRCA1 62%; BRCA2 74%) with OR significantly favouring TALA over PCT in both groups. Of pts receiving TALA, anaemia was the most common adverse event (AE) in BRCA1 pts (56%) and fatigue in BRCA2 pts (50%). Serious AEs occurred in both BRCA1 and BRCA2 pts (32%) receiving TALA.

Conclusions: In pts with advanced gBRCAm breast cancer, TALA demonstrated statistically significant improvements in clinical outcomes for both BRCA1 and BRCA2 subgroups compared with PCT.

Clinical trial identification: NCT01945775.

Editorial acknowledgement: Editorial and medical writing support funded by Pfizer Inc. were provided by Edwin Thrower, PhD, Mary Kacillas and Paula Stuckart of Ashfield Healthcare Communications, Middletown, Connecticut.

Legal entity responsible for the study: Pfizer, Inc.

Funding: his study was sponsored by Medivation LLC, a Pfizer company.

Disclosure: H.S. Rugo: Fees for contracted research to the University of California: Eisai, Genentech, GSK, Lilly, Macrogenics, Merck, Novartis, OBI Pharma, Pfizer, Plexxikon; Travel: Lilly, Mylan, Puma. J. Ettl: Consulting fees: Novartis, Pfizer, Roche, and Eisai; Contracted research: Celgene; Honoraria: Pfizer, Roche, Teva, Pierre Fabre. S.A. Hurvitz: Contracted research: Amgen, Bayer, BioMarin, BI, Cascadian Therapeutics, Dignitana, Genentech/Roche, GSK, Lilly, Medivation, Merrimack, Novartis, OBI Pharma, Pfizer, Puma Biotechnology, Sanofi; Travel: Bayer, Lilly, Novartis, OBI Pharma. Martín: Consulting fees: Pfizer and fees for non-CME services received directly from commercial interests or their agents: Pfizer. M. Al-Adhami, I.C. Tudor: Employment: Pfizer, Inc. J.L. Blum: Consulting fees: Pfizer. A.L. Hannah: Consulting fees: Basilea, Medivation/Pfizer and Nektar; Ownership interest: NeoGenomics Laboratories. J.K. Litton: Institutional-contracted research: Pfizer, Novartis, EMD-Serono, AstraZeneca, GlaxoSmithKline, Genentech; Advisory board participation: AstraZeneca and Pfizer, both uncompensated. All other authors have declared no conflicts of interest.

305P Exposure-efficacy progression-free survival (PFS) analyses of breast cancer patients with germline BRCA1/2 mutations receiving talazoparib in the phase III EMBRACA trial

Y. Yu[1], M. Elmeliegy[1], J.K. Litton[2], I.C. Tudor[3], A. Czibere[4], J. Zheng[5], D.D. Wang[1]

[1]Oncology, Pfizer, Inc., La Jolla, CA, USA, [2]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Biostatistics, Pfizer, Inc., San Francisco, CA, USA, [4]Oncology, Pfizer, Inc., Cambridge, MA, USA, [5]Oncology, Pfizer, Inc., Collegeville, PA, USA

Background: Talazoparib is a potent, orally bioavailable, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor that is currently under development for the treatment of a variety of cancers. This exposure-response (ER) analysis characterized the relationship between talazoparib exposure and PFS in patients with locally advanced and/or metastatic breast cancer with germline breast cancer susceptibility gene (BRCA) mutations based on the phase 3 EMBRACA trial.

Methods: 285 patients, who were treated with talazoparib and had available pharmacokinetic (PK) parameters from the phase 3 EMBRACA trial, were included in the analysis. There were 185 PFS events at the data cut of the analysis. The apparent talazoparib clearance (CL/F) for each patient was obtained from a population PK analysis. To account for dose modifications over time, the ER analysis used a time-varying exposure metric ($C_{avg,t}$) for talazoparib exposure. At each PFS event, the talazoparib exposures up to the time of the PFS event t were calculated for all patients at risk using average daily dose intensity up to time t and CL/F and correlated with the probability of having a PFS event using the Cox proportional hazards model. Other potential prognostic factors were also tested as covariates for PFS. The significant covariates identified in univariate analyses were further examined for significance in multi-variate analyses.

Results: The ER analysis for PFS showed that there was a significant correlation between PFS and talazoparib exposure. A longer PFS was associated with higher talazoparib exposure. In addition, longer PFS was also associated with lower baseline lactate dehydrogenase. PFS was longer in patients without visceral disease than patients with visceral disease. A diseasefree interval of >12 months was associated with a longer PFS than that of ≤ 12 months.

Conclusions: PFS was found to be associated with $C_{avg,t}$, and a longer PFS was associated with a higher talazoparib exposure. This supports using 1 mg QD, the maximum tolerated dose, as the recommended dose for talazoparib.

Clinical trial identification: NCT01945775.

Editorial acknowledgement: Editorial and medical writing support funded by Pfizer Inc. were provided by Edwin Thrower, PhD, Mary Kacillas and Paula Stuckart of Ashfield Healthcare Communications, Middletown, Connecticut.

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer, Inc.

Disclosure: J.K. Litton: Institutional-contracted research: Pfizer, Novartis, EMD-Serono, AstraZeneca, GlaxoSmithKline, Genentech; Advisory board participation: AstraZeneca and Pfizer, both uncompensated. Y. Yu, M. Elmeliegy, I.C. Tudor, A. Czibere, J. Zheng, D.D. Wang: Employment: Pfizer, Inc.

306P Exposure-safety analyses in breast cancer patients with germline BRCA1/2 mutations receiving talazoparib (TALA) in EMBRACA and ABRAZO trials

M. Elmeliegy[1], Y. Yu[1], J.K. Litton[2], N.C. Turner[3], A. Czibere[4], G.G. Wilson[5], I.C. Tudor[6], J. Zheng[7], D.D. Wang[1]

[1]Oncology, Pfizer, Inc., La Jolla, CA, USA, [2]Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Toby Robins Breast Cancer Research Centre, The Royal Marsden, London, UK, [4]Oncology, Pfizer, Inc., Cambridge, MA, USA, [5]Oncology, Pfizer, Inc., New York, NY, USA, [6]Biostatistics, Pfizer, Inc., San Francisco, CA, USA, [7]Oncology, Pfizer, Inc., Collegeville, PN, USA

Background: TALA is a potent PARP inhibitor. Efficacy and safety profiles of once-daily TALA 1 mg were established in advanced breast cancer patients (pts) in the phase 3 EMBRACA and phase 2 ABRAZO trials. Approximately 60% of pts experience dose modification due to an adverse event (AE). This analysis characterized the relationship between TALA exposure and grade 3 or higher anemia, neutropenia, and thrombocytopenia, the most common AEs leading to dose modification.

Methods: Safety and pharmacokinetic (PK) data from 367 TALA-treated pts (285 EMBRACA, 82 ABRAZO) were included in a pooled analysis. To account for dose modifications over time, individual time-varying concentration from time 0 up to the time of each safety event ($C_{avg,t}$) was calculated at each event time using average daily dose intensity and apparent TALA clearance as obtained from population PK analysis. The relationship between $C_{avg,t}$, as well as other potential prognostic factors and the selected safety events was evaluated using Cox proportional hazard (PH) models. Significant covariates in univariate analyses were further examined in multi-variate analyses.

Results: Visual examination suggested a higher $C_{avg,t}$ in pts with anemia and thrombocytopenia events vs pts without events. Cox PH models indicated that a higher risk of anemia and thrombocytopenia was associated with higher $C_{avg,t}$. For anemia, the HR (95% CI) for $C_{avg,t}$ (ng/mL) was 1.3 (1.12, 1.4), $P = 3.03$. For thrombocytopenia, the HR (95% CI) for $C_{avg,t}$ (ng/mL) was 1.2 (1.01, 1.3), $P = 0.0394$. A trend for association between higher $C_{avg,t}$ and neutropenia was observed although the relationship was not statistically significant ($P = 0.0633$). Higher risk of all tested safety endpoints was associated with lower baseline hemoglobin. Higher risk of neutropenia was associated with lower absolute neutrophil count and lower body weight.

Conclusions: A higher risk of anemia and thrombocytopenia was associated with higher TALA exposure. This finding supports the proposed management of TALA-related AEs through dosing interruption and reduction.

Clinical trial identification: NCT01945775, NCT02034916.

Editorial acknowledgement: Editorial and medical writing support funded by Pfizer Inc. were provided by Edwin Thrower, PhD, Mary Kacillas and Paula Stuckart of Ashfield Healthcare Communications, Middletown, Connecticut.

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer, Inc.

Disclosure: J.K. Litton: Institutional-contracted research: Pfizer, Novartis, EMD-Serono, AstraZeneca, GlaxoSmithKline, and Genentech; Advisory board participation: AstraZeneca and Pfizer, both uncompensated. N.C. Turner: Advisory board, honoraria and research funding: Pfizer and BioMarin. M. Elmeliegy, A. Czibere, Y. Yu, G.G. Wilson, I.C. Tudor, J. Zheng, D.D. Wang: Employment: Pfizer, Inc.

307P An international systematic review (SR) of breast cancer (BC) BRCA mutation (BRCAm) prevalence

N. Armstrong[1], S. Ryder[1], C. Forbes[1], A. Chalker[1], J. Ross[1], R. Quek[2]

[1]Health Economics, Kleijnen Systematic Reviews Ltd, York, UK, [2]Health Economics, Pfizer, Inc., San Francisco, CA, USA

Background: Carriers of BRCAm have an increased risk of developing BC. Considering the availability of BRCAm-targeted advanced breast cancer (aBC) drugs and evolving treatment guidelines, an SR was conducted to summarise the prevalence of BRCAm carriers in the overall BC population and stratified by clinical and demographic subgroups in different countries.

Methods: This SR adhered to the Cochrane method. Electronic databases (eg, Medline & Embase; $n = 7$) and grey literature sources were searched (Jan 2012 to Nov 2017). Studies reporting on BC BRCAm prevalence were included. BRCA1/2m prevalence (including germline) in BC (overall and aBC), clinical (TNBC, HR+/HER2- BC), and demographic subgroups (race/ethnicity) were summarised.

Results: 17,872 records were retrieved; 70 studies were included. Regions/countries: Europe ($n = 16$), USA ($n = 33$), Canada ($n = 2$), Australia ($n = 2$), Japan ($n = 1$), South Korea ($n = 11$), Russia ($n = 2$), and Israel ($n = 3$). Only 29 studies explicitly reported BRCA germline status with prevalence ranging from 1.8% in an overall BC population (Sardinia) to 59.52% in a study of BC with family history (Spain). BRCAm prevalence varied widely in 16 overall BC population studies ranging from 2.7% (France) to 23.6% (Italy). Broader BRCAm prevalence ranges were observed in 5 aBC studies, varying from 2% in an overall BC population (France) to 53.8% in a study of Ashkenazi Jews (Israel). 42 reported BRCA1m and BRCA2m separately with no consistent distribution pattern between the 2. In the 24 TNBC studies, prevalence varied from 9.3% in an overall BC population (Australia) to 73.3% in a study of BC with a family history (Israel). BRCA1m prevalence was higher in TNBC studies that reported

BRCA1m separately from BRCA2m (16 of 24 studies). In 3 studies of HR+/HER2- BC, BRCAm prevalence varied from 5% (USA) to 9.9% (South Korea). BRCAm prevalence ranged from 14.2% (USA) to 53.8% (Israel) in those of Ashkenazi Jewish ancestry.

Conclusions: Reported BRCAm prevalence in BC varies widely in clinical and demographic subgroups across countries; there are few studies on aBC and most lack germline BRCAm status specification. Further BC BRCAm epidemiologic studies are warranted to validate the prevalence of BRCAm with germline status.

Editorial acknowledgement: Editorial and medical writing support funded by Pfizer Inc. were provided by Edwin Thrower, PhD, Mary Kacillas and Paula Stuckart of Ashfield Healthcare Communications, Middletown, Connecticut.

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer, Inc.

Disclosure: N. Armstrong, S. Ryder, C. Forbes, A. Chalker, J. Ross, R. Quek: Employee: KSR Ltd. who was paid by Pfizer Inc. to carry out this work.

308P Genetic screening, counselling, and treatment of BRCA mutation (BRCAm) carriers: A systematic review (SR) of international breast cancer (BC) guidelines

C. Forbes[1], D. Fayter[1], C. Clar[1], K. Reid[1], S. de Kock[1], R. Quek[2]

[1]Health Economics, Kleijnen Systematic Reviews Ltd, York, UK, [2]Health Economics, Pfizer, Inc., San Francisco, CA, USA

Background: Considering the availability of BRCAm-targeted therapeutic drugs in BC and an evolving clinical guidelines landscape, an SR of international guidelines on screening and management of BRCAm BC patients was carried out.

Methods: The current SR adhered to Cochrane's guidance. Major electronic databases (eg, Medline & Embase; n = 7) and grey literature sources were searched (Jan 2007 to Dec 2017). Latest guideline reporting recommendations (and evidence grades) on genetic screening, counselling, and BC treatment of BRCAm carriers were summarised. Guidelines specific to germline (gBRCAm) (ie, hereditary) were captured where available.

Results: 3775 records were retrieved and 33 guidelines from Europe (n = 17), USA (n = 11), Canada (n = 3), Australia (n = 1), and Japan (n = 1) were included. Genetic counselling was recommended at multiple points in the care pathway, though the format (eg, frequency, decision tools) was not always clearly defined. US guidelines emphasised BRCAm testing should occur after specialised genetic counselling; other European guidelines were less prescriptive. BRCA testing eligibility criteria differed with some guidelines being less restrictive; US NCCN BC guidelines specified that HER2- BC patients eligible for single-agent therapy should strongly consider gBRCAm testing, while also having separate more restrictive high-risk BRCA testing criteria. Similar restrictive criteria were observed in some European guidelines. Fast-track BRCAm testing was recommended in the Netherlands if treatment choice affects BC survival, but only as part of a clinical trial in the UK. Other guidelines suggest testing only if it affects therapy decisions. ESMO ABC3 guidelines recommended platinum therapy for advanced BRCAm BC; more recent ESO-ESMO BCY3 and US NCCN guidelines recommended newly approved gBRCAm-targeted PARP inhibitor therapy.

Conclusions: Differences exist between regions and within organizations for guidelines regarding genetic screening, counselling, and treatment of BRCAm BC patients. Harmonisation of guidelines could optimise the identification and management of BRCAm BC patients.

Editorial acknowledgement: Editorial and medical writing support funded by Pfizer Inc. were provided by Edwin Thrower, PhD, Mary Kacillas and Paula Stuckart of Ashfield Healthcare Communications, Middletown, Connecticut.

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer, Inc.

Disclosure: C. Forbes, D. Fayter, S. de Kock: Employee: KSR Ltd. who were paid by Pfizer Inc. to carry out this work. C. Clar, K. Reid: Freelance reviewer working on behalf of KSR Ltd. who were paid by KSR Ltd to carry out this work. R. Quek: Employee: Pfizer Inc.

309P Efficacy and toxicity of endocrine therapy + cyclin-dependent kinases 4/6 inhibitors (iCDK4/6) in metastatic breast cancer patients according to gBRCA status

L.I. Bruno, M.V. Costanzo, C.A. Ostinelli, A.A. Nervo, J. Nadal, F. Colo, J. Loza, C.M. Loza, C. Ponce, V. Fabiano, A.G. Blanco, C. Perez de la Puente, R.D. Chacon

Clinical Oncology, Alexander Fleming Institute, Buenos Aires, Argentina

Background: Endocrine therapy (ET) and iCDK4/6 has demonstrated efficacy in terms of progression free survival (PFS), and clinical benefit as first and second line treatment in hormone receptor positive (HR+), Her2 negative, metastatic breast cancer (MBC). Cost and toxicity has limited its worldwide indication. No predictive biomarkers of response or toxicity have been validated. The aim of this analysis is to explore the utility of the gBRCA status as a predictive factor of efficacy and toxicity in HR+, Her2 negative, MBC treated with the combination of ET + iCDK4/6.

Methods: Prospective cohort study of patients under ET+ iCDK4/6 toxicity registry. Next Generation Sequencing (NGS) for gBRCA1 and 2 and genetic counseling was offered according to physician regular practice.

Results: 92 patients were available for analysis, 24 had been studied for gBRCA. Still 3/24 (12%) have pending results, but 21% (5/24) were positive (2 gBRCA1+, and 3 gBRCA2+), and 67% (16/24) were negative (gBRCAneg). Median age of the global cohort was 46 years old (range 27-84), only 21% were stage IV at onset. The overall clinical benefit was 48%, significantly better for gBRCAneg 81% (13/16) versus 20% (1/5), p-value 0.011213. PFS was 46 weeks for the global cohort (CI95% 43.7-57.4 months), with tendency to better results among gBRCAneg 57 weeks (CI95% 42.2-80.5) versus 47 weeks (CI95% 21.2-72.7) for gBRCA+. The overall toxicity grade 3-4 was 24% (23/96) without differences according to gBRCA status (gBRCA+ 20% versus gBRCAneg 25%, p-value 0.818769).

Conclusions: We observed a significantly higher clinical benefit with a tendency to higher PFS in gBRCAneg HR+, Her2 negative MBC under ET + iCDK4/6 treatment and similar toxicity in both groups. This exploratory analysis suggests a potential role for gBRCA status as a biomarker of efficacy in this scenario. We believe that prospective, pre-stratified and adequately powered studies warrants further investigation and could help to design the proper sequence of treatments in light of the availability of upcoming target therapies such as PARP inhibitors.

Legal entity responsible for the study: Alexander Fleming Institute.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

310P Clinical outcomes, treatment patterns and health resource utilization (HRU) among metastatic breast cancer (mbc) patients (pts) with germline BRCA mutation (gBRCAm)

R. Quek, J. Mardekian

Health Economics, Pfizer, Inc., San Francisco, CA, USA

Background: With evolving gBRCAm BC guideline landscape, we present latest gBRCA testing rates among mBC US pts with HR+/HER2- or triple negative BC (TNBC); including clinical outcomes, treatment patterns and HRU in gBRCAm pts.

Methods: The Flatiron Health database was used in a real world retrospective analysis of mBC pts with HR+/HER2- or TNBC, ≥18 yrs old, diagnosed between Jan 2011-Feb 2018. Rates of gBRCA testing were assessed. One- to 5-yr overall survival (OS) post mBC diagnosis for gBRCAm HR+/HER2- and TNBC pts were estimated. Cox proportional hazards model was used to estimate OS of TNBC vs HR+/HER2-. Outcomes between TNBC vs HR+/HER2- pts were compared while adjusting for imbalances. Antineoplastic treatment was summarized and HRU patterns were analyzed using t-tests.

Results: The study included 12,021 mBC pts (10,291 HR+/HER2-; 1730 TNBC). Results for gBRCA testing were available for 16.7% of pts overall; (HR+/HER2-: 15.4%, TNBC: 24.2%). The most common 1st line treatments for gBRCAm TNBC were capecitabine (19%) and carboplatin/gemcitabine (15%) and 1st line treatments for gBRCAm HR+/HER2- included letrozole (10%) and fulvestrant (7%). Pts counts, OS estimates and HRU for gBRCAm carriers are shown in the table; Cox regression results showed lower OS for gBRCAm TNBC pts vs gBRCAm HR+/HER2- mBC pts, Hazard Ratio (HR+/HER2- / TNBC) and 95% CI 0.59 (0.34, 1.01). Estimated median OS and 5-yr OS rates are (33.9 mths, 22.3 mths) and (28.9%, 26.4%) for gBRCAm HR+/HER2- and TNBC pts respectively. Number of HRU visits per-pts-per-year were significantly higher among TNBC pts.

Conclusions: gBRCA testing rates among mBC pts with HR+/HER2- or TNBC were low. Among mBC pts with gBRCAm, 5-yr OS rates were < 29% for both HR+/HER2- and TNBC; poor prognosis and HRU burden demonstrates a significant unmet need for more targeted, less HRU-intensive treatment options among these pts.

Table: 310P

	HR+/HER2-	TNBC
Total Patients (N = 12,021) n (%)	10,291 (85.6)	1730 (14.4)
Patients with gBRCA test results (n = 2005) n (%)	1587 (79.2)	418 (20.8)
Patients with gBRCAm (n = 229) n (%)	165 (72.1)	64 (27.9)
gBRCAm patients with ≥ 1st Line antineoplastic treatment (n = 188) n (%)	142 (75.5)	46 (24.5)
Year	Overall Survival Estimates (%)	
1	93.4	69.5
2	58.6	46.3
3	45.8	26.4
4	30.7	26.4
5	28.9	26.4

Continued

Table: 310P *Continued*

	HR+/HER2-	TNBC
Number of Health Resource Utilization Visits (per patient per year) mean (std dev) *p < 0.05		
Treatment Visits*	17.4 (14.4)	40.8 (21.8)
Lab Visits*	24.2 (10.1)	40.3 (44.2)
Vital Visits*	27.4 (14.3)	49.9 (66.8)
ALL*	35.2 (30.3)	65.0 (84.7)

Legal entity responsible for the study: Pfizer, Inc.
Funding: Pfizer, Inc.
Disclosure: R. Quek, J. Mardekian: Employee: Pfizer Inc.

311P Early results from an open-label phase 1b/II study of eribulin mesylate (EM) + pegvorhyaluronidase alfa (PEGHP20) combination for the treatment of patients with HER2-negative, high-hyaluronan (HA) metastatic breast cancer (MBC)

M. Shum[1], V.J. Assikis[2], C. Savulsky[3], W. Zhu[4], P. Iyer[4], D. Xing[5], C. Berman[6], N.A. Lokker[6], R.H. Alvarez[7]
[1]*The Oncology Institute Whittier, Oncology Institute of Hope and Innovation, Whittier, CA, USA,* [2]*Medical Department, Piedmont Cancer Institute, Newman, GA, USA,* [3]*Clinical Research, Eisai Ltd., Hatfield, UK,* [4]*Clinical Research, Eisai Inc., Woodcliff Lake, NJ, USA,* [5]*Clinical Biostatistics, Eisai Inc., Woodcliff Lake, NJ, USA,* [6]*Clinical Development, Halozyme Therapeutics, Inc, San Diego, CA, USA,* [7]*Southeastern Regional Medical Center, Cancer Treatment Centers of America, Atlanta, GA, USA*

Background: HA in the tumor microenvironment can inhibit the effectiveness of anti-cancer agents. The novel biologic PEGPH20 degrades pathological HA accumulation. EM is a microtubule inhibitor approved for the treatment of pts with MBC who previously received ≤2 lines of systemic anticancer therapy for metastatic disease. Preclinical data showed the PEGPH20+EM combination resulted in enhanced anti-tumor effectiveness in HAaccumulating, triple-negative breast cancer (TNBC) xenografts. The primary objective of this Phase 1b study (NCT02753595) was to determine safety, tolerability and RP2D of PEGPH20+EM in pts with HER2neg MBC previously treated with ≤2 lines of systemic anticancer therapy in the metastatic setting.

Methods: Overall, 14 enrolled pts were treated IV at 2 PEGPH20 dose levels (DL1=3 μg/kg or DL0=1.6 μg/kg on D1, D7) + EM 1.4 mg/m^2 on D1, D8 of a 21day cycle. 5 pts were treated at DL1, with 2 DLTs observed (G3 muscle cramp, G3 knee/leg pain); 6 pts were enrolled in DL0 with no further DLTs. An additional 3 pts were enrolled at DL0 (RP2D).

Results: All 14 pts were evaluable for safety and efficacy. Median age was 53 years (33–78 years); 14% (2/14) of pts had TNBC. Median number of treatment cycles was 6.0. Drug-related TEAEs occurred in 86% of pts during PEGPH20+EM therapy. 79% of pts had G ≥ 3 TEAEs. There were 3 SAEs (1 in DL1 and 2 in DL0). As of April 2018, the individual safety profile was as expected for PEGPH20 and EM; no new significant safety signals identified. Key pt characteristics and BORs are shown below. Out of the 5 pts with confirmed PR, 3 had 1 prior and 2 had no prior systemic anticancer therapy in the metastatic setting.

Table: 311P

Category	PEGPH20 (3 μg/kg)/ EM (1.4 mg/m^2) (n = 5)	PEGPH20 (1.6μg/kg)/ EM (1.4 mg/m^2) (n = 9)	Total (N = 14)
Enrollment Strata – n (%)			
TNBC	0 (0)	2 (22)	2 (14)
ER and/or PRo-positive	5 (100)	7 (78)	12 (86)
ECOG Status – n (%)			
0	4 (80)	4 (44)	8 (57)
1	1 (20)	5 (56)	6 (43)
No. Prior Systemic Anticancer Therapy in Metastatic Setting – n (%)			
0	1 (20)	4 (44)	5 (36)
1	3 (60)	5 (56)	8 (57)
2	1 (20)	0 (0)	1 (7)

Continued

Table: 311P *Continued*

Category	PEGPH20 (3 μg/kg)/ EM (1.4 mg/m^2) (n = 5)	PEGPH20 (1.6μg/kg)/ EM (1.4 mg/m^2) (n = 9)	Total (N = 14)
Confirmed BOR – n (%)			
CR	0 (0)	0 (0)	0 (0)
PR	2 (40)	3 (33)	5 (36)
SD	1 (20)	2 (22)	3 (21)
PD	1 (20)	3 (33)	4 (29)
Not evaluable/Unknown	1 (20)	1 (11)	2 (14)
ORR (CR+PR) – n (%)	2 (40)	3 (33)	5 (36)
DCR (CR+PR+SD) – n (%)	3 (60)	5 (56)	8 (57)

Abbreviations: BOR=best overall response; CR=complete response; DCR=disease control rate; ECOG=Eastern Cooperative Oncology Group; EM=eribulin mesylate; ER=estrogen receptor; MBC=metastatic breast cancer; ORR=objective response rate; PD=progressive disease; PEGPH20=pegvorhyaluronidase alfa; PR=partial response; PRo=progesterone receptor; SD=stable disease; TNBC=triple-negative breast cancer

Conclusions: These early results are encouraging with a 36% ORR and 57% DCR, suggesting that PEGPH20 + anti-breast cancer agents such as EM warrant further investigation in pts with HER-2 neg MBC. A complete dataset is expected in October 2018.

Clinical trial identification: NCT02753595.
Editorial acknowledgement: Editorial assistance provided by Paragon, Knutsford, UK.
Legal entity responsible for the study: Eisai, Inc.
Funding: Eisai, Inc. in collaboration with Halozyme Therapeutics, Inc.
Disclosure: C. Savulsky, W. Zhu, P. Iyer, D. Xing: Employee: Eisai C. Berman, N.A. Lokker: Employee: Halozyme Therapeutics. All other authors have declared no conflicts of interest.

312P Phase II clinical trial of first-line eribulin plus trastuzumab for advanced or recurrent HER2-positive breast cancer

K. Sakaguchi[1], K. Nakatsukasa[2], T. Taguchi[2]
[1]*Endocrine and Breast Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan,* [2]*Department of Endocrine and Breast Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan*

Background: Eribulin mesylate has been approved for advanced or metastatic breast cancers subjected to at least two previous chemotherapy regimens. The present multicenter, phase II, single-arm study assessed the efficacy and safety of a first-line regimen of eribulin plus trastuzumab for untreated advanced or metastatic HER2-positive breast cancer.

Methods: Enrolled patients received eribulin (1.4 mg/m^2 intravenously; I.V.) on days 1 and 8 of each 21-day cycle, an initial trastuzumab dose (8 mg/kg I.V.) on day 1, and 6 mg/kg of trastuzumab on day 1 of each subsequent cycle. The primary endpoint was the RR. The secondary endpoints were PFS, OS, DOR, and safety. Twenty-eight patients (median age: 62.5 years) received a median of 12 (range: 2–53) cycles of eribulin plus trastuzumab.

Results: The RR was 53.6% (CR, 4; PR, 11) with a median PFS of 344 days. The clinical benefit rate was 64.0%. Grade 3/4 adverse events were observed in 12 (42.9%) patients. For details, neutropenia in 8 (28.6%) patients, peripheral neuropathy in 2 (7.1%) patient, interstitial pneumonia in 1 (3.6%) patient, ALT elevation in 1 (3.6%) patient, osteonecrosis of the jaw in 1 (3.6%) patient, and fatigue in 1 (3.6%) patient. The patient with osteonecrosis received denosumab, too. No symptomatic congestive heart failure was observed.

Conclusions: Combination therapy of eribulin plus trastuzumab is acceptable in efficacy and safety, and a capable option for first-line advanced or recurrent HER2-positive breast cancer.

Clinical trial identification: UMIN000009890.
Editorial acknowledgement: Editage edited English language.
Legal entity responsible for the study: Translational Reseach Informatics Center, Kobe, Japan.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

313P Eribulin in metastatic breast cancer the UK experience: A multi-centre retrospective 577 patient study

M. Jafri[1], H. Kristeleit[2], V. Misra[3], M.A. Baxter[4], S. Ahmed[5], A. Jegnnathen[6], A. Jain[7], D. Maskell[8], U. Barthakur[9], G. Edwards[10], H. Walter[11], R. Walter[3], M.A. Khan[12], A. Borley[10], P. Nightingale[1], D. Rea[13]

[1]*Medical Oncology, Queen Elizabeth-University Hospital Birmingham NHS Foundation Trust, Birmingham, UK,* [2]*Medical Oncology, Guy's Cancer Centre, London, UK,* [3]*Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK,* [4]*Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK,* [5]*Leicester Cancer Research Centre, University Hospitals of Leicester NHS Trust Leicester Royal Infirmary, Leicester, UK,* [6]*Clinical Oncology, University Hospitals of North Midlands, Stoke, UK,* [7]*Oncology, The Royal Wolverhampton Hospitals NHS Trust New Cross Hospital, Wolverhampton, UK,* [8]*Oncology, Norfolk and Norwich University Hospitals, Norfolk, UK,* [9]*Medical Oncology, Taunton and Somerset NHS Foundation Trust, Taunton, UK,* [10]*Clinical Oncology, Velindre Cancer Centre, Cardiff, UK,* [11]*Medical Oncology, University Hospitals of Leicester NHS Trust Leicester Royal Infirmary, Leicester, UK,* [12]*Oncology, Guy's and St. Thomas' Hospital NHS Trust, London, UK,* [13]*Clinical Trials Unit, The University of Birmingham Institute for Cancer Studies, Birmingham, West Midlands, UK*

Background: The EMBRACE trial demonstrated significantly improved survival with eribulin compared to physicians' choice (13.1 vs 10.9 months ($p = 0.041$). Eribulin has been funded by the NHS in the UK for the management of locally advanced or metastastic breast cancer after at least two lines of treatment. We describe the UK experience of eribulin in this setting.

Methods: Data from 577 patients was analyzed on an individual patient basis from 14 different hospitals after institutional review board approval. Data was collected retrospectively using computerized records and chemotherapy records. Data was collated on: age, breast cancer characteristics, prior chemotherapy regimes, toxicity, PFS and OS. Statistical analysis was performed using SPSS.

Results: Data from 577 patients who received eribulin in specialist cancer centres, teaching hospitals and cancer units throughout the UK between 2011-2017 were included. The median age of patients was 56 (33-84). 447 were ER positive, 129 triple negative, 100 patients were Her2 positive, 1 unknown. The cohort was heavily pre-treated with eribulin being received on average 4thline (median (range 2-11)). The median number of eribulin cycles received were 4 (range 1-29). The OS of the cohort was 288 days (95%CI 260-315), triple negative patients had a worse outcome than ER/Her2 expressing patients (198 c.f. 278 days ($p = 0.02$)). Less heavily pre-treated patients ($\leq$2 prior treatments) had significantly better survival (328 c.f. 264 days). Patients aged over 65 had better survival 325 c.f. 285 days. 11% experienced grade 3-4 neuropathy, 14% experienced nausea, 19% experienced G3-4 neutropenia, there were no treatment related deaths.

Conclusions: This real world data demonstrates that even in a heavily pretreated population eribulin was associated an OS approaching a year. Eribulin was well tolerated even in patients over 65 and is associated with better survival if used earlier in metastatic patients.

Legal entity responsible for the study: The authors.

Funding: Eisai.

Disclosure: M. Jafri: Advisory board: PharmaMar; Speaker fees: Roche, Pfizer, PharmaMar. H. Kristeleit: Advisory board: Amgen and Roche; Speaker fees: Eisai and Roche. S. Ahmed: Consultancy: Eisai, Novartis, Roche, Pfizer, MSD, AstraZeneca, Takeda. A. Borley: Consultancy: Eisai, Roche, Pfizer. P. Nightingale: Educational grant: Eisai for statistical support. D. Rea: Roche, Novartis, Diachi Sankyo, AstraZeneca, Eisai. All other authors have declared no conflicts of interest.

314P Eribulin as first- or second-line chemotherapy for advanced or metastatic HER2-negative breast cancer: A real-world prospective study

M. Takahashi[1], K. Inoue[2], H. Mukai[3], T. Yamanaka[4], C. Egawa[5], Y. Sakata[6], H. Ikezawa[7], T. Matsuoka[6], J. Tsurutani[8]

[1]*Breast Surgery, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan,* [2]*Breast Oncology, Saitama Cancer Center, Kita-adachi Ina, Japan,* [3]*Breast and Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan,* [4]*Breast and Endocrine Surgery, Kanagawa Cancer Center, Yokohama, Japan,* [5]*Breast Surgery, Kansai Rosai Hospital, Amagasaki, Japan,* [6]*Oncology Medical, Eisai Co., Ltd., Tokyo, Japan,* [7]*Clinical Data Science, Eisai Co., Ltd., Tokyo, Japan,* [8]*Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan*

Background: A global phase III study confirmed the effect of eribulin mesylate (ERI) as third- or later-line chemotherapy on overall survival (OS) for advanced or metastatic breast cancer. Meanwhile, in Japan, ERI can be used as first- or second-line. However, limited reports can be found on time to treatment failure (TTF) and/or OS for ERI as first- or second-line therapy comparing to late-line therapy in clinical practice.

Methods: We conducted a prospective study in patients with inoperable or recurrent HER2-negative breast cancer starting in September, 2014. We enrolled a similar number of patients receiving ERI as first- or second-line therapy and those receiving ERI as third- or later-line therapy, and with follow-up planned for up to two years (ClinicalTrials.gov: NCT02371174). The data collected by November 2017 was analyzed. TTF and OS were estimated using the Kaplan–Meier method. Multivariate Cox regression was used to identify the factors influencing TTF and OS.

Results: We analyzed 634 patients. The mean age ($\pm$ standard deviation) was 59.6 years ($\pm$ 11.0), and 157 patients (24.8%) had triple-negative breast cancer. Of these patients, 319 received ERI as first- or second-line therapy and 315 as third- or later-line therapy. The median TTF (95% confidence interval [CI]) was 135 (121–164) and 119 (106–128) days, and the median OS (95% CI) was 555 (475–628) and 383 (342–459) days for first- or second-line- and third- or later-line therapy, respectively. A history of radiation therapy, complication of diabetes, liver metastasis, ECOG performance status, blood hemoglobin and aspartate aminotransferase levels at baseline, triple-negative breast cancer, and development of peripheral neuropathy after ERI treatment were significant factors influencing both TTF and OS.

Conclusions: Our real-world study showed patients with first- or second-line therapy of ERI have longer OS and TTF than those in third- or later-line therapy. These results suggested that patients with first- or second-line therapy of ERI have the potential for similar or more favorable outcomes from the ERI treatment compared with patients with third- or later-line therapy of ERI.

Clinical trial identification: NCT02371174, First release November 21, 2014.

Legal entity responsible for the study: Eisai Co., Ltd.

Funding: Eisai Co., Ltd.

Disclosure: M. Takahashi: Honorarium: Eisai, AstraZeneca, Pfizer. K. Inoue: Research funding (institutional): Eisai, Parexel, Puma Biotechnology, MSD, Novartis, GSK, Pfizer, Chugai Pharmaceutical, Daiichi Sankyo. Y. Sakata, H. Ikezawa, T. Matsuoka: Employee: Eisai Co. J. Tsurutani: Adviser: Eisai Co., Ltd. and Asahi Kasei Corporation; Honoraria: Eisai Co., Ltd., Taiho Pharmaceutical Co., Ltd., Roche Diagnostics K.K., Novartis Pharma, AstraZeneca K.K. All other authors have declared no conflicts of interest.

315P Prospective cohort study of real world chemotherapy sequence for metastatic breast cancer (KBCRN A001: E-SPEC study)

K. Nakatsukasa[1], Y. Kikawa[2], T. Kotake[3], K. Yamagami[4], S. Tsuyuki[5], H. Yamashiro[6], H. Suwa[7], T. Sugie[8], T. Okuno[9], H. Kato[2], S. Takahara[10], I. Nakayama[11], N. Ogura[12], Y. Moriguchi[13], M. Takata[3], E. Suzuki[3], H. Yoshibayashi[14], H. Ishiguro[15], T. Taguchi[1], M. Toi[16]

[1]*Department of Endocrine and Breast Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan,* [2]*Department of Breast Surgery, Kobe City Medical Center General Hospital, Kobe, Japan,* [3]*Breast Surgery, Kyoto University-Graduate School of Medicine, Kyoto, Japan,* [4]*Department of Breast Surgery, Shinko Hospital, Kobe, Japan,* [5]*Department of Breast Surgery, Osaka Red Cross Hospital, Osaka, Japan,* [6]*Department of Breast Surgery, Tenri Hospital, Nara, Japan,* [7]*Department of Breast Surgery, Hyogo Prefectural Amagasaki General Medical Center, Hyogo, Japan,* [8]*Department of Breast Surgery, Kansai Medical University Hospital, Osaka, Japan,* [9]*Department of Breast Surgery, Kobe City Nishi-Kobe Medical Center, Kobe, Japan,* [10]*Breast Surgery, Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan,* [11]*Department of Breast Surgery, Kyoto Min-iren Chuo Hospital, Kyoto, Japan,* [12]*Department of Breast Surgery, Kansai Electric Power Hospital, Osaka, Japan,* [13]*Department of Breast Surgery, Kyoto City Hospital, Kyoto, Japan,* [14]*Department of Breast Surgery, Japanese Red Cross Wakayama Medical Cente, Wakayama, Japan,* [15]*Department of Medicine, International University of Health and Welfare, Nasushiobara, Japan,* [16]*Department of Breast Surgery, Kyoto University-Graduate school of medicine, Kyoto, Japan*

Background: The prognosis for triple negative (TN) and hormone-refractory metastatic breast cancer (MBC) remains poor and treatment options are limited to cytotoxic agents. Furthermore, the optimal sequence of chemotherapy (CT) is unclear. In this prospective cohort study (E-SPEC), we observed optimal sequences of CT for improving long-term survival. This trial was registered with ClinicalTrials.gov (no. NCT02551263).

Methods: The study was conducted under a multi-institutional prospective observational design and involved patients with HER2-negative hormone-refractory MBC. Eligibility criteria were age 20-75 years; refractory to hormone therapy defined as TN type or recurrence during or within 6 months after the end of adjuvant treatment or refractory to at least one previous hormone therapy for MBC; and scheduled for first- and second-line CT after registration. All treatments were performed according to physician's choice. Treatment regimens, efficacies and quality of life (QoL) were prospectively surveyed. Baseline data analysis included patient characteristics, real-world CT sequence of first- and second-line CT regimen and the reason for cessation of first-line CT.

Results: Between June 2015 and July 2017, a total of 201 patients were enrolled, 194 of whom were analyzed. Mean age was 58.9 years; 142 patients (73.2%) had ER- and/or PgR-positive disease; 52 patients (26.8%) had TN. Most frequent regimen for first- or second-line CT was eribulin (ERI) (88.9%) among patients who received second-line CT. Frequent sequences were oral fluorouracil (FU) followed by ERI (18.3%), bevacizumab/paclitaxel (Bev/PTX) followed by ERI (13.5%), and ERI followed by Bev/PTX (11.1%). Patients who received taxanes as first-line CT had significantly more adverse event discontinuation than those with oral FU or ERI ($p < 0.01$).

Conclusions: In this real-world setting, ERI was administered in almost all first- or second-line regimens and taxane-based regimens were associated with more adverse event discontinuations. We intend to further investigate overall survival among CT sequences, as well as progression-free survival, new metastasis-free survival, type of progression and QoL.

Clinical trial identification: NCT02551263.

Legal entity responsible for the study: Masakazu Toi.

Funding: Eisai.

Disclosure: All authors have declared no conflicts of interest.

316P Comparative effectiveness of nab-paclitaxel vs. paclitaxel monotherapy as first-line (1L) treatment of metastatic triple-negative breast cancer (mTNBC) in US clinical practice

T. Luhn[1], S. Chui[2], A. Hsieh[3], J. Yi[4], A. Mecke[5], P. Bajaj[6], W. Hasnain[7], A. Falgas[8], T.G.N. Ton[9], A. Kurian[10]

[1]Product Development, Genentech, Inc., South San Francisco, CA, USA, [2]Product Development Oncology, Genentech, Inc., South San Francisco, CA, USA, [3]Center for Outcomes Research and Evaluation, Genentech, Inc., South San Francisco, CA, USA, [4]Epidemiology, Genesis Research, Hoboken, NJ, USA, [5]PDB Biostatistics, Roche, Basel, Switzerland, [6]Health Economics, Genentech, Inc., South San Francisco, CA, USA, [7]Global Pricing and Market Access, Genentech, Inc., South San Francisco, CA, USA, [8]PDR Department, Roche, Basel, Switzerland, [9]Real World Data Oncology, Genentech, Inc., South San Francisco, CA, USA, [10]Medicine - Med/Oncology, Stanford University School of Medicine, Stanford, CA, USA

Background: Taxanes are commonly used as a standard of care treatment for 1L mTNBC. Few studies have directly compared the effectiveness of nab-paclitaxel and paclitaxel in the real world setting, however. This study investigated the overall survival (OS) of nab-paclitaxel vs. paclitaxel as monotherapy in 1L treatment of mTNBC in routine practice.

Methods: A total of 200 patients in the Flatiron Health EHR-derived database were included based on a confirmed diagnosis of mTNBC from 1 Jan 2011 and 31 October 2016 and receipt of nab-paclitaxel or paclitaxel monotherapy as 1L treatment. The primary outcome, OS, was estimated by Kaplan-Meier methods and compared by the log-rank test and by univariate and multivariate Cox regression models. Time to next treatment (TTNT) was assessed as a secondary outcome.

Results: Compared with pts who received paclitaxel (n = 95), at baseline, those who received nab-paclitaxel (n = 105) were more likely to have been diagnosed at an earlier stage (I-III), have a treatment free ≤ 12 months (in pts with recurrent disease), adjuvant treatment with a taxane, a prior diagnosis of neuropathy and coverage by commercial healthcare insurance. Other characteristics were balanced between groups. Over 90% of pts with evaluable dosing data (179 of 195) received weekly doses of either taxane, with 100 mg/m^2 as the most common dose for nab-paclitaxel and 80 mg/m^2 for paclitaxel. Median OS was 11.2 months in pts treated with nab-paclitaxel and 10.8 months in paclitaxel-treated pts (log-rank P = 0.82). The OS hazard ratio (HR) from the adjusted Cox model was 0.90 (95% CI: 0.61, 1.32), indicating a similar risk of death between the two groups. The robustness of this result was confirmed in several sensitivity analyses. TTNT for nab-paclitaxel and paclitaxel was 4.7 and 4.3 months (log-rank P = 0.44), respectively, and did not differ in adjusted analyses (HR = 0.95 [95% CI: 0.65, 1.38]).

Conclusions: Nab-paclitaxel and paclitaxel monotherapy demonstrated similar outcomes, suggesting they may be considered interchangeable as 1L treatments for mTNBC.

Editorial acknowledgement: Editorial assistance was provided by Health Interactions.

Legal entity responsible for the study: F. Hoffmann-La Roche AG.

Funding: F. Hoffmann-La Roche AG.

Disclosure: T. Luhn, S. Chui, A. Hsieh, P. Bajaj, W. Hasnain, T.G.N. Ton: Employee: Genentech, Inc. Stocks: Roche. J. Yi: Consulting agreement: AbbVie, Inc. A. Mecke, A. Falgas: Employee and stock owner: Roche. All other authors have declared no conflicts of interest.

317P Clinical efficacy of eribulin as first- or second-line treatment for patients with recurrent HER2-negative breast cancer: A phase II randomized study (JBCRG-19)

K-I. Watanabe[1], K. Aogi[2], M. Kitada[3], T. Sangai[4], S. Ohtani[5], T. Aruga[6], H. Kawaguchi[7], T. Fujisawa[8], S. Maeda[9], T. Morimoto[10], S. Morita[11], N. Masuda[12], M. Toi[13], S. Ohno[14]

[1]Breast Surgery, Hokkaido Cancer Center, Sapporo, Japan, [2]Breast Oncology, Shikoku Cancer Center, Matsuyama, Japan, [3]Breast Disease Center, Asahikawa Medical University Hospital, Asahikawa, Japan, [4]General Surgery, Chiba University Graduate School of Medicine, Chiba, Japan, [5]Breast Surgery, Hiroshima City Hospital, Hiroshima, Hiroshima, Japan, [6]Breast Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [7]Breast Surgery, Matsuyama Red Cross Hospital, Matsuyama, Japan, [8]Breast Oncology, Gunma Prefectural Cancer Center, Gunma, Japan, [9]Breast Surgery, National Nagasaki Medical Center, Omura, Japan, [10]Breast Surgery, Yao Municipal Hospital, Yao, Japan, [11]Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [12]Breast Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [13]Surgery, Kyoto University-Graduate School of Medicine, Kyoto, Japan, [14]Breast Oncology Center, The Cancer Institute Hospital of JFCR, Tokyo, Japan

Background: Anthracycline- or taxane-based regimens are the standard early-line chemotherapy for metastatic breast cancer. However, adverse effects of these treatments, such as neutropenia, peripheral neuropathy, edema, and alopecia, are a concern. The EMBRACE study has shown that eribulin is effective for metastatic breast cancer, even as a late-line treatment. The aim of this study was to investigate the usefulness of eribulin as first- or second-line treatment.

Methods: Patients with recurrent HER2-negative breast cancer who had received previous chemotherapy including both an anthracycline and a taxane were eligible for this phase II study. They were randomly allocated to receive eribulin or treatment of physician's choice (TPC) as first- or second-line treatment. TPC was selected in advance from paclitaxel, docetaxel, nab-paclitaxel, and vinorelbine. The primary endpoint was progression-free survival (PFS). Secondary endpoints included time to treatment failure (TTF), response rate (RR), duration of response, and safety. (UMIN000009886).

Results: From May 2013 to January 2017, 72 patients were enrolled. The full analysis set comprised data from 58 patients (median age, 58 years; range, 33–82 years); 38 (65.5%) received first-line treatment and 20 (34.5%) received second-line treatment. 43 patients (74.1%) were ER- positive. The per protocol set comprised data from 57 patients. PFS, TTF, RR, and duration of response in both groups are shown in the table. The most common grade 3 or worse adverse events were neutropenia (6/27 [22.2%] in the eribulin group versus 5/31[16.1%] in the TPC group). The incidence of sensory neuropathy was low in both groups.

Table: 317P

		Eribulin (n = 26)	TPC (n = 31)	p-value
PFS	Median(M)	6.6(5.0-8.1)	4.2(0.8-7.6)	0.273
TTF	Median(M)	6.0(4.7-7.3)	3.6(2.3-4.9)	0.131
Tumor response	CR	0(0.0%)	0(0.0%)	0.190
	PR	5(19.2%)	6(19.4%)	
	SD	16(61.5%)	11(35.5%)	
	PD	5(19.2%)	13(41.9%)	
ORR		5(19.2%)	6(19.4%)	
Duration of response	Median(M)	3.0(2.1-3.9)	2.8(2.4-3.3)	0.794

Conclusions: Eribulin was not shown to be superior to TPC in terms of efficacy. However, patients in the eribulin group had slightly longer PFS and TTF.

Clinical trial identification: UMIN000009886.

Legal entity responsible for the study: Japan Breast Cancer Research Group (JBCRG).

Funding: Japan Breast Cancer Research Group (JBCRG).

Disclosure: K. Aogi: Honoraria: Chugai, Eisai, Sanofi, AstraZeneca, Taiho, Daiichi Sankyo, Ono, Otsuka, Nihon Medi-physics, Terumo, Becton Dickinson and Company; Research funding: Chugai, Eisai, Takeda and Sanofi. S. Ohtani: Speakers bureau: Chugai and Eisai. H. Kawaguchi: Honoraria: Chugai, AstraZeneca, Eisai, Kyowa-Kirin, Novartis, Taiho, Pfizer and Nippon Chemiphar; Consulting or advisory role: Chugai and AstraZeneca; Speakers bureau: Chugai, AstraZeneca, Eisai, Kyowa-Kirin, Novartis, Taiho, Pfizer and Nippon Chemiphar. S. Morita: Honoraria: Eisai and Taiho; Research funding: Eisai. N. Masuda: Honoraria: Chugai, Takeda, Pfizer and AstraZeneca; Research funding: Chugai, AstraZeneca, Kyowa-Kirin, MSD, Novartis, Pfizer, Eli-Lilly. M. Toi: Honoraria: Novartis, MSD, Takeda, AstraZeneca, Eisai, Genomic Health, Chugai, Taiho, Bayer, Eli Lilly, Daiichi Sankyo, Kiowa-Kirin, C&C Research Laboratories, Yakult, Sanofi, Shimadzu, Pfizer; Consulting or advisory role: Daiichi Sankyo, Kiowa-Kirin and Taiho; Research funding: Taiho, Chugai, Shimadzu, Astellas Phama, AFI technology and C&C Research Laboratories. S. Ohno: Speakers bureau: Chugai Pharmaceutical, Eisai, Pfizer, Novartis, Taiho, Kyowa-Kirin, AstraZeneca. All other authors have declared no conflicts of interest.

318P Clinical utility of hepatic arterial infusion chemotherapy for heavily pretreated metastatic breast cancer patients: A review of a single institution

M. Furuta[1], J. Watanabe[1], T. Aramaki[2]

[1]Division of Breast Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [2]Division of Radiology, Shizuoka Cancer Center, Shizuoka, Japan

Background: Liver metastasis is recognized as a risk factor for metastatic breast cancer (MBC). Hepatic arterial infusion chemotherapy (HAIC) is a treatment option for MBC in patients with extensive hepatic lesions; however, there is no standard regimen, and the effects have not been well discussed.

Methods: We reviewed our medical records of MBC to extract patients with resistance to standard systemic chemotherapies, critical liver metastasis, and who received HAIC with an FEM regimen (5-fluorouracil 333 mg/m^2 [weekly], epirubicin 30 mg/m^2 [every 4 weeks], and mitomycin-C 2.7mg/m^2 [every 2 weeks]) in our institute.

Results: We identified 58 patients who received HAIC (median age at initiation, 58 [30-80] years) in our institute between 2002 and 2017. Their ECOG performance (PS) statuses were as follows: PS0, 44; PS1, 10; and PS 2, 4. Their receptor statuses were as follows: hormone receptor positive (HR+)/HER2+, 9; HR+/HER2-, 38; HR-/HER2+, 4; HR-/HER2-, 7. The median number of systemic regimens (including endocrine therapy) prior to HAIC was 6 (2-17). The median number of liver metastases was 8 (1-≥20); the median maximum size of liver metastases was 5.2 cm (1.6-20.1). The median number of extrahepatic metastatic site was 2 (0-5). The median overall survival (days) was as follows: overall, 371 (95% confidence interval [CI] 260-475); HER2+, 441 (95% CI 166-652); HER2-, 344 (95% CI 279-475). The median time to progression of

intrahepatic lesions (days) was as follows: overall, 303 (95% CI 184-491); HER2+, 491 (95% CI 90-NR); HER2-, 298 (95% CI 184-387). An objective response (CR+PR) of intrahepatic lesions was observed in 37 patients (63.8%). The reasons for the discontinuation of HAIC included: progression of extrahepatic lesion(s), 20 (34.5%); progression of intrahepatic legion(s), 16 (27.6%); clinical progression, 7 (12.1%); transition to maintenance therapy, 6 (10.3%); catheter-related events, 5 (8.6%); and duodenal ulcer, 1 (1.7%).

Conclusions: HAIC with an FEM regimen offers an effective treatment for patients with liver metastasis from MBC that shows resistance to systemic therapy.

Legal entity responsible for the study: Junichiro Watanabe.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

319P A randomized, open label, phase II study of prophylactic octreotide (OCT) to prevent/reduce the frequency and severity of diarrhea in patients (pts) receiving lapatinib (LAP) with capecitabine (CAP) for the treatment of metastatic breast cancer (mBC)

P. Krivorotko[1], B. Karaszewska[2], S. Chan[3], M. Wieczorek-Rutkowska[4], T. Sarosiek[5], M.V. Shomova[6], E. Ovchinnikova[7], J.P. Zarate[8], C. Babanrao Pisal[9], L. Smith[10], A. Manikhas[11]

[1]Department of Breast Tumors, N.N.Petrov Research Inst. of Oncology, St. Petersburg, Russian Federation, [2]Oncology Outpatient Clinic, The Chemotherapy Clinic and the One Day Chemotherapy Department, Przychodnia Lekarska KOMED, Konin, Poland, [3]Clinical Oncology Department, Nottingham University Hospital NHS Trust, Nottingham, UK, [4]Chemotherapy Department, Copernicus PL Sp.z o.o Wojewodzkie Centrum Onkologii, Gdansk, Poland, [5]Department of Oncology, Magodent Szpital Elbląska, Warsaw, Poland, [6]Department of Oncology, Ryazan Regional Clinical Oncology Center, Ryazan, Russian Federation, [7]City Oncological Dispensary, Nizhny Novgorod Regional Hospital, Nizhny Novgorod, Russian Federation, [8]Breast - Kisqali, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [9]Biostatistics & Pharmacometrics, Novartis Healthcare Private Limited, Hyderabad, India, [10]Oncology Medical Affairs, Novartis Pharmaceutical Corporation, East Hanover, NJ, USA, [11]Breast Cancer Department, St. Petersburg, City Oncology Dispensary, St. Petersburg, Russian Federation

Background: The combination of LAP+CAP is approved for the treatment of pts with HER2+ mBC who progressed on prior therapy, which must have included anthracyclines, taxanes and trastuzumab. Octreotide long acting release (OCT) is approved for the treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid and vasoactive intestinal polypeptide-secreting tumors. Here we investigated the efficacy of the prophylactic use of OCT in the prevention or reduction of diarrhea associated with the treatment involving LAP+CAP.

Methods: Pts (N = 62) were randomized (1:1) to OCT (0.1mg/mL) + LAP (1250 mg/day) + CAP (2000 mg/m^2/day) (n = 30) or LAP+CAP (n = 32), between 17-Dec-2014 and 13-Jan-2016. The primary objective was to determine the efficacy of prophylactic OCT in reducing the proportion of pts experiencing diarrhea with a severity of ≥grade 2 based on NCI-CTCAE version 4.03 during the first 3 cycles. The secondary objectives were ORR, CBR and other safety. Pearson chi-square test was used to compare the superiority of OCT+LAP+CAP arm with LAP+CAP arm.

Results: All pts enrolled in the study (database lock: 13-Feb-2018) were female with a median age of 56.5 years, and the majority was non-Hispanic or Latino (98%). Seven (23.3%) pts in the OCT+LAP+CAP arm and 9 (28.1%) pts in the LAP+ CAP arm had at least one episode of ≥grade 2 diarrhea within the first 3 cycles. The difference between the 2 arms was -4.8% with 95% exact CI: (-29.2%, 20.0%) and was not statistically significant (P = 0.775). The ORR and CBR in OCT+LAP+CAP vs LAP+CAP arms was 20.0% vs 18.7%, and 23.3% vs 28.1%, respectively. Two (7%) pts from OCT+LAP+CAP arm and 3 (9%) pts from LAP+CAP arm, died due to the disease under study. The most common all grade adverse events in OCT+LAP+CAP and LAP+CAP (>15% in either arm), respectively, were diarrhea (59% vs 45%), palmar-plantar erythrodysesthesia syndrome (45% vs 33%), rash (14% vs 21%), asthenia (7% vs 21%) and anemia (3% vs 18%).

Conclusions: Prophylactic use of OCT did not result in a lower incidence of ≥grade 2 diarrhea in mBC pts receiving LAP+CAP. No new safety issues were identified.

Clinical trial identification: NCT02294786.

Editorial acknowledgement: Medical editorial assistance was provided by Sai Krishna Arepalli, PhD (Novartis Healthcare Pvt Ltd).

Legal entity responsible for the study: Novartis Healthcare Private Limited.

Funding: Novartis Healthcare Private Limited.

Disclosure: P. Krivorotko: Personal fees: Novartis, during the conduct of the study and outside the submitted work. J.P. Zarate, C. Babanrao Pisal, L. Smith: Employee: Novartis. All other authors have declared no conflicts of interest.

320P Nab-paclitaxel (nab-P) in metastatic breast cancer (MBC) in elderly patients: A real life setting (NEREIDE study)

V. Adamo[1], G.R.R. Ricciardi[1], S. Schifano[1], A. Russo[2], V. Gebbia[3], L. Blasi[4], D. Giuffrida[5], G. Scandurra[6], A. Savarino[7], A. Butera[8], N. Borsellino[9], F. Verderame[10], M. Caruso[11]

[1]Department of Human Pathology University of Messina, Medical Oncology Unit A.O. Papardo, Messina, Italy, [2]Department of Surgical, Oncological, and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy, [3]La Maddalena Clinic for Cancer, Medical Oncology Unit, Palermo, Italy, [4]ARNAS Civico, Medical Oncology Unit, Palermo, Italy, [5]Instituto Oncologico del Mediterraneo, Medical Oncology Unit, Viagrande, Italy, [6]Cannizzaro Hospital, Medical Oncology Unit, Catania, Italy, [7]Ospedale Barone Lombardo-Presidio Ospedaliero Canicattì, Medical Oncology Unit, Canicattì, Italy, [8]Azienda Ospedaliera St. Giovannino di Dio, Medical Oncology Unit, Agrigento, Italy, [9]Buccheri La Ferla Fatebenefratelli Hospital, Medical Oncology Unit, Palermo, Italy, [10]Medical Oncology Unit, Cervello Hospital, Palermo, Italy, [11]Medical Oncology Unit, Humanitas Centro Catanese di Oncologia, Catania, Italy

Background: Elderly patients (pts) with MBC are under-represented in clinical studies and treatment is largely based on limited retrospective subgroup analyses. However, the 3 ESO-ESMO guidelines for Advanced Breast Cancer suggest that the management decisions should not be based on age alone.

Methods: This is an observational, retrospective, multicenter study conducted in 11 Oncology Sicilian Centers that evaluated safety and efficacy of nab-P in pts with HER2 negative MBC with age ≥ 65 years. We included 70 pts. Intrinsic molecular subtype: Luminal A (18.8%), Luminal B HER-2 negative (62.5%) and Triple negative (18.8%). The most common metastatic sites were: visceral plus bone (31.4%), bone (15.7%), lung (10%), visceral plus lymph nodes (10%). 33% of pts received nab-P as 4th line treatment. 87.1% of all pts received nab-P at doses 260 mg/m^{2}3-weekly and 12.9% received nab-P 125 mg/m^{2}weekly. 28.6%, 25.7% and 26.2% of pts received previous treatment with taxanes in the neo-adjuvant and metastatic setting, respectively. Primary endpoint was safety of nab-P treatment. Secondary endpoints were overall response rate (ORR), progression free survival (PFS) and overall survival (OS).PFS and OS curves were estimated using the Kaplan-Meier method. ORR was defined as complete or partial response (CR+PR) according to RECIST 1.1 criteria. Adverse events (AEs) were assessed according to CTCAEv4.0.

Results: Median (m) age of pts who received nab-P: 67 years (65-83). mECOG PS: 1 (range 0-2). The m cycles administrated was 6 (range 1-21). 35.5% of pts had a dose reduction and 11.5% of pts had treatment interruptions due to toxicity. The most frequent AEs were G2-3 and were observed in 47% of pts. The main toxicities were fatigue (61.5%), neuropathy (53.8%) and leukopenia (39.1%) and occurred in the 85.7% of pts treated with 3-weekly nab-P. ORR was 31.3% (CR in 6.3% and PR in 25% of pts). 39.1% of pts reported a stable disease. mPFS was 6 months (95% CI 2-38) and mOS was 40.5 months (95% CI 7-255).

Conclusions: Our real-life study showed that the treatment with nab-P is an effective and well-tolerated regimen in MBC elderly pts, even if previously treated with other taxanes. In particular, our data indicate that the weekly nab-P can be safely administered in elderly MBC pts.

Legal entity responsible for the study: Vincenzo Adamo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

321P Response evaluation of cancer therapeutics in metastatic breast cancer to the bone: A single arm phase II study of whole-body magnetic resonance imaging

M. Kosmin[1], A.R. Padhani[2], A. Gogbashian[2], D. Woolf[3], M-L. Ah-See[1], P. Ostler[4], S. Sutherland[1], D. Miles[1], J. Noble[5], A. Marshall[6], J. Dunn[6], A. Makris[1]

[1]Breast Cancer Research Unit, Mount Vernon Cancer Centre, Northwood, UK, [2]Radiology, Paul Strickland Scanner Centre, Northwood, UK, [3]Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [4]Clinical Oncology, Mount Vernon Cancer Centre, Northwood, UK, [5]Medical Oncology, The Royal Marsden Hospital, Sutton, UK, [6]Warwick Clinical Trials Unit, University of Warwick, Coventry, UK

Background: Accurate and reliable evaluation of response to systemic anti-cancer therapy (SACT) is fundamental in the management of metastatic breast cancer (MBC). CT and bone scans (BS) have significant limitations in assessing SACT response in bone disease in MBC, whereas whole-body magnetic resonance imaging (WB-MRI) shows significant promise. Published retrospective data show that the addition of WB-MRI to body CT alters treatment decisions in MBC. The primary objective of this study was to evaluate whether WB-MRI identifies progressive disease (PD) earlier than CT scans in patients with bone-only MBC.

Methods: Participants were enrolled when starting first or subsequent SACT for bone-only MBC, as established initially by BS and CT thorax, abdomen and pelvis. Baseline WB-MRI was performed within 2 weeks of trial entry. CT and WB-MRI were performed every 12 weeks until definitive PD was evident in one or both modalities. At PD, BS was assessed for bone disease progression. Radiologists independently reported CT, WB-MRI or BS and were blinded to the other modalities. Participant questionnaires were undertaken at weeks 12 and 36 to evaluate tolerability and satisfaction with WB-MRI and CT.

Results: Forty-five participants were enrolled, with a median time on-study of 24 weeks (range 1-84 weeks). Two patients were excluded due to unequivocal liver metastases on

baseline WB-MRI; two had clinical progression before imaging PD; one was lost to follow up. Twenty-nine have had PD on imaging; eleven continue on-study. In 65.5%, PD was evident on WB-MRI only; 34.5% had PD on CT and WB-MRI concurrently; none had PD on CT only (McNemar's test $p < 0.0001$). PD on BS was reported in 55.6% of cases of bone CT/MRI progression. Overall questionnaire response rate was 63.8%. No differences were found between CT and WB-MRI in levels of concern, comfort or pain at week 12 or 36. All participants reported satisfaction levels as 'good' or 'very good' for both modalities.

Conclusions: WB-MRI identifies PD before CT in most patients with bone-only MBC. Further studies will evaluate whether earlier identification of PD with WB-MRI and earlier SACT changes can lead to improved patient outcomes.

Clinical trial identification: NCT03266744.

Legal entity responsible for the study: East and North Hertfordshire NHS Trust.

Funding: Paul Strickland Scanner Centre.

Disclosure: M.-L. Ah-See: Consulting or advisory role: AstraZeneca, Novartis, Pierre Fabre, Merck Sharp and Domme; Honoraria: Roche. A. Marshall: Educational research grant: Bayer AG outside of this submitted work that was used in part to pay for salary for research undertaken. All other authors have declared no conflicts of interest.

322P Anti-tumor cell activity and in vitro profile of the next generation CXCR4 antagonist Balixafortide

J. Zimmermann[1], T. Remus[2], G. Lemercier[2], D. Barker[3], D. Obrecht[1], G. Gambino[1], G. Douglas[2]

[1]BUP, Polyphor Ltd, Allschwil, Switzerland, [2]Clinical Development, Polyphor Ltd, Allschwil, Switzerland, [3]Clinical Development, Polyphor AG, Allschwil, Switzerland

Background: Balixafortide is a very potent, well tolerated and highly selective next generation CXCR4 antagonist derived over the past decade through multiple rounds of optimization starting from the natural product polyphemusin. Clinical proof-of-concept was achieved in a Ph 1/2 study in combination with Eribulin in metastatic HER2-neg breast cancer. The anti-cancer effects and pluripotent action of Balixafortide may include sensitization of tumor cells to chemotherapy, suppression of metastatic spread, inhibition of angiogenesis, and activation of the immune system.

Methods: Balixafortide was tested in a HTRF-based CXCR4 ligand binding assay, in functional assays (Calcium flux and beta arrestin), and further profiled in a large panel of other receptors including CXCR7. Effects on tumor cell sensitization were followed with an intracellular pERK / pAKT signaling assay. Tumor cell migration was assessed by chemotaxis assays, and inhibition of angiogenesis was determined by HUVEC sprouting. Evidence for immune cell activation came from evaluation of corresponding marker such as interferon gamma. Balixafortide was in detail profiled in an extensive in vitro ADME panel.

Results: Balixafortide binds CXCR4 with high affinity (IC50 < 10nM). It blocks beta arrestin recruitment and Calcium flux with IC50s < 10nM. A high 1000-fold selectivity window was demonstrated in a large panel of receptors including CXCR7. Balixafortide potently inhibits pERK / pAKT signaling in the lymphoma lines Namalwa (IC50 < 200 nM) and Jurkat (IC50 < 400 nM). Balixafortide efficiently blocks SDF-1 dependent chemotaxis of MDA MB 231 breast cancer cells (IC50 < 20 nM), Namalwa and Jurkat cells (IC50 < 10 nM). Receptor occupancy wash-out studies with competitive antibody 12G5 revealed prolonged binding of Balixafortide to CXCR4. In addition, Balixafortide was optimized for favorable mouse and human ADME properties with balanced plasma protein binding, greater plasma and microsomal stability.

Conclusions: Balixafortide is a product of an extensive optimization process which started from polyphemusin and now represents a favorable balance between ADMET properties, potency and tolerability which allows high and frequent dosing of a CXCR4 antagonist in cancer patients.

Legal entity responsible for the study: Polyphor Ltd.

Funding: Has not received any funding.

Disclosure: J. Zimmermann: Employee and shareholder: Polyphor Ltd. T. Remus, G. Lemercier, D. Barker, D. Obrecht, G. Douglas, G. Gambino: Employee: Polyphor Ltd.

323P Subcutaneous trastuzumab (H SC) with intravenous pertuzumab (P IV) and docetaxel (D IV) in HER2-positive advanced breast cancer (BC): MetaPHER second interim analysis

S. Kümmel[1], C.A. Tondini[2], J. Abraham[3], Z.I. Nowecki[4], B. Itrych[5], E. Hitre[6], B. Karaszewska[7], A. Juarez[8], F. Morales-Vásquez[9], J.M. Pérez García[10], S. Cardona-Huerta[11], D. Heinzmann[12], J. He[13], A.N. Duc[12], A. Crepelle-Fléchais[12], M. Martín[14]

[1]Breast Unit, Kliniken Essen-Mitte, Essen, Germany, [2]Department of Onco-Hematology, ASST Papa Giovanni XXIII, Bergamo, Italy, [3]Department of Clinical Oncology, Velindre Cancer Centre, Cardiff, UK, [4]Centrum Onkologii-Instytut, Klinika Nowotworów Piersi i Chirurgii Rekonstrukcyjnej, Warsaw, Poland, [5]Department of Oncology, Magodent, Warsaw, Poland, [6]Department of Medical Oncology and Clinical Pharmacology "B", National Institute of Oncology, Budapest, Hungary, [7]Przychodnia Lekarska, KOMED, Konin, Poland, [8]Medical Oncology, CME Consultorio De Medicina Especializada, Mexico City, Mexico, [9]FUCAM, Instituto Nacional de Cancerologia de Mexico, Mexico City, Mexico, [10]Medical Oncology, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [11]Centro de Cancer de Mama, Hospital Zambrano-Helion, Tecnológico de Monterrey, Monterrey, Mexico, [12]Global Product Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland, [13]Global Product Development, Genentech, Inc., South San Francisco, CA, USA, [14]Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain

Background: H SC (Herceptin® SC) was approved based on the HannaH study (Ismael Lancet Oncol 2012). The single-arm, open-label MetaPHER study (NCT02402712) is the first large Phase IIIb study to evaluate the safety and tolerability of H SC + P IV (PERJETA®) + D IV as first-line treatment in patients (pts) with HER2-positive metastatic/locally advanced BC. Here, we report interim safety and preliminary efficacy.

Methods: Pts are ≥18-year-old females whose disease was not previously treated with systemic non-hormonal anticancer therapy. Pts receive 600 mg fixed-dose H SC q3w + 840 mg loading/420 mg maintenance P IV q3w + ≥6 cycles D IV q3w (>6 at investigator's discretion; 75 mg/m^2 initial dose) until disease progression (PD), unacceptable toxicity, withdrawal of consent, death or predefined study end. The primary endpoint is overall and cardiac safety and tolerability. Adverse events (AEs) are graded per NCI–CTCAE v4.0.

Results: Of 418 enrolled pts, 412 started study treatment; 330 (196 on treatment, 134 in follow-up [FU]) were on study by data cutoff (5 Jan 18). Median FU duration was 16.3 months. In the safety population 406/412 pts (98.5%) experienced ≥1 any-grade AE; 213 (51.7%) grade ≥3 AEs; 101 (24.5%) serious AEs (SAEs); and 86 (20.9%) AEs leading to P IV, H SC or D IV discontinuation. 47 pts (11.4%) died: 38 (9.2%) due to PD; 9 (2.2%) due to AEs; none from cardiac death. AEs of interest included grade ≥3 cardiac AEs (3 pts; 0.7%); ejection fraction decrease to < 50% and ≥10% points from baseline (32; 7.8%); investigator-reported administration-related and local injection-site reactions (80; 19.4%, including 19 [4.6%] with an AE related to H SC only). No MedDRA-preferred-term congestive heart failure was reported. 249/336 pts with baseline measurable disease had an objective response (74.1% [95% CI 69.1–78.7]). The clinical benefit rate was 81.1% (334/412 pts [95% CI 77.3–84.9]). 1-year progression-free survival was 63.1% (95% CI 58.4–68.2).

Conclusions: Safety and efficacy profiles of H SC + P IV as first-line treatment for pts with HER2-positive advanced BC were consistent with the known profiles for the H IV + P IV combination, and no new safety signals identified. The final analysis is planned for 2019.

Clinical trial identification: NCT02402712.

Editorial acknowledgement: Support for third-party writing assistance for this abstract, furnished by Helen Keyworth, PhD, of Health Interactions, was provided by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: S. Kümmel: Honoraria: Roche, Celgene, Novartis, Amgen and Daiichi Sankyo; Consultant/advisor: Roche; Travel/accommodations/expenses: Roche and Celgene. C.A. Tondini: Consultant/advisor: Myriad Genetics; Speakers' bureau: Amgen; Travel/accommodations/expenses: Roche/Genentech, Novartis and Celgene. J. Abraham: Honoraria, including travel expenses for advisory roles: Novartis and Genomic Health. Z.I. Nowecki: Travel/accommodations/expenses: Roche/Genentech, Novartis and Amgen. A. Juarez: Honoraria, support for national and international congresses and clinical trials: Roche. F. Morales-Vásquez: Honoraria, educational grants and Speakers' bureaus: Roche, AstraZeneca, Pfizer, MSD, Novartis, Teva and Eli Lilly. S. Cardona-Huerta: Honoraria for advisory and consulting/speaker roles: Roche. D. Heinzmann: Employee: F. Hoffmann-La Roche; Shares: Roche. J. He: Employee: F. Hoffmann-La Roche. A.N. Duc, A. Crepelle-Fléchais: Employee: F. Hoffmann-La Roche. M. Martín: Honoraria: Roche, Genentech, Novartis, Lilly and AstraZeneca; Research grants: Roche and Novartis. All other authors have declared no conflicts of interest.

324P Settings-based efficacy comparison of trastuzumab biosimilars in breast cancer: A systematic literature review

H.S. Rugo[1], G. Curigliano[2], F. Cardoso[3], W.J. Gradishar[4], M. Pegram[5], C.H.H. Barrios[6], J. Cortes Castan[7], E. Pennella[8], R. Muniz[8]

[1]Breast Cancer Center, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [2]Early Drug Development for Innovative Therapies Division, Istituto Europeo di Oncologia, Milan, Italy, [3]Breast Unit, Champalimaud Foundation Cancer Center, Lisbon, Portugal, [4]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [5]Medicine, Stanford Comprehensive Cancer Institute, Stanford, CT, USA, [6]School of Medicine, PUCRS-Pontifícia Universidade do Rio Grande do Sul, Porto Alegre, Brasil, [7]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [8]Medical Affairs, Mylan, Canonsburg, PA, USA

Background: The US Food and Drug Administration (FDA) recently approved the trastuzumab biosimilar Ogivri™ (trastuzumab-dkst) for treatment of breast cancer based on physicochemical and functional biosimilarity and phase 3 efficacy and safety data in metastatic breast cancer (MBC). Clinical trials evaluating trastuzumab biosimilars for treatment of ERBB2-positive breast cancer have assessed bioequivalence through comparative efficacy outcomes as neoadjuvant therapy for early-stage breast cancer (EBC) or first-line therapy for MBC. We conducted a systematic review to examine whether demonstrating bioequivalence in terms of efficacy is different in EBC vs MBC.

Methods: MEDLINE and conference abstracts were identified using the search terms "biosimilar" AND "trastuzumab" from 1 January 2013 to 14 March 2018. Abstracts and manuscripts were manually reviewed to assess availability of efficacy data comparing the proposed biosimilar with reference trastuzumab.

Results: A total of 84 results were obtained. After selection for studies with comparative clinical efficacy results, 8 phase 3 clinical trials for 6 proposed biosimilars were included in the final analysis: 4 in EBC (primary efficacy outcome, pathologic complete response [pCR]) and 4 in MBC (primary efficacy outcome, overall response rate [ORR]). In all trials, the proposed biosimilar was equivalent to reference trastuzumab in terms of efficacy. Two biosimilars (CT-P6 [2 different formulations], Celltrion, Incheon, Republic of Korea; PF-05280014, Pfizer, New York, NY) showed equivalent efficacy in both the EBC and MBC settings.

Conclusions: All biosimilars assessed demonstrated equivalent efficacy to reference trastuzumab, regardless of clinical setting. Two biosimilars demonstrated equivalent efficacy in both the EBC and MBC settings. Although the FDA and European Medicines Agency determine biosimilarity based on totality of evidence, both the EBC and MBC settings appear to have similar sensitivity and be appropriate for determination of equivalent efficacy based on regulatory guidelines and clinical results. Together, these data support extrapolation between settings.

Editorial acknowledgement: Editorial assistance was provided under the direction of the authors by Tyler Rork, PhD, and Jennifer Rossi, MA, ELS, MedThink SciCom, with support from Mylan Inc.

Legal entity responsible for the study: Mylan Inc.

Funding: Mylan Inc.

Disclosure: H.S. Rugo: Travel, accommodations, expenses: Puma Biotechnology, Mylan, Lilly, Pfizer, Merck, Amgen, Teva research funding (all to the UC Regents): Merck, Pfizer, Lilly, Novartis, Macrogenics, Eisai, Genentech/Roche, OBI Pharma. G. Curigliano: Speaker fees: Pfizer, Novartis, Roche and Lilly. F. Cardoso: Consultant or advisor: Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Seattle Genetics, and Teva. J. Cortes Castan: Honoraria: Roche, Novartis, Eisai, Celgene, Pfizer; Consultant or advisor: Roche, Celgene, AstraZeneca, Cellestia Biotech, Biothera, and Merus. E. Pennella, R. Muniz: Employee of Mylan Inc. and may hold stock with the company. All other authors have declared no conflicts of interest.

325P Pertuzumab, trastuzumab and taxane combination for visceral organ metastatic patients: Real life practice results

E. Esin[1], O.B. Cakmak Oksuzoglu[2], A. Bilici[3], I. Cicin[4], S. Aksoy[5], A. Alacacioglu[6], M.A. Kaplan[7], D. Cabuk[8], A.T. Sumbul[9], S. Paydas[10], A. Sakin[11], Ö. Er[12], T. Korkmaz[13], N. Yildirim[14], M. Artac[15], H. Harputluoglu[16], P.F. Yumuk[17], G. Basaran[13], B. Oyan Uluc[18], U. Demirci[2]

[1]Medical Oncology, University of Health Sciences, Ankara Oncology Education and Research Hospital, Ankara, Turkey, [2]Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey, [3]Department of Medical Mer, Medipol Mega Hospitals Complex, Istanbul, Turkey, [4]Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Turkey, [5]Medical Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [6]Medical Oncology, Ataturk Training and Research Hospital, Izmir Katip Celebi University, Izmir, Turkey, [7]Medical Oncology, Dicle University, Diyarbakir, Turkey, [8]Medical Oncology, Kocaeli University, Kocaeli, Turkey, [9]Medical Oncology, Baskent University Faculty of Medicine Adana Uygulama Ve Arastirma Mer, Adana, Turkey, [10]Department of Medical Oncology, Faculty of Medicine, Cukurova University, Adana, Turkey, [11]Department of Medical Oncology, Okmeydanı Education and Research Hospital, Istanbul, Turkey, [12]Medical Oncology, Acıbadem Maslak Hastanesi, Istanbul, Turkey, [13]Medical Oncology, Istanbul Acibadem University, Istanbul, Turkey, [14]Oncology, Gaziantep Dr. Ersin Arslan Goverment Hospital, Gaziantep, Turkey, [15]Medical Oncology, Necmettin Erbakan University, Konya, Turkey, [16]Medical Oncology, Inonu University Turgut Ozal Institute, Diyarbakir, Turkey, [17]Medical Oncology, Marmara University, Istanbul, Turkey, [18]Medical Oncology, Acibadem Antunizade Hospital, Istanbul, Turkey,

Background: Anti-HER2 agents were a breakthrough in the treatment of HER2-enriched breast cancer (BC). In this study, we aimed to describe the real-life efficacy and safety of pertuzumab-trastuzumab-taxane (PTT) combination in BC patients.

Methods: This study was conducted by the Turkish Oncology Group and reached 35 centers nationwide. 309 visceral metastatic, and trastuzumab naive patients who received first line PTT were included.

Results: Patients' characteristics and treatment details are summarized in the table. Median progression-free survival (PFS) was 28.5 months (95% CI:15.6-41.4), while median overall survival (OS) was 40.3 months (95%CI: 26.9-53.7). Brain metastatic patients (n = 13, 4.2%) had worse PFS (16.8m vs. 28.5m; HR:3.9, 95% CI:1.7-9.2, p = 0.002) and OS (26.7m vs. 40.3m; HR:3.2, 95% CI:1.3-7.6, p = 0.009). Elderly patients (>65y) had significantly lower OS results (19.8m vs. 40.3m; HR:0.4, %95 CI:0.2-0.8, p = 0.01). Docetaxel was the choice in 268 patients (86.7%), while 41 patients (13.3%) received paclitaxel. There was no statistically significant difference in PFS (28.5 m vs. 24.1 m; p = 0.61) and OS (40.3 m vs. NR; p = 0.17) between taxane groups. Additionally, ≥10 cycles of docetaxel were not associated with improvement in outcomes compared with 6-10 cycles. One treatment-related death due to sepsis was noted. In 8 patients (2.6%), 5-40% ejection fraction decrease from baseline was detected without any sign of heart failure.

Table: 325P Demographic characteristics and treatment details

	N = 309	%
Median age (year, range)	51 (22-82)	
>65 years-old patients	39	12.6
De-novo metastatic patients	258	83.5
Histopathology		
IDC	290	93.9
ILC	3	1
Mixt	5	1.6
Others	11	3.5
Hormone receptor status		
ER and/or PR positive	170	55.2
ER/PR negative	138	44.8
Unknown	1	0.3
Metastatic site distribution		
Liver ± LN/skeletal	112	36.3
Lung ± LN/skeletal	120	38.8
Brain only	6	1.9
Brain + liver + lung	7	2.3
Liver + lung	16	5.2
Other	48	15.5
Only skeletal or only LN	-	-
Prior therapies		
Prior anthracyclines	51	16.5
Prior trastuzumab	NA	NA
Treatment details		

Continued

Table: 325P *Continued*

	N = 309	%
	Median number of cycle (range)	
Pertuzumab-trastuzumab	10 (1-75)	
Docetaxel	6 (1-23)	
Paclitaxel	3 (1- 26)	

IDC: Invasive Ductal Carcinoma ILC: Invasive lobular carcinoma LN: Lymph Node

Conclusions: This real-life practice population differs from the CLEOPATRA study in terms of visceral only metastatic disease, and inclusion of brain metastatic patients. Regardless of these negative prognostic characteristics, results are concordant with the pivotal study. Elderly patients had overall lower PFS, which necessitates further investigation of pertuzumab-trastuzumab combination with cytotoxic/antihormonal therapies. To our knowledge, this is the largest scale real-life clinical practice study of PTT to date.

Legal entity responsible for the study: Ece ESIN, on behalf of Turkish Oncology Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

326P Effectiveness of trastuzumab emtansine (TDM1) in patients with HER2-positive advanced breast cancer (ABC) progressing after taxane plus pertuzumab plus trastuzumab

B. Conte[1], A. Fabi[2], F. Poggio[3], E. Blondeaux[1], C. Dellepiane[1], A. D'Alonzo[1], A. Staiano[1], G. Buono[4], G. Arpino[4], V. Magri[5], G. Naso[5], D. Presti[6], S. Mura[7], A. Fontana[8], F. Cognetti[2], C. Molinelli[1], S. Pastorino[1], C. Bighin[1], M. Lambertini[3], L. Del Mastro[1]

[1]Medical Oncology, Ospedale Policlinico San Martino, Genoa, Italy, [2]Medical Oncology, Istituto Nazionale Tumori Regina Elena, Rome, Italy, [3]Medical Oncology, Institut Jules Bordet, L'Université Libre de Bruxelles, Brussels, Belgium, [4]Medical Oncology, AOU Policlinico Federico II, Naples, Italy, [5]Medical Oncology, Policlinico Umberto I, Rome, Italy, [6]Medical Oncology, Istituto Fondazione Maugeri, Pavia, Italy, [7]Medical Oncology, Ospedale Santissima Annunziata, Sassari, Italy, [8]Medical Oncology, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

Background: In patients with HER2-positive ABC who were previously treated with taxane and trastuzumab without pertuzumab, TDM1 showed a progression free survival (PFS) of 9.6 months and an overall survival (OS) of 29.9 months. Paucity of data is available on the efficacy of TDM1 in patients progressing after the current standard first-line therapy in this setting, based on the association of a taxane plus trastuzumab and pertuzumab (i.e. the TPH regimen). The present study aims to evaluate the effectiveness of TDM1 after first-line TPH.

Methods: The Gruppo Italiano Mammella (GIM) 14/BIOMETA is a retrospective/prospective multicenter study on treatment patterns and outcomes of patients with ABC. The present analysis was performed on patients who received second-line TDM1 after previous TPH between January 2012 and March 2017. Median PFS, 1-year OS (i.e. percentage of patients alive 1 year after the starting of TDM1) and clinical benefit rate (CB) were calculated. Descriptive statistics are reported with point estimated and 95% CIs. PFS was estimated with the Kaplan-Meier method.

Results: Out of 1858 patients included in the GIM14/BIOMETA study, 70 were eligible for the present analysis. Median age was 54 years; 36 patients (51%) had hormone receptor-positive/HER2-positive disease, and 27 (39%) had visceral involvement. All patients received TPH in the first-line setting, and 35 (50%) received taxane and trastuzumab in the adjuvant setting. At the time of data cutoff (April 30, 2018; median duration of follow-up 17.8 months), 30 patients (43%) were still receiving TDM1. Disease progression was the reason for treatment discontinuation in the remaining cases. Median PFS was 8.5 months (95% confidence intervals [CI] 5.3-12 months), and CB rate was 73%. One-year survival rate was 91%.

Conclusions: Our findings suggest that TDM1 is effective in patients progressing after TPH. A better performance was observed as compared to data previously published on TDM1 effectiveness after first-line TPH.

Clinical trial identification: NCT02284581.

Legal entity responsible for the study: Consorzio Oncotech.

Funding: Roche.

Disclosure: L. Del Mastro: Honoraria: Ipsen, Roche, Pfizer, Novartis, Eli Lilly, Eisai. All other authors have declared no conflicts of interest.

327P Survival of HER2-positive advanced breast cancer patients treated with lapatinib plus capecitabine: A national population-based study: Long-term analysis

B. Jagielska[1], P. Tokajuk[2], T. Pieńkowski[3], A. Czubek[1], M.J. Krzakowski[4], M.Z. Wojtukiewicz[5]

[1]Department of Oncology Diagnostics, Cardioncology and Palliative Medicine, Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology (MCMCC), Warsaw, Poland, [2]Clinical Oncology, Comprehensive Cancer Center Bialostockie Centrum Onkologii, Bialystok, Poland, [3]Onkologia Kliniczna, Radomskie Centrum Onkologii, Radom, Poland, [4]Department of Lung & Thoracic Tumours, The Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland, [5]Clinical Oncology, Comprehensive Cancer Center Bialostockie Centrum Onkologii, Bialystok, Podlaskie, Poland

Background: In Poland, governmental policy was to offer a uniform, national therapeutic programme for the treatment of HER2-positive advanced breast cancer (ABC) patients (pts). Accordingly, the Polish Breast Cancer Treatment Programme was introduced. Herein, we present first results of this effort from the cohort of previously-treated patients who underwent anti-HER2 palliative therapy with lapatinib plus capecitabine.

Methods: The aim of the study was to assess the population-based value of lapatinib plus capecitabine therapy of HER2-positive ABC patients treated within the Polish Breast Cancer Treatment Programme during the years 2008-2015. Patients have been prospectively enrolled into aforementioned programme and treated according to the specified protocol. We used Kaplan-Meier method to evaluate progression-free survival (PFS), time to tumor progression (TTP) and overall survival (OS). The effects of clinical and demographic factors on PFS and OS were assessed using Cox's proportional hazards regression model.

Results: A total of 1018 HER2-positive ABC women were enrolled into the Polish Breast Cancer Treatment Programme on a national level. Patients who progressed after regimens that included, but were not limited to, anthracyclines, taxanes, and trastuzumab were eligible to this study. Median age of the patients was 56.6 years (range, 22.8 to 86.1). Previous adjuvant therapy: 35.7% pts; ER(+)/PgR(+): 47.5% pts; number of metastatic sites $\geq$2: 45.9% pts. The median PFS was 6.4 months and median TTP was 6.7 months. The median OS was 11.76 months (range, 0.36-70.32). The overall response rate was 13%. Cox regression model data will be presented.

Conclusions: To our knowledge this study represents one of the first reports assessing the population-based value of a lapatinib/capecitabine treatment in clinical practice. Our data essentially corroborated findings obtained from randomized clinical trials. It seems that treatment with lapatinib and capecitabine is associated with a meaningful clinical effectiveness and therefore warrants consideration in the treatment algorithm of HER2-positive ABC patients.

Legal entity responsible for the study: Beata Jagielska.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

328P Ribociclib (RIBO) + letrozole (LET) in premenopausal patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC) with no prior endocrine therapy (ET) for ABC: Preliminary subgroup results from the phase IIIb CompLEEment-1 trial

H. Abdel-Razeq[1], P.H. Cottu[2], A. Ring[3], M. De Laurentiis[4], J. Lu[5], H.A. Azim[6], C. Zamagni[7], K. Zhou[8], J. Wu[8], L. Menon[8], M. Martín[9]

[1]Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan, [2]Department of Medical Oncology, Institut Curie, Paris, France, [3]Medical Oncology, The Royal Marsden NHS Foundation Trust, Sutton, UK, [4]Department of Breast and Thoracic Oncology, Istituto Nazionale Tumori, Naples, Italy, [5]Keck School of Medicine, Division of Medical Oncology, University of Southern California, Los Angeles, CA, USA, [6]Clinical Oncology, Cairo Oncology Center, Cairo University-CairoCure, Cairo, Egypt, [7]Breast and Gynaecological Medical Oncology Unit, Policlinico S. Orsola-Malpighi - "F. Addarii", Bologna, Italy, [8]Novartis Pharmaceuticals, East Hanover, NJ, USA, [9]Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain

Background: CDK4/6 inhibitor RIBO significantly improved progression-free survival in combination with ET versus placebo + ET in pre- and postmenopausal women with HR+, HER2– ABC and no prior therapy for advanced disease in the pivotal phase 3 MONALEESA-7 and MONALEESA-2 trials (Tripathy et al. SABCS 2018; Hortobagyi et al. NEJM 2016). Here, we report additional safety data for RIBO+LET in premenopausal female pts enrolled in CompLEEment-1, an open-label, phase 3b trial evaluating RIBO+LET as first-line therapy in an expanded pt population.

Methods: Premenopausal pts with HR+, HER2– ABC, $\leq$1 line of prior chemotherapy, and no prior ET for ABC received RIBO (600 mg/day, 3 wk on/1 wk off) + LET (2.5 mg/day) and goserelin (3.6-mg subcutaneous implant every 28 days). The primary outcome was safety and tolerability. A pre-planned interim analysis was conducted $\sim$15 months after first pt first visit.

Results: Of the first 1,008 pts enrolled who completed 56 days of follow-up or discontinued before data cut-off, 153 were premenopausal women. Median age was 45.0 years

and the majority of pts (99.3%) had an Eastern Cooperative Oncology Group performance status ≤1; 40.5% had stage IV disease at diagnosis. Bone (73.9%), lung (31.4%), and liver (30.7%) were the most common metastatic sites. The most frequent adverse events (AEs) were neutropenia (53.6%), nausea (30.1%), hot flush (20.9%), headache (17.0%), and asthenia (16.3%). The most frequent grade ≥3 AE was neutropenia (34.0%). QT prolongation was infrequent (2.0%). Dose adjustment/treatment interruption due to AEs was required for 48.4% of pts. Four patients (2.6%) discontinued treatment due to AEs.

Conclusions: Initial safety results from CompLEEment-1 demonstrate the tolerability of RIBO+LET + ovarian functional suppression in premenopausal women, consistent with previous reports. NCT02941926.

Clinical trial identification: NCT02941926.

Editorial acknowledgement: Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals. We thank Elise Blankenship, PhD, ProEd Communications, Inc., for her medical editorial assistance with this abstract.

Legal entity responsible for the study: Novartis Pharmaceuticals.

Funding: Novartis Pharmaceuticals.

Disclosure: P.H. Cottu: Consulting or advisory role: Novartis and Pfizer; Travel, accommodations, expenses: Novartis, Pfizer, Roche; Honoraria: AstraZeneca, NanoString Technologies, Novartis, Pfizer, Roche; Research funding: AstraZeneca, Genentech/Roche, Novartis, Pierre Fabre, and Pfizer. A. Ring: Consulting or advisory role: Pfizer and Roche; Honoraria: AstraZeneca, Lilly, Novartis, Pfizer, Roche; Research funding: AstraZeneca. M. De Laurentiis: Consulting or advisory role: AstraZeneca, Celgene, Lilly, Novartis, Pfizer, Roche Honoraria: AstraZeneca, Celgene, Novartis, Pfizer, and Roche. J. Lu: Personal fees: Novartis; Personal fees from outside the submitted work; Syndex. H.A. Azim: Employment: Innate, France (immediate family member); Consulting or advisory role: AstraZeneca, Bristol-Myers Squibb, Janssen, MSD, Novartis, Pfizer, Roche; Honoraria: Amgen, AstraZeneca, Bristol-Myers Squibb, MSD, Novartis, Pfizer, Roche; Research funding: Pfizer. C. Zamagni: Consulting or advisory role: AstraZeneca, Eisai, Novartis, Pfizer, PharmaMar, Pierre Fabre, Roche; Travel, accommodations, expenses: Celgene, Novartis, Pierre Fabre, Roche; Research funding: AbbVie, Array BioPharma, AstraZeneca, Celgene, Medivation, Morphotek, Novartis, Pfizer, Roche, Roche/Genentech. K. Zhou, L. Menon: Employee: Novartis. J. Wu: Employee of Novartis; Employment: Janssen (immediate family member); Travel, accommodations, expenses: Janssen (immediate family member). M. Martín: Consulting or advisory role: Amgen, Lilly, Novartis, Pfizer, PharmaMar, Roche/Genentech; Research funding: Novartis. All other authors have declared no conflicts of interest.

329P Abemaciclib with fulvestrant in patients with HR+, HER2- advanced breast cancer (ABC) that exhibited primary or secondary resistance to prior endocrine therapy (ET)

E-M. Grischke[1], P. Neven[2], Y. Lin[3], P.A. Kaufman[4], G.W. Sledge[5]

[1]Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany, [2]Gynaecological Oncology / Multidisciplinary Breast Center, University Hospitals Leuven - Campus Gasthuisberg, Leuven, Belgium, [3]Oncology, Eli Lilly and Company, Indianapolis, IN, USA, [4]Hematology Oncology, Norris Cotton Cancer Center Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA, [5]Medical Oncology, Stanford University, Stanford, CA, USA

Background: Abemaciclib, a selective inhibitor of CDK4 & 6, dosed on a continuous schedule is approved for the treatment of HR+, HER2- ABC. In the intent-to-treat population, abemaciclib with fulvestrant (F) demonstrated improved progression-free survival (PFS) and objective response rate (ORR) compared to placebo (P) + F (16.4 vs 9.3 mos, HR: 0.553; P<.0000001; ORR in measurable disease 48.1 vs 21.3%; P<.001). ET resistance (ETR) were classified into primary ETR, which includes pts whose disease relapsed while receiving the first 2 years of (neo)adjuvant ET or progressed while receiving the first 6 mos of ET for ABC, and secondary ETR. Here, we compare the efficacy and safety of abemaciclib + F vs P + F in the primary and secondary ETR subgroups.

Methods: MONARCH 2 was a phase 3 randomized, double-blind, placebo-controlled study of abemaciclib + F vs P + F in pts with HR+, HER2- ABC that progressed on ET. Key eligibility criteria were previously discussed. Pts received orally administered abemaciclib 150 mg Q12H + 500 mg F (per label) or P + F. Pts were stratified by sensitivity to ET. Primary objective was investigator-assessed PFS. Secondary objectives included efficacy, safety and tolerability.

Results: 169 pts (25.3%) had primary ETR and 489 pts (73.1%) had secondary ETR. Key efficacy endpoints are summarized (Table). The most frequent adverse events in primary and secondary ETR population are similar. For primary ETR, abemaciclib + F vs P + F were diarrhea (87.3 vs 22.4%), neutropenia (43.6 vs 5.2%), nausea (41.8 vs 25.9%), abdominal pain (36.4 vs 13.8%), and anemia (31.8 vs 5.2%), respectively.

Table: 329P Summary of PFS and ORR in primary and secondary ETR population

	Primary Resistance		Secondary Resistance	
	Abemaciclib + F	Placebo + F	Abemaciclib + F	Placebo + F
PFS				
Median (months)	15.3	7.9	16.6	9.6
Hazard Ratio [HR] (95% CI)	0.45 (0.31, 0.67)		0.59 (0.46, 0.75)	
Pvalue	<.001		<.001	
ORR in measurable disease, (%)	53.9	17.9	46.2	22.6
Pvalue	<.001		<.001	

Conclusions: Abemaciclib + F improved PFS and ORR in pts with primary and secondary ETR, and had a generally tolerable safety profile. Although pts with primary ETR typically have poor prognosis the benefit for abemaciclib + F was maintained in pts HR+, HER2- ABC.

Clinical trial identification: NCT02107703.

Legal entity responsible for the study: Eli Lilly and Company.

Funding: Eli Lilly and Company.

Disclosure: Y. Lin: Employee and stakeholder: Eli Lilly and Company. All other authors have declared no conflicts of interest.

330P Tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) with ribociclib (RIB) in premenopausal patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC): MONALEESA-7 subgroup analysis

A. Bardia[1], S. Campos-Gomez[2], S.A. Hurvitz[3], Y-S. Lu[4], S-A. Im[5], F. Franke[6], L. Chow[7], P. Wheatley-Price[8], F. Melo Cruz[9], J. Alam[10], O. Kong[10], I. Diaz-Padilla[11], M. Miller[10], D. Tripathy[12]

[1]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA, [2]Instituto de Seguridad Social del Estado de México y Municipios, Centro Oncológico Estatal, Toluca, Mexico, [3]UCLA Jonsson Comprehensive Cancer Center, UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA, [4]National Taiwan University Hospital, National Taiwan University Hospital, Taipei, Taiwan, [5]Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [6]CACON, Hospital de Caridade de Ijuí, Ijuí, Brazil, [7]Organisation for Oncology and Translational Research, Organisation for Oncology and Translational Research, Hong Kong, China, [8]Ottawa Hospital Cancer Centre, Ottawa Hospital Cancer Centre, Ottowa, ON, Canada, [9]ABC Foundation School of Medicine, ABC Foundation School of Medicine, Santo André, Brazil, [10]Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [11]Oncology, Novartis Pharma AG, Basel, Switzerland, [12]MD Anderson Cancer Center, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: In the MONALEESA-7 study (NCT02278120), RIB + TAM/NSAI + goserelin significantly prolonged progression-free survival (PFS) and had a manageable safety profile vs placebo (PBO) + TAM/NSAI in premenopausal pts with HR+, HER2– ABC. Here we present data for the TAM and NSAI subgroups.

Methods: Premenopausal pts (N = 672) with HR+, HER2– ABC (≤1 line of chemotherapy; no prior endocrine therapy [ET] for ABC) were randomized 1:1 to RIB (600 mg/day, 3 weeks on/1 week off) or PBO + either TAM (20 mg/day) or NSAI (letrozole [2.5 mg/day] or anastrozole [1 mg/day]) + goserelin (3.6 mg every 28 days). Primary endpoint: locally assessed PFS. A predefined subgroup analysis evaluated PFS by ET partner (TAM or NSAI).

Results: 177 (26%) pts received TAM (RIB vs PBO: 87 vs 90) and 495 (74%) received an NSAI (248 vs 247). As of August 20, 2017, treatment was ongoing in 49% vs 31% of pts in the TAM subgroup and 53% vs 38% in the NSAI subgroup; the most common reason for discontinuation was disease progression (TAM 39% vs 54%; NSAI 35% vs 51%). PFS was prolonged for RIB vs PBO in the TAM (median 22.1 months [mo] vs 11.0 mo; hazard ratio 0.585; 95% CI 0.387–0.884) and NSAI (median 27.5 mo vs 13.8 mo; hazard ratio 0.569; 95% CI 0.436–0.743) subgroups. The most common Grade (G) 3 adverse events (AEs; regardless of causality; ≥5% of pts; RIB vs PBO) were neutropenia (TAM 39% vs 2%; NSAI 55% vs 3%), leukopenia (TAM 8% vs 1%; NSAI 15% vs 1%), elevated GGT (TAM 6% vs 3%; NSAI <1% vs 4%), elevated ALT (TAM 7% vs 2%; NSAI 5% vs 1%), and hypertension (TAM 6% vs 2%; NSAI 2% vs 3%); the only G4 AE in ≥ 5% of pts was neutropenia (TAM 9% vs 1%; NSAI 10% vs < 1%). Increases >60 ms from baseline in the QTcF interval (RIB vs PBO; TAM 16% vs 7%; NSAI 7% vs 0%) and new QTcF >480 ms (TAM 11% vs 1%; NSAI 5% vs 1%) were more common with TAM; there were no associated clinical symptoms or arrhythmias.

Conclusions: RIB demonstrated consistent treatment benefit vs PBO in premenopausal pts with HR+, HER2– ABC regardless of ET partner (TAM or NSAI). The safety profiles of RIB + ET were manageable and consistent, with the exception of QTc findings, which were more prevalent with TAM.

Clinical trial identification: NCT02278120 and October 29, 2014.

Editorial acknowledgement: Editorial assistance was provided by Kate Gaffey PhD of ArticulateScience Ltd.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: A. Bardia: Advisory role: Novartis, Genentech, Pfizer, Spectrum Pharma and Biothernostics. S. Campos-Gomez: Consulting/advisory role: Roche, outside submitted work. S.A. Hurvitz: Grants: Amgen, Bayer, BI Pharma, Genentech, GSK, Lilly, Novartis, Pfizer, Roche, PUMA, Merrimack, Medivation, Dignatana, OBI Pharma, Biomarin, Cascadian, Seattle Genetics; Travel expenses: Lilly, Novartis, OBI Pharma, Bayer outside the submitted work. Grants: Novartis, grants and non-financial support: Roche, grants and non-financial support: Merck, grants: AstraZeneca, outside the submitted work; Honoraria, speaker/consulting role, speakers bureau: Roche, Novartis, AstraZeneca, Pfizer. S-A. Im: Personal fees: Novartis; Advisory role: Pfizer, during the conduct of the study; Advisory role: Hanmi, Roche; Research grants: AstraZeneca, outside the submitted work. L. Chow: Travel, accommodation and expenses fees: Roche, Novartis, Pfizer. P. Wheatley-Price: Personal fees: Novartis, AstraZeneca, Lilly Oncology, BMS, Merck, Takeda, during the conduct of the study. J. Alam: Employment: Novartis Pharmaceutical Corporation. O. Kong, I. Diaz-Padilla, M. Miller: Employment and equity ownership: Novartis Pharmaceutical Corporation. D. Tripathy: Grants, personal fees and support for abstract/manuscript and support for conducting trial (paid to institution), consulting fees for service on the trial Steering Committee from Novartis, during the conduct of the study; Consulting fees: Pfizer, outside the submitted work. All other authors have declared no conflicts of interest.

331P Ribociclib (RIB) + fulvestrant (FUL) for advanced breast cancer (ABC): Progression-free survival (PFS) subgroup and tumor response analyses from MONALEESA-3

G. Jerusalem[1], P.A. Fasching[2], M. Martín[3], X. Pivot[4], K. Petrakova[5], G.V. Bianchi[6], A. Nusch[7], G.S. Sonke[8], L. De La Cruz Merino[9], E. Vagnon[10], J. Alam[11], O. Kong[11], D. Chandiwana[11], M. De Laurentiis[12]

[1]Medical Oncology, CHU Liege and Liege University, Liège, Belgium, [2]Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany, [3]Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense de Madrid, Madrid, Spain, [4]Department of Medical Oncology, Institut Régional du Cancer, Strasbourg, France, [5]Medical Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic, [6]Oncologia Medica, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [7]Haematology and Internal Oncology, Onkologische Praxis Velbert, Velbert, Germany, [8]Medical Oncology, Netherlands Cancer Institute/ BOOG Study Center, Amsterdam, Netherlands, [9]Clinical Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, [10]Oncology, Novartis Pharma AG, Basel, Switzerland, [11]Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [12]Senology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy

Background: RIB + FUL prolonged PFS vs placebo (PBO) + FUL in postmenopausal patients (pts) with HR+, HER2– ABC in the Phase 3 MONALEESA-3 study (NCT02422615). Consistent PFS benefit was observed in pts receiving treatment in either the first- (1L) or combined second-line (2L)/early relapse settings. Here we present additional efficacy and pain reduction results from MONALEESA-3.

Methods: Pts who received no or ≤ 1 line of prior endocrine therapy for ABC (i.e. receiving treatment in the 1L or 2L/early relapse settings, respectively) received RIB + FUL (n = 484) or PBO + FUL (n = 242). Endpoints included, primary: local PFS; secondary: overall response rate and health-related quality of life (HRQoL).

Results: As of Nov 3, 2017, median PFS was prolonged for RIB vs PBO in the separate 2L and early relapse settings (Table). Amongst the full population, 155/379 pts with measurable disease at baseline (41%; 95% CI 35.9–45.8) in the RIB arm and 52/181 (29%; 95% CI 22.1–35.3) in the PBO arm had a complete or partial response (P=0.003). The probability of a response by 6 months (RIB vs PBO arm) was 27% (95% CI 22.7–31.0) vs 16% (95% CI 12.0–21.6). At Week 8, a decrease from baseline in target lesion(s) size per RECIST was observed in (RIB vs PBO) 232/484 (48%) vs 92/242 (38%; P=0.006). A decrease in best % change from baseline in target lesion(s) size per RECIST was reported in 79% of 344 pts in the RIB arm and 66% of 166 pts in the PBO arm. At Cycle 3 Day 1 (Week 8), the absolute mean change from baseline in EORTC QLQ-C30 pain score was similar in both arms: –4.2 RIB (n = 361); –2.9 PBO (n = 169; P=0.517).

Conclusions: RIB + FUL consistently prolonged PFS in the separate 2L and early relapse settings. In the full population, RIB + FUL demonstrated early tumor size reduction and a higher response rate vs PBO + FUL, consistent with other RIB studies. Pain reduction was similar in both arms, suggesting addition of RIB to FUL does not negatively affect HRQoL.

Clinical trial identification: NCT02422615 April 21, 2015.

Editorial acknowledgement: Editorial assistance was provided by Cassandra Krone PhD of ArticulateScience Ltd.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: G. Jerusalem: Grants and personal fees: Novartis, during the conduct of the study; Grants, personal fees and non-financial support: Novartis, Roche; Personal fees and non-financial support: Lilly, Celgene, BMS; Grants and personal fees: Amgen; Personal fees: Pfizer, Puma, Daiichi-Sankyo; Grants from MSD; Personal fees and non-financial support: AstraZeneca, outside the submitted work. P.A. Fasching: Grants and personal fees: Novartis; Personal fees: Roche, Pfizer, Celgene, Teva, during the conduct of the study. M. Martín: Consulting/advisory role and research funding: Novartis, Roche/Genentech; Consulting/advisory role funding: Lilly; Consulting/advisory role funding: Pfizer, during the conduct of the study. K. Petrakova: Consulting/advisory role, Speaker's bureau, Travel/accommodation/expenses: Roche, Pfizer, Novartis, during the conduct of the study. G.S. Sonke: Institutional reimbursement for patient accrual: Novartis, during the conduct of the study; Institutional reimbursement for education and steering committee activities: Novartis; Institutional research support: Merck, AstraZeneca, Roche, outside the submitted work. E. Vagnon, J. Alam: Employment with Novartis. O. Kong, D. Chandiwana: Employment and stock ownership: Novartis. M. De Laurentiis: Grants and personal fees: Novartis, during the conduct of the study; Grants and personal fees: Pfizer, Roche, Astra Zeneca, Amgen; Grants: MSD, outside the submitted work.

332P Clinical outcomes in patients (pts) with estrogen receptor–positive (ER+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC) with objective response (OR) or without objective response (non-OR) in PALOMA-2

H.S. Rugo[1], R.S. Finn[2], K.A. Gelmon[3], A.A. Joy[4], O.N. Lipatov[5], N. Harbeck[6], A. Castrellon[7], H. Mukai[8], J.M. Walshe[9], A. Mori[10], E. Gauthier[11], D.R. Lu[12], E. Bananis[13], M. Martín[14], V. Dieras[15]

[1]Department of Medicine (Hematology/Oncology), University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [2]Division of Hematology/Oncology, David Geffen School of Medicine at UCLA, Santa Monica, CA, USA, [3]Department of Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, [4]Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada, [5]Department of Oncology, Republican Clinical Oncology Dispensary, Ufa, Russian Federation, [6]Department of Obstetrics and Gynecology, Brustzentrum der Universität München (LMU), Munich, Germany, [7]Breast Cancer Center, Memorial Healthcare System, Pembroke Pines, FL, USA, [8]Department of Breast and Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [9]Medical Oncology Department, Cancer Trials Ireland, Dublin, Ireland, [10]Global Product Development, Clinical, Pfizer S.r.l., Milan, Italy, [11]Global Product Development, Clinical, Pfizer Inc., San Francisco, CA, USA, [12]Global Product Development, Statistics, Pfizer Inc., La Jolla, CA, USA, [13]US Medical Affairs, Pfizer Oncology, New York, NY, USA, [14]Universidad Complutense, Hospital Gregorio Maranon, Madrid, Spain, [15]Department of Medical Oncology, Centre Eugène Marquis and Institut Curie, Rennes, France

Background: In the phase 3 PALOMA-2 trial, palbociclib (PAL) + letrozole (LET) significantly improved progression-free survival (PFS) vs placebo (PBO) + LET in pts with ER+/HER2– ABC. We investigated clinical outcomes of pts who achieved a confirmed OR compared with those who did not (data cutoff date: 31 May 2017).

Table: 331P

	2L setting		Early relapse setting	
	• Relapse >12 months from (neo)adjuvant endocrine therapy and subsequent progression on endocrine therapy for ABC • ABC at diagnosis that progressed after 1 line of endocrine therapy for ABC		Relapse on or ≤ 12 months after (neo)adjuvant endocrine therapy with no treatment for ABC	
	RIB + FUL	**PBO + FUL**	**RIB + FUL**	**PBO + FUL**
Pts, n	99	38	137	71
Median PFS, months	18.8	11.4	13.1	8.6
Hazard ratio (95% CI)	0.539 (0.333–0.873)		0.591 (0.422–0.830)	

Methods: Postmenopausal pts untreated for ER+/HER2- ABC were randomized 2:1 to PAL (125 mg/d [Schedule 3/1]) + LET (2.5 mg/d) or PBO+LET. Median PFS (mPFS), median duration of OR (mDOR), baseline characteristics, safety, and PAL exposure were compared in pts with or without OR by treatment arm.

Results: The PAL+LET and PBO+LET groups comprised 444 and 222 pts, respectively; 338 and 171 pts had measurable disease (MD) at baseline. Baseline characteristics were similar in OR and non-OR pts. OR was achieved by 194 (overall, 44%; MD, 57%) and 77 (35%; 45%) pts in the PAL and PBO arms, respectively. Of the pts who achieved OR in the PAL arm, 49% occurred within the first 3 months, 75% within 6 months, and 90% within 1 year. In the PAL arm, more OR than non-OR pts had visceral disease (62% vs 38%), de novo metastatic disease (50% vs 28%), and no prior hormonal therapy (55% vs 35%); fewer OR than non-OR pts had a disease-free interval of ≤ 12 months (14% vs 28%). mPFS was significantly prolonged with PAL+LET vs PBO+LET in both OR and non-OR pts (overall and with MD; Table); in OR pts, mDOR was longer with PAL+LET vs PBO+LET. Safety profiles were similar and independent of response; neutropenia was the most common all-grade AE in the PAL arm (OR, 86%; non-OR, 78%) and rates of PAL dose reduction due to AEs were similar (41%; 38%).

Conclusions: PAL+LET provided significant clinical benefit vs PBO+LET in both OR and non-OR pts; the safety profile was similar to previously reported results in the overall population. PAL is an effective treatment regardless of OR. Pfizer (NCT01740427)

Table: 332P Clinical benefit in patients with or without confirmed OR in PALOMA-2

	OR		Non-OR	
	PAL+LET	PBO+LET	PAL+LET	PBO+LET
All pts, n	194	77	250	145
mPFS (95% CI), mo	37.2 (28.1–NE)	27.4 (22.0–31.1)	16.5 (12.8–22.2)	8.2 (5.6–11.0)
HR (95% CI)	0.65 (0.46–0.92)		0.55 (0.43–0.70)	
mDOR (95% CI), mo	27.7 (24.7–36.1)	20.9 (16.5–27.6)	–	–
Pts with MD, n	194	76	144	95
mPFS (95% CI), mo	37.2 (28.1–NE)	27.4 (22.2–31.1)	10.9 (8.2–11.2)	5.6 (5.3–8.3)
HR (95% CI)	0.66 (0.47–0.94)		0.72 (0.54–0.97)	

HR=hazard ratio; NE=not estimable.

Clinical trial identification: NCT01740427.

Editorial acknowledgement: Editorial support was provided by Jennifer Fetting, PhD, and Kevin O'Regan, PhD, of Complete Healthcare Communications, LLC (West Chester, PA), a CHC Group company, and funded by Pfizer Inc.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: H.S. Rugo: Research funding: Plexxikon, Macrogenics, OBI Pharma, Eisai, Pfizer, Novartis, Eli Lilly, Genentech, Merck; Travel support: Mylan, Puma Biotechnology Merck, Pfizer, Amgen. R.S. Finn: Honoraria: Bayer, Pfizer, Bristol-Myers Squibb, Novartis, Eisai; Consulting or advisory role: Pfizer, Bayer, Novartis, Bristol-Myers Squibb, Merck; Research funding: Pfizer. K.A. Gelmon: Consulting or advisory role: Pfizer, Novartis, AstraZeneca, NanoString Technologies, Merck. A.A. Joy: Consulting or advisory role: Pfizer, Novartis, Roche, Eli Lilly, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Abbvie. N. Harbeck: Honoraria: Lilly, Novartis, Pfizer. A. Castrellon: Consulting or advisory role: Myriad, Biotheranostics; Research funding: Pfizer, Puma Biotechnology, Novartis, Cascadian Therapeutics. H. Mukai: Honoraria: AstraZeneca, Eisai, Novartis Pharma, Taiho Pharmaceutical; Research funds: Chugai Pharmaceutical, Nippon Kayaku, Novartis Pharma, Pfizer Japan, Sanofi. J.M. Walshe: Honoraria: Genomic Health, Roche. A. Mori, E. Gauthier, D.R. Lu, E. Bananis: Employee and shareholder: Pfizer M. Martín: Honoraria: AstraZeneca, Roche, Novartis, PharmaMar, Celgene, Eli Lilly; Research funds: Roche, Novartis. V. Dieras: Consulting and advisory role: Genentech, Lilly, Pfizer, AbbVie, Novartis Pharma KK, Roche-Peru; Speakers bureau: Pfizer, Novartis Pharma KK, Roche-Peru. All other authors have declared no conflicts of interest.

333P Ribociclib (RIBO) + letrozole (LET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC) who received prior chemotherapy (CT) for advanced disease: Preliminary subgroup results from the phase IIIb CompLEEment-1 trial

F. Cardoso[1], K. Papazisis[2], M. De Laurentiis[3], A. Ring[4], J. Lu[5], M. Martín[6], H.A. Azim[7], C. Zamagni[8], K. Zhou[9], J. Wu[9], J.P. Zarate[9], P.H. Cottu[10]

[1]Breast Unit, Champalimaud Foundation Cancer Center, Lisbon, Portugal, [2]Department of Medical Oncology, Euromedica General Clinic, Thessaloniki, Greece, [3]Department of Breast and Thoracic Oncology, Istituto Nazionale Tumori, Naples, Italy, [4]Medical Oncology, The Royal Marsden NHS Foundation Trust, Sutton, UK, [5]Keck School of Medicine, Division of Medical Oncology, University of Southern California, Los Angeles, CA, USA, [6]Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain, [7]Department of Clinical Oncology, Cairo Oncology Center, Cairo University-CairoCure, Cairo, Egypt, [8]Addarii Medical Oncology Unit, Policlinico S. Orsola-Malpighi-"F.Addarii", Bologna, Italy, [9]Novartis Pharmaceuticals, East Hanover, NJ, USA, [10]Department of Medical Oncology, Institut Curie, Paris, France

Background: CDK4/6 inhibitor RIBO is approved in combination with an aromatase inhibitor (AI) for HR+, HER2– ABC in postmenopausal women with no prior therapy for ABC, based on the MONALEESA-2 trial (Hortobagyi et al. NEJM 2016). Previous first-line studies of CDK4/6 inhibitors plus an AI have excluded pts who have received prior CT for ABC, and as such it is important to define safety in this population. Here, we report early safety results for pts who had received prior CT for ABC enrolled in CompLEEment-1, an open-label, phase 3b trial evaluating RIBO+LET as first-line endocrine-based therapy in an expanded pt population.

Methods: Pts with HR+, HER2– ABC, ≤1 line of prior CT, and no prior endocrine therapy for ABC received RIBO (600 mg/day, 3 wk on/1 wk off) + LET (2.5 mg/day); men and premenopausal women received concomitant goserelin (3.6-mg subcutaneous implant q28 days). The primary outcome was safety and tolerability. A pre-planned interim analysis was conducted ~15 months after first pt first visit.

Results: Of the first 1,008 pts enrolled with 56 days of follow-up or discontinued before the data cut-off, 188 had received prior CT for ABC. In this subgroup, the median age was 56.5 years; 2 pts were men and 39 were premenopausal women. The majority of pts (95%) had an Eastern Cooperative Oncology Group performance status ≤1; 45.7% presented with stage IV disease at diagnosis. The most common sites of metastasis were lung (38.8%), liver (33.0%), and lymph nodes (30.0%). The most common all-grade adverse events (AE) were neutropenia (48.9%), nausea (30.3%), and fatigue (20.7%). The most common grade ≥3 AEs were neutropenia (28.2%) and leukopenia (3.2%). QT prolongation events were mild and occurred in 5.9% of pts. Dose reduction or interruption due to AEs occurred in 48.4% of pts; 5 pts discontinued due to AEs.

Conclusions: Initial safety results from CompLEEment-1 demonstrate the tolerability of RIBO+LET in pts who had received prior CT for ABC, consistent with previous reports in pts without CT for ABC. NCT02941926.

Clinical trial identification: NCT02941926.

Editorial acknowledgement: Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals. We thank Holly C. Cappelli, PhD, ProEd Communications, Inc., for her medical editorial assistance with this abstract.

Legal entity responsible for the study: Novartis Pharmaceuticals.

Funding: Novartis Pharmaceuticals.

Disclosure: F. Cardoso: Consulting role: Astellas/Medivation, AstraZeneca, Celgene, Daichii-Sankyo, Eisai, GE Oncology, Genetech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Mylan, Novartis, Pfizer, Amgen, Mundipharma, Pierre-Fabre, Roche, Sanofi, Seattle Genetics, Teva. K. Papazisis: Personal fees from Novartis, during the conduct of the study; Personal fees from Novartis, BMS; Personal fees and non-financial support from Roche, Amgen; Personal fees from AstraZeneca, outside the submitted work. M. De Laurentiis: Consulting or advisory role: AstraZeneca, Celgene, Lilly, Novartis, Pfizer, and Roche; Honoraria: AstraZeneca, Celgene, Novartis, Pfizer, and Roche. A. Ring: Consulting or advisory role: Pfizer and Roche; Honoraria: AstraZeneca, Lilly, Novartis, Pfizer, and Roche; Research funding; AstraZeneca. J. Lu: Travel, accommodations, expenses: Novartis. M. Martín: Consulting or advisory role: Amgen, Lilly, Novartis, Pfizer, PharmaMar, Roche/Genentech Research funding: Novartis. H.A. Azim: Employment: Innate, France (immediate family member); Consulting or advisory role: AstraZeneca, Bristol-Myers Squibb, Janssen, MSD, Novartis, Pfizer, and Roche; Honoraria: Amgen, AstraZeneca, Bristol-Myers Squibb, MSD, Novartis, Pfizer, and Roche; Research funding: Pfizer. C. Zamagni: Consulting or advisory role: AstraZeneca, Eisai, Novartis, Pfizer, PharmaMar, Pierre Fabre, and Roche; Travel, accommodations, expenses: Celgene, Novartis, Pierre Fabre; Roche Research funding: AbbVie, Array BioPharma, AstraZeneca, Celgene, Medivation, Morphotek, Novartis, Pfizer, Roche, and Roche/Genentech. K. Zhou, J.P. Zarate: Employee: Novartis. J. Wu: Employee of Novartis; Employment: Janssen (immediate family member); Travel, accommodations, expenses: Janssen (immediate family member). P.H. Cottu: Consulting or advisory role: Novartis and Pfizer; Travel, accommodations, expenses: Novartis, Pfizer, and Roche; Honoraria: AstraZeneca, NanoString Technologies, Novartis, Pfizer, and Roche; Research funding: AstraZeneca, Genentech/Roche, Novartis, Pierre Fabre, and Pfizer.

334P Health related quality of life in women with HR+/HER2- advanced or metastatic breast cancer treated in real world settings in Italy and Germany

M. De Laurentiis[1], A. König[2], K.L. Davis[3], D. Mitra[4], C.M.A. Nuzzo[5], M. Ajmera[3], S. de Placido[6], S. Brucker[7], N. Harbeck[2]

[1]Department of Breast and Thoracic Oncology, National Cancer Institute "Fondazione Pascale", Naples, Italy, [2]Department of Obstetrics and Gynecology, Brustzentrum der Universitaet Muenchen (LMU), Munich, Germany, [3]Health Economics, RTI Health Solutions, Research Triangle Park, NC, USA, [4]Patient Health & Impact, Pfizer Inc, New York, NY, USA, [5]Pfizer Oncology, Pfizer Inc, Rome, Italy, [6]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy, [7]Department of Obstetrics and Gynecology, Tübingen University Hospital, Tübingen, Germany

Background: Real-world data on health-related quality of life (HRQoL) in women with HR+/HER2- advanced/metastatic breast cancer (ABC/mBC) are limited. This study aims to address this gap.

Methods: MARIA is a non-interventional, prospective, multi-center study that includes women in Italy and Germany initiating their first or second therapy in the HR+/ HER2- ABC/mBC setting. Breast cancer specific HRQoL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B). We report baseline clinical characteristics and HRQoL assessments at enrollment (baseline) and at 3 and 6 months for the first 262 patients enrolled. Change from baseline was calculated for patients with both baseline and follow-up measurement and tested for statistical significance using t-tests for the overall cohort and within subgroups stratified by visceral and bone metastases status.

Results: Median age was 61 years and 46% had visceral disease. At enrollment, 32% were receiving endocrine monotherapy, 34% chemotherapy alone, 28% endocrine/ targeted therapy combinations, and 7% other regimens. A statistically significant ($p < 0.05$) deterioration was observed in the overall cohort at Month 3 for both FACT-B (-4.9 [14.9]) and FACT-G (-4.1 [13.2]) and at Month 6 for the total FACT-G score (-2.1 [12.7]). In the subgroup with visceral and bone metastases, a statistically significant ($p < 0.05$) deterioration was observed in FACT-G scores at 3 months: (-6.6 [16.1]) and at 6 months (-3.6 [12.3]) while no significant change was observed in FACT-B scores. A statistically significant ($p < 0.05$) deterioration from baseline was observed in the subgroup with visceral disease and without bone metastases in FACT- B score at 3 months (mean [SD]: -6.7 [13.9] and at 6 months (-3.9 [16.6]), respectively while no significant change was observed in FACT-G scores.

Conclusions: A statistically significant deterioration was observed in HRQOL scores at some time points after initiating a new line of therapy in the overall cohort and some subgroups of HR+ HER2- MBC patients in a prospective study In Italy and Germany. Further follow-up is ongoing to examine the longer-term impact of therapy on HRQoL.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: M. De Laurentiis: Honoraria; Pfizer, Novartis, Roche, Celgene, AstraZeneca, Eisai, Eli Lilly. K.L. Davis, M. Ajmera: Employee: RTI Health Solutions, who were paid consultants to Pfizer in connection with the development of this abstract. D. Mitra, C.M.A. Nuzzo: Employment and stock ownership: Pfizer. N. Harbeck: Honoraria: Lilly, Novartis, Pfizer. All other authors have declared no conflicts of interest.

335P Breast cancer (BC) treatment (tx) with everolimus (EVE) and exemestane (EXE) in hormone receptor positive (HR+)/ HER2-negative (HER2−) postmenopausal women: Final analysis of the French observational TANGO study

C. Villanueva[1], G. Yazbek[2], P. Beuzeboc[3], E. Viel[4], N. Dohollou[5], E. Luporsi[6], J-C. Eymard[7], E. Levy[8], M-A. Mouret-Reynier[9], L-M. Dourthe[10], E. Malaurie[11], M. Madelenat[12], A. Denden[12], E-C. Antoine[13]

[1]Medical Oncology, Centre de Cancérologie du Grand Montpellier, Montpellier, France, [2]Service d'Oncologie Médicale, Institut Jean Godinot, Reims, France, [3]Medical Oncology, Hôpital Foch, Suresnes, France, [4]Medical Oncology, Cabinet D'Oncologie Médicale, Chalon-sur-Saône, France, [5]Medical Oncology, Polyclinique Bordeaux Nord Aquitaine, Bordeaux, France, [6]Medical Oncology, Hopital de Mercy – CHR Metz Thionville, Ars Laquenexy, France, [7]Medical Oncology, Institut Jean Godinot, Reims, France, [8]Medical Oncology, Clinique Bizet, Paris, France, [9]Medical Oncology, Centre Jean Perrin, Clermont-Ferrand, France, [10]Medical Oncology, Clinique Sainte-Anne, Strasbourg, France, [11]Medical Oncology, CHI de Créteil, Créteil, France, [12]Medical Oncology, Novartis Pharma S.A.S., Rueil-Malmaison, France, [13]Medical Oncology, Clinique Hartmann, Neuilly-sur-Seine, France

Background: TANGO is a French observational prospective study of women with advanced BC treated with EVE/EXE. The main objective was to describe the management of stomatitis and noninfectious pneumonitis (NIP) in clinical practice. Overall safety, duration of EVE/EXE tx and progression-free survival (PFS) were also assessed.

Methods: Eligible patients (pts) were postmenopausal women ≥18 years with advanced HR+/HER2− BC, for whom EVE/EXE was initiated. Statistical analyses were mainly descriptive. Tx duration and PFS were estimated with Kaplan-Meier methods.

Results: From Nov 2014 to Mar 2016, 596 pts had received EVE/EXE (Pts characteristics: see table).

Table: 335P Pts baseline characteristics at EVE/EXE initiation

	Pts who received EVE/EXE (N = 596)
Age	
Mean (standard deviation) age, years	65.1 (10.8)
Pts aged ≥75 years – n (%)	131 (22%)
Median (range) time since initial BC diagnosis to inclusion, years	7.5 (0.1 – 44.3)
Pts with de novo metastatic BC at diagnosis n (%)	145 (24%)
Pts with ECOG ≤1 n (%)	527 (88%)
Metastases	
Pts with bone-only metastases – n (%)	199 (33%)
Pts with visceral metastases – n (%)	290 (49%)
Previous lines of tx for metastatic disease	
Pts without previous line – n (%)	113 (19%)
Pts with 1 previous line – n (%)	208 (35%)
Pts with 2 previous lines – n (%)	126 (21%)
Pts with ≥3 previous lines – n (%)	149 (25%)
BC relapses relative to adjuvant hormonal tx (N, available data)	375
<2 years after the beginning of tx – n (%)	57 (15%)
≥2 years after the beginning of tx and <1 year after the end of tx – n (%)	165 (44%)
≥1 year after the end of tx – n (%)	142 (38%)

305 pts (51%) experienced stomatitis and 80 (13%) experienced NIP (median time to 1st event [range]: 21 [1 – 333] and 104 days [1 – 396], respectively). Most stomatitis (87%) and NIP (91%) were grade 1-2. Stomatitis were mainly treated with mouthwashes (77%), topical analgesics (19%) and antifungals (15%), and NIP with corticosteroids (40%) and antibiotics (10%). 509 pts (85%) had EVE-related adverse events (AE), the most common (excluding stomatitis/NIP) being asthenia (19%), diarrhoea (11%) and rash (10%). 90 pts (15%) had EVE-related serious AE, the most common (excluding stomatitis/NIP) being asthenia (2%). 5 pts (<1%) had EVE-related fatal AE: health deterioration, multiple organ failure, epistaxis, interstitial lung disease, pleural metastases and disorientation. With 562 analysed pts, the median PFS was 6.9 months (95% confidence interval [CI]: 6.2 – 7.8) and median duration of EVE/EXE tx was 5.3 months (95% CI: 4.8 – 6.0). After EVE discontinuation, most pts continued EXE alone (55%) or had chemotherapy (8%).

Conclusions: Results from this real-life observational study reinforce the known safety profile of EVE and better characterize stomatitis and NIP, as well as their management in EVEtreated pts.

Clinical trial identification: EU PAS: EUPAS7325.

Editorial acknowledgement: Florence Arts and Jérôme Leemans; Keyrus Biopharma, Belgium.

Legal entity responsible for the study: Novartis Pharma S.A.S. (France).

Funding: Novartis Pharma S.A.S. (France).

Disclosure: C. Villanueva, E.-C. Antoine: Investigator and Scientific Committee member on this study sponsored by Novartis Pharma S.A.S. G. Yazbek, P. Beuzeboc, N. Dohollou, E. Luporsi, E. Levy; L.-M. Dourthe, E. Malaurie: Investigator on this study sponsored by Novartis Pharma S.A.S. E. Viel: Investigator on this study sponsored by Novartis Pharma S.A.S; Advisory boards: Bristol-Myers Squibb and Sanofi. J-C. Eymard, M-A. Mouret-Reynier: Investigator on this study sponsored by Novartis Pharma S.A.S; Advisory boards: Novartis Pharma S.A.S. M. Madelenat, A. Denden: Employee: Novartis Pharma S.A.S.

336P Everolimus in advanced breast cancer: A systematic review and meta-analysis

J. Raphael[1], C. Lefebvre[1], A. Allan[2], J. Helou[3], G. Boldt[1], T. Vandenberg[1]

[1]Oncology, Western University, London Regional Cancer Program, London, ON, Canada, [2]Oncology and Anatomy and Cell Biology, Western University - London Regional Cancer Program, London, ON, Canada, [3]Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Everolimus (E) plus exemestane are approved for advanced hormone receptor (+) breast cancer (BC) after progression on non-steroidal aromatase inhibitors. The role of E is less well defined in other BC phenotypes and with other drugs. We conducted a systematic review and meta-analysis to assess the efficacy and safety of adding E to standard of care (SoC) in advanced BC regardless of tumor phenotype and treatment type.

Methods: The electronic databases PubMed and EMBASE, were searched for eligible randomized trials. Pooled hazard ratios (HR) for progression free survival (PFS) and overall survival (OS) and pooled risk ratios (RR) and odds ratios (OR) for objective response rates (ORR), clinical benefit rates (CBR) and grade 3 or higher toxicity were meta-analyzed using the generic inverse variance, the Mantel-Henszel and Peto method. To account for between-studies heterogeneity, random-effect models were used. Subgroup analyses compared survival outcomes by tumor phenotype.

Results: Data of 2,693 patients from 7 trials were analyzed. The addition of E to the SoC reduced the risk of disease progression by 33% (7 trials, HR 0.67, 95%CI 0.52-0.86). This did not translate into an OS benefit (4 trials, HR 0.91, 95%CI 0.62-1.33). In addition, E improved the ORR (6 trials, RR 0.91, 95%CI 0.85-0.97) and CBR (7 trials, RR 0.79 95%CI 0.65-0.97) while it increased the risk of developing $\geq$ grade 3 toxicity including stomatitis (OR 5.00, 95%CI 3.63-6.89) and pneumonitis (OR 3.13, 95%CI 1.83-5.36). The PFS benefit was more prominent for patients with hormone receptor (+) / HER2 (-) (HR 0.51, 95%CI 0.43-0.59) than HER2 (+) disease (HR 0.83, 95%CI 0.73-0.96; p for subgroup differences<0.001). For the HER2 (+) subgroup, the PFS benefit was restricted to hormone receptor (-) patients (HR 0.65, 95%CI 0.53-0.81 and HR 0.99, 95%CI 0.83-1.19 for hormone receptor (+) patients; p for subgroup differences 0.004).

Conclusions: E reduces the risk of disease progression in hormone receptor (+) advanced BC independent of endocrine therapy type. In HER2 (+) patients, the benefit is limited for hormone receptor (-) patients. Given the use of newer drugs in the first line, real-world data are needed to confirm whether the benefit persists for patients who develop resistance to CDK4/6 inhibitors.

Legal entity responsible for the study: Jacques Raphael.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

337P First-line treatment for endocrine sensitive bone-only metastatic breast cancer: Is more always better?

A. Toss[1], M. Venturelli[1], I. Sperduti[2], C. Isca[1], E. Barbieri[1], F. Piacentini[1], C. Omarini[1], L. Cortesi[1], S. Cascinu[1], L. Moscetti[1]

[1]*Department of Oncology and Haematology, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy,* [2]*Bio-Statistics Unit, IRCCS Regina Elena National Cancer Institute, IRCCS Regina Elena National Cancer Institute, Rome, Italy*

Background: The standard first-line for endocrine sensitive metastatic breast cancer (BC) is represented by endocrine therapy. Several phase III clinical trials searched for more effective strategies. The SWOG, FACT and FALCON trials analyzed the role of Fulvestrant (Fv), producing contradictory results. The Monaleesa2, Monaleesa7, Monarch3 and Paloma2 trials showed that the addition of a CDK4/6 inhibitor to an aromatase inhibitor (AI) increases the PFS. The use of the combination for the first-line treatment of bone-only disease (BoD) is widely discussed. Our meta-analysis aims to explore the role of the new endocrine strategies in BoD.

Methods: The Prisma statement was used. A systematic review of electronic databases identified the phase III clinical trials comparing the standard AI to a novel experimental strategy. The hazard ratios (HR) for PFS for the subgroup of BoD were pooled in a meta-analysis. The heterogeneity of the data was evaluated by Chi-square Q test and I^2 statistic.

Results: 7 studies were included in the analyses. 4 trials explored the role of CDK4/6 inhibitors (Monaleesa2 and 7, Monarch3 and Paloma2), 2 trials analyzed Fv + AI (SWOG and FACT), while one trial studied Fv monotherapy (FALCON). 5 trials reported data regarding the BoD, while 2 trials included the BoD in the non-visceral disease. Overall, the meta-analyses showed a PFS advantage for the experimental arms [HR 0.67 p 0.01], with a significant moderate/high heterogeneity [I^2 69.88% p 0.003]. Only the FALCON and Paloma2 showed a significant improvement in PFS, respectively for Fv and Palbociclib + Letrozole. Considering only trials reporting data for BoD, the experimental arms significantly improved the PFS [HR 0.60 p 0.001], with a low/moderate non-significant heterogeneity [I^2 37.73% p 0.17].

Conclusions: The meta-analyses of trials reporting data for BoD, showed that the novel strategies are able to improve the PFS. Nonetheless, only Palbociclib + Letrozole provided statistically significant data of advantage in this setting. In clinical trials, BoD is often included in the non-visceral disease subgroup. Future clinical trials should take into account the differences in natural history and better prognosis of BoD, in order to define the best approach to these patients.

Legal entity responsible for the study: Angela Toss.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

338P Real world treatment patterns associated with palbociclib combination therapy in Germany: Results from the IRIS study

D. Mitra[1], G. Taylor-Stokes[2], J. Waller[3], K. Gibson[3], G. Milligan[4], S. Iyer[1]

[1]*Patient Health & Impact, Pfizer Inc., New York, NY, USA,* [2]*Oncology, Adelphi Real World, Bollington, UK,* [3]*Observational Research, Adelphi Real World, Bollington, UK,* [4]*Statistics, Adelphi Real World, Bollington, UK*

Background: Following the approval of palbociclib as the first CDK4/6 inhibitor for HR+/HER2- advanced/metastatic breast cancer (ABC/ MBC), a need exists to understand treatment patterns associated with palbociclib combination therapies in real world clinical settings. The Ibrance Real World Insights (IRIS) study aims to address this evidence gap.

Methods: A retrospective chart review of HR+/HER2- ABC/ MBC patients who received palbociclib combination therapies was conducted in Germany. Physicians completed electronic case report forms (eCFRs), extracting data on patient demographics, clinical characteristics and treatment patterns from an index date (60 days after physician's first prescription of palbociclib) until the most recent record available.

Results: 42 physicians completed 257 eCRFs with 48% representing academic centers. The mean (SD) age of patients at palbociclib initiation was 59.6 (9.4) years (median, 60 years). ECOG status at palbociclib initiation was mostly 0 (48.2%) or 1 (33.5%). Visceral disease was present in 65.6% of patients. Approximately 75% of patients received palbociclib in combination with aromatase inhibitors (AI) and 25% in combination with fulvestrant. Overall, 97% patients received palbociclib + AI as 1st line advanced therapy, the remaining having received chemotherapy previously in the advanced setting. Letrozole was the most common AI partner therapy (63.4%) followed by anastrozole (23.2%), and exemestane (13.4%). Palbociclib + fulvestrant was mostly used in first (44.4%) and second (52.4%) lines. The most frequently prescribed starting dose was 125 mg/day (73.2%), followed by 100mg/day (26.1%) and 75 mg/day (0.8%). 76% of palbociclib + AI patients started on 125 mg compared to 65% of palbociclib + fulvestrant patients. Dose reductions occurred in only 28 (10.9%) patients (7.4% of those who started at 125 mg/day) and a cycle delay occurred in 1 (3.4%) patient. Dose reduction rates were 10.8% in palbociclib + AI and 11.1% in palbociclib + fulvestrant.

Conclusions: In the real world setting, rates of dose reduction were low, and were similar between palbociclib + AI and palbociclib + fulvestrant in HR+/HER2- ABC/ MBC patients in Germany.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: D. Mitra: Employment and stock ownership: Pfizer. G. Taylor-Stokes, J. Waller, K. Gibson, G. Milligan: Employee: Adelphi Real World, who were paid consultants to Pfizer in connection with the development of this abstract. S. Iyer: Employment and stock ownership at Pfizer.

339P Management of abemaciclib associated adverse events in patients with hormone receptor positive (HR+), HER2- advanced breast cancer: Analysis of the MONARCH trials

H.S. Rugo[1], S.M. Tolaney[2], J. Huober[3], M. Toi[4], V. André[5], S. Barriga[6], T. Forrester[7], G.W. Sledge[8], M.P. Goetz[9]

[1]*Breast Cancer Center, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA,* [2]*Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA,* [3]*Gynecol. & Obstetrics, Universitaetsfrauenklinik Ulm, Ulm, Germany,* [4]*Breast Surgery, Kyoto University-Graduate School of Medicine, Kyoto, Japan,* [5]*Oncology, Eli Lilly and Company, Paris, France,* [6]*Oncology, Eli Lilly and Company, Madrid, Spain,* [7]*Oncology, Eli Lilly and Company, Indianapolis, IN, USA,* [8]*Medical Oncology, Stanford University, Stanford, CA, USA,* [9]*Alliance Foundation for Clinical Trials in Oncology, Mayo Clinic, Rochester, NY, USA*

Background: Abemaciclib is a CDK4 & 6 inhibitor dosed continuously with demonstrated efficacy and an acceptable safety profile in pts with HR+, HER2-negative advanced breast cancer as monotherapy (MONARCH 1) and in combination with endocrine therapy; with fulvestrant (MONARCH 2) or with non-steroidal aromatase inhibitors (MONARCH 3). The most frequent adverse event (AE) is low-grade diarrhea; neutropenia is the most frequent grade 3/4 AE. We describe the timing and management of common AEs in the MONARCH trials.

Methods: Enrollment criteria, study designs and key eligibility criteria of MONARCH 1, 2 and 3 have been reported (Dickler et al. 2017; Sledge et al. 2017; Goetz et al. 2017). Pts were advised to initiate antidiarrheal therapy at first sign of diarrhea and notify the investigator, drink fluids. If not improved within 24 hours to < grade 1, treatment was suspended until diarrhea resolved. Dose reductions required for grade $\geq$3 or persistent grade 2 diarrhea. For grade 3 neutropenia, abemaciclib was held until < grade 2. The dose was reduced for recurrent grade 3 or grade 4 neutropenia.

Results: Across MONARCH, the median time to onset of diarrhea was between day 6-8. First dose reductions for diarrhea occurred at a median of 28-41 days. Dose holds for diarrhea were brief, constituting 1.7-3.8% off total treatment time. The median time to onset of grade 3/4 neutropenia was 29-36.5 days, and resolved at a median of 11-15 days. AEs were managed by dose adjustments and/or supportive medication (Table).

Table: 339P

Summary of Dose Adjustments in Pts Experiencing Diarrhea or Neutropenia

Characteristics	MONARCH 1 Abemaciclib N = 132	MONARCH 2 Abemaciclib + F N = 441	MONARCH 3 Abemaciclib + NSAI N = 327
Diarrhea (any grade), n(%)	119 (90.2)	381 (86.4)	269 (82.3)
Grade 3	26 (19.7)	59 (13.4)	31 (9.5)
Incidences per patient, n (%)			
1	60 (50.4)	185 (48.6)	124 (46.1)
2	29 (24.4)	90 (23.6)	52 (19.3)
≥3	30 (25.2)	106 (27.8)	93 (34.6)
Outcome, number (%) of events	263	995	802
Not recovered/resolved	15 (5.7)	106 (10.7)	70 (8.7)
Treatment change, n (%)	119	381	269
Dose reduction of study drug	27 (22.7)	83 (21.8)	45 (16.7)
Dose omission	32 (24.2)	83 (21.8)	51 (19.0)
Treatment discontinuation	1 (0.8)	13 (3.4)	6 (2.2)
Antidiarrheal medication, n (%)	80 (60.6)	333 (75.5)	226 (69.1)
Neutropenia (any grade), N (%)	49 (37.1)	203 (46.0)	143 (43.7)
Grade ¾	32 (24.2)	117 (26.5)	78 (23.9)
Treatment change, n (%)			
Dose reduction of study drug	14 (10.6)	44 (10.0)	42 (12.8)
Dose omission	21 (15.9)	72 (16.3)	57 (17.4)
Treatment discontinuation	0	7 (1.6)	9 (2.8)

Conclusions: The dose adjustment strategy used in the MONARCH studies was effective at managing AEs by dose adjustment and/or supportive medication. Understanding the safety profile of abemaciclib can inform AE management and can extend time on treatment.

Clinical trial identification: NCT02102490 (MONARCH 1), NCT02107703 (MONARCH 2), NCT02246621 (MONARCH 3).

Legal entity responsible for the study: Eli Lilly and Company.

Funding: Eli Lilly and Company.

Disclosure: H.S. Rugo: Grants/research support: GSK, Genentech/Roche, Novartis, Pfizer, Merck, Eisai, Plexxikon, Macrogenics, Lilly, OBI (all funding to UC Regents only). V. André, S. Barriga, T. Forrester: Employee and stakeholder: Eli Lilly and Company. M.P. Goetz: Consultant: Eli Lilly and Company, bioTheranostics, Novartis, Genomic Health, Eisai, Biovica, and Sermonix; Grant/Research support from Eli Lilly and Pfizer. All other authors have declared no conflicts of interest.

340P Progression free survival (PFS) benefit from first line endocrine based therapies in postmenopausal women with HR+ HER2- metastatic breast cancer (MBC) according to different prognostic subgroups: A combined analysis of data from PALOMA 2, MONALEESA 2, MONARCH 3, FALCON, SWOG and FACT trials

V. Rossi[1], D. Giannarelli[2], P. Berchialla[3], C. Nisticò[4], G. Ferretti[5], S. Gasparro[4], P. Malaguti[4], M. Russillo[6], G. Catania[4], L. Vigna[1], R.L. Mancusi[6], F. Cognetti[6], A. Fabi[9]

[1]Breast Unit, Azienda Ospedaliera S. Camillo Forlanini, Rome, Italy, [2]Statistica Medica, Istituto Regina Elena, Rome, Italy, [3]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy, [4]Medical Oncology, Istituto Regina Elena, Rome, Italy, [5]Medical Oncology, Istituto Regina Elena, Rome, Italy, [6]Medical Oncology, Istituto Nazionale Tumori Regina Elena, Rome, Italy, [7]Scienze Statistiche, Università Tor Vergata, Rome, Italy

Background: This analysis combines data from six phase III trials investigating the role of endocrine-based therapies in the first-line setting of MBC to identify which factors may guide the clinical choice among available drugs.

Methods: For PFS, Hazard Ratio (HR) and 95% CI were reported. Subgroup meta-analysis was conducted stratifying by age, ECOG, ethnicity, prior chemotherapy or endocrine therapy exposure, measurable disease at the time of metastasis occurrence, visceral or bone only disease, time from the initial diagnosis of breast cancer to the metastasis onset. Random-effect model was used and heterogeneity was quantified by I^2 statistics. Test of interaction was performed to compare treatment effect in sub-groups. Data analysis was performed using R Statistical Software version 3.4.3.

Results: In absence of indirect comparison between cycline dependend kinase (CDK) 4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib) combined to nonsteroidal aromatase inhibitors (AIs) and Fulvestrant endocrine-based therapies, all these therapeutic options resulted in significant PFS benefit compared to AIs endocrine-monotherapy (HR: 0.74; 95% CI 0.67-0.80). Test of interaction showed similar treatment effects among sub-groups with the exception of Ethnicity and ECOG. Specifically, a longer PFS from CDK 4/6 inhibitors plus AIs strategies was observed in Asian (Asian HR: 0.38; 95% CI 0.20-0.72 versus non-Asian population HR: 0.61; 95% CI 0.50-0.75, $p < 0.001$) and ECOG≥1 patients (ECOG≥1 HR: 0.53; 95% CI 0.51-0.56 versus ECOG=0 HR: 0.60; 95% CI 0.49-0.74, $p < 0.02$).

Conclusions: CDK 4/6 inhibitors or Fulvestrant endocrine-based therapies as first-line treatment for postmenopausal women with HR+/HER2- MBC showed significant PFS improvement in comparison with AIs endocrine-monotherapy. Further indirect comparison by a network meta-analysis is needed to explore which patients may derive the greatest benefit from the different therapeutics options.

Legal entity responsible for the study: Valentina Rossi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

341P Palbociclib in combination with letrozole as first or later line therapy for patients with locally advanced, inoperable or metastatic HR+/HER2- breast cancer in Germany: Interim results of the INGE-B phase II study

M.K. Welslau[1], M. Zaiss[2], U. Söling[3], M. Untch[4], L. Müller[5], D. Lüftner[6], J. Meiler[7], A. Welt[8], J. Sahlmann[9], L. Houet[10], E. Runkel[10], N.W. Marschner[10]

[1]Medical Oncology, MVZ am Klinikum Aschaffenburg GmbH, Aschaffenburg, Germany, [2]Medical Oncology, Praxis für Interdisziplinaere Onkologie, Freiburg, Germany, [3]Medical Oncology, Onkologische Gemeinschaftspraxis, Kassel, Germany, [4]Clinic for Gynecology, Gynecologic Oncology and Obstetrics, Helios Klinikum Berlin Buch, Berlin, Germany, [5]Medical Oncology, Onkologie UnterEms, Leer, Germany, [6]Klinik für Hämatologie, Onkologie und Tumorimmunologie, Charité Campus Benjamin Franklin, Berlin, Germany, [7]Medical Oncology, Klinik Dr. Hancken GmbH, Stade, Germany, [8]Klinik für Innere Medizin/ Tumorforschung, Universitätsklinikum Essen (AöR), Essen, Germany, [9]Data Management, Statistics and Medical Informatics, iOMEDICO, Freiburg, Germany, [10]Medical Department, iOMEDICO, Freiburg, Germany

Background: Based on the pivotal PALOMA trials investigating the combination of the CDK4/6 inhibitor palbociclib with letrozole or with fulvestrant after prior endocrine therapy, extended European approval was granted for this patient population to receive palbociclib in combination with any aromatase inhibitor or with fulvestrant after prior endocrine therapy. The prospective multi-centre phase 2 study INGE-B was designed to a) investigate the combination of palbociclib with letrozole or with fulvestrant in accordance with the PALOMA trials in Germany and b) to obtain so far lacking data on the combination of palbociclib with the aromatase inhibitors exemestane or anastrozole.

Methods: In total, 360 patients with locally advanced, inoperable or metastatic HR+/HER2- breast cancer were recruited at 82 sites across Germany. Eligible patients are treated with palbociclib either in combination with letrozole, anastrozole, exemestane or fulvestrant as first-line therapy or in combination with letrozole or fulvestrant as later-line therapy. Primary objective is the clinical benefit rate (CBR), defined as the percentage of patients with response or stable disease at week 24. Key secondary endpoints include progression-free survival (PFS), overall survival (OS), overall response rate (ORR) and safety. Quality of life, fatigue, anxiety and depression are assessed with validated questionnaires. Data were analysed for each treatment group separately with descriptive statistics.

Results: The first interim analysis of the INGE-B study was scheduled to analyse data of patients receiving palbociclib and letrozole in first or later line. Between 09/2016 and 01/2018, 63 first- and 59 later-line patients were enrolled at 38 sites and observed for at least 6 months of treatment, unless discontinued earlier for disease progression or any other reason. Baseline patient and tumour characteristics will be presented. Efficacy in terms of CBR and best response and treatment-emergent adverse events will be described.

Conclusions: The results of the first interim analysis of the INGE-B study will be discussed with respect to data from the PALOMA 1/2 trials.

Clinical trial identification: NCT02894398.

Legal entity responsible for the study: iOMEDICO AG.

Funding: Pfizer.

Disclosure: D. Lüftner: Membership on an advisory board or board of directors, remunerations: Amgen, Pfizer, Eli Lilly, Celgene, Loreal. A. Welt: Membership on an advisory board or board of directors: Roche, Pfizer, Novartis. All other authors have declared no conflicts of interest.

342P Response to primary treatment for first recurrence independently influences survival of patients with hormone receptor-positive, HER2-negative breast cancer: A multicenter study of 236 recurrent metastatic patients

J. Yamamura[1], S. Kamigaki[1], M. Tsujie[1], J. Fujita[1], H. Osato[1], C. Higashi[2], H. Kanaizumi[2], Y. Tanaka[2], M. Hamada[2], W. Shinzaki[2], Y. Hasimoto[2], Y. Komoike[2]

[1]*Department of Surgery, Breast Oncology, Sakai City Medical Center, Sakai, Japan*
[2]*Department of Breast and Endocrine Surgery, Kindai University Faculty of Medicine, Sayama, Japan*

Background: There is little current evidence for the optimal primary treatment (PT) for patients with recurrent metastatic hormone receptor-positive (HR+), HER2-negative (HER2-) breast cancer. These patients may be resistant to metastatic treatment due to continuous adjuvant endocrine therapy (ET). Here, we identify the significant factors correlating to prognosis in a retrospective study. Recognizing the prognostic factors for recurrent HR+/HER2- breast cancer may improve the delivery of healthcare to at-risk groups and play an important role in the treatment and care for these patients.

Methods: We performed a retrospective review of records from 236 patients with recurrent metastatic HR+/HER2- breast cancer who were diagnosed between January 2000 and December 2013 at Sakai City Medical Center and Kindai University Hospital, Japan. We assessed the clinicopathologic features, treatment patterns, and overall survival (OS) following diagnosis of first distant recurrence.

Results: Median OS after first recurrence was 3.73 years. Patients with longer disease free-survival (DFI) ($\geq$2 years), a longer interval after the end of adjuvant ET ($\geq$1 year), or first recurrence without liver metastasis had a significantly better prognosis ($p < 0.001$, $p = 0.007$, and $p < 0.001$, respectively). Patients with a good response to PT for first recurrence also had significantly better prognosis, regardless of ET or chemotherapy ($p < 0.001$). Longer DFI, no liver metastasis, and good response to PT were found to be independent prognostic factors for better OS in multivariate analysis (HR:0.467; 95%CI:0.291-0.750, $p = 0.002$, HR:0.443; 95%CI:0.285-0.688, $p < 0.001$, and HR:0.312; 95%CI:0.201-0.484, $p < 0.001$, respectively). Good responders to PT were also shown to have a significantly longer response to subsequent lines ($p = 0.007$).

Conclusions: Good response to PT for first recurrence may be the key to favorable OS for recurrent metastatic HR+/HER2- patients, regardless of visceral metastasis. In addition to a novel targeted agent, more optimal treatment to first recurrence could improve drug resistance and eventually lead to better prognosis.

Legal entity responsible for the study: Sakai City Hospital Organization.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

343P Application of CDK4/6 inhibitors in practice: Effect of online education on clinician competence and confidence

C. Day[1], D. Middleton[2], S. Loibl[3]

[1]*Global Education, Medscape, London, UK,* [2]*Global Education, Medscape, New Jersey, NJ, USA,* [3]*Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany*

Background: This study determined whether online continuing professional development (CPD) activity could improve oncologists (Oncs) and obstetrician/gynaecologists (Obs/Gyns) competence and confidence in the use of CDK4/6I in practice.

Methods: An interactive text-based activity that included discussion of 2 detailed patient cases was launched for countries outside the United States in March 2017, with data collected until April 2017. Educational effect was assessed with a repeated-pairs pre-/post-assessment study design, where individual participants served as his/her own control. 3 multiple-choice, knowledge questions and 1 self-efficacy, 5-point Likert scale (confidence) question were analyzed. Chi-squared test assessed pre- to post-assessment change (5% significance level, $P < .05$). Magnitude of change in proportion of correct responses overall, and for each question, were determined with Cramer's V (effect size: <0.05 none/minimal; 0.06-0.15 small, 0.16-0.30 medium, >0.30 large).

Results: 204 Oncs and 51 Obs/Gyns completed both pre- and post-assessments. A large education effect was observed for both Oncs ($V = 0.311$) and Obs/Gyns ($V = 0.459$). At baseline, 46% of Oncs and 16% of Obs/Gyns answered all 3 questions correctly, increasing to 91% and 76%, respectively, post-assessment. An average of 75% of oncs selected the best response on pre-assessment (range, 66% to 80%), improving to 96% post-assessment (range, 96% to 97%). Statistically significant change for all 3 questions and a medium to large education effect was observed for the questions covering appropriate treatment selection, patient monitoring and management of neutropenia. Baseline understanding was lower for obs/gyns with a large education effect seen for all 3 questions. 38% of Oncs and 45% of Obs/Gyns reported increased confidence managing neutropenia due to CDK4/6I.

Conclusions: This on-demand, text-based activity with 2 interactive cases resulted in a significant, positive education effect. Baseline findings indicate that both specialties, would benefit from education to facilitate application of CDK4/6I in practice. Online medical education is important in supporting the practical application of new treatment regimens in practice.

Legal entity responsible for the study: Medscape.

Funding: Pfizer.

Disclosure: All authors have declared no conflicts of interest.

344P First report of real-world patient characteristics and treatment patterns from POLARIS: Palbociclib in hormone receptor-positive (HR+) advanced breast cancer: A prospective, multicenter, noninterventional study

J.L. Blum[1], S.L. McCune[2], M.A. Salkeni[3], D.M. Anderson[4], J.J. Migas[5], S. Lakhanpal[6], K. Patel[7], A. Bardia[8], G. Rocque[9], J. Wang[10], J.C. Cappelleri[11], G. Comstock[12], Y. Wang[13], D. Tripathy[14]

[1]*Medical Oncology, Texas Oncology, Baylor-Sammons Cancer Center, US Oncology, Dallas, TX, USA,* [2]*Hematology/Oncology, Northwest Georgia Oncology Centers, Marietta, GA, USA,* [3]*Hematology/Oncology, West Virginia University Cancer Institute, Morgantown, WV, USA,* [4]*Hematology, Oncology and Transplantation, Health Partners Institute, St Paul, MN, USA,* [5]*Hematology/Oncology, OSF St. Joseph Medical Center, Bloomington, IL, USA,* [6]*Hematology/Oncology, Saint Vincent's Birmingham, Birmingham, AL, USA,* [7]*Medical Oncology and Hematology, CARTI Cancer Center, Little Rock, AR, USA,* [8]*Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA,* [9]*Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL, USA,* [10]*Biostatistics, Cytel Inc, Waltham, MA, USA,* [11]*Biostatistics, Pfizer Inc, Groton, CT, USA,* [12]*Breast Cancer, Oncology, Pfizer Inc, Santa Rosa, CA, USA,* [13]*Oncology Clinical Development and Medical Affairs, Pfizer Inc, New York, NY, USA,* [14]*Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Background: This study describes real-world use and population characteristics in HR+/HER2- advanced breast cancer (ABC) patients receiving palbociclib (PAL) in routine practice.

Methods: This prospective, noninterventional study has a targeted enrollment of 1500 men and women from ~110 sites. Site and patient data, monitored remotely for clarity/completeness, are collected from medical charts, physician surveys, and patient-reported outcomes; optional blood samples are collected during standard-of-care lab draws.

Results: This is an interim report of the first 312 patients with completed baseline case report forms as of 9Mar18 from 66 US sites (data snapshot: 9Apr18). Most sites were community sites (79%) with 1-10 treating physicians (61%). Of 33 sites that use clinical pathways, 45% were based on NCCN and 42% on US Oncology guidelines. Selected patient characteristics are shown (Table). Before starting PAL at enrollment, 18% of patients received chemotherapy, 21% hormonal therapy, 11% radiotherapy, 4% surgical resection, and 66% had no prior ABC therapy. Overall, 72% of patients received PAL combination first-line, of whom 56% received PAL+letrozole or anastrozole, 41% PAL+fulvestrant, and 4% PAL+exemestane. Of patients receiving $\geq$second-line PAL, 46% received prior hormonal monotherapy, 43% prior chemotherapy alone, and 6% both.

Table: 344P Selected patient demographic and clinical characteristics

	All Patients (N = 312)
Age at study enrollment, y	
Median (range)	63 (29-92)
Distribution, n (%)	
<40	12 (3.8)
40-50	40 (12.8)
51-69	156 (50.0)
70-74	41 (13.1)
75-84	51 (16.3)
≥85	12 (3.8)
Sex, n (%)	
Women	308 (98.7)
Men	4 (1.3)
Race, n (%)	
White	256 (82.1)
Black or African American	46 (14.7)
Other	7 (2.2)
Not reported	3 (1.0)
Hispanic/Latino ethnicity, n (%)	31 (9.9)
Insurance provider, n (%)	
Private insurance	152 (48.7)
Medicare	133 (42.6)
Medicaid	14 (4.5)
Uninsured	5 (1.6)
Pre/perimenopausal, n (%)	40 (12.8)

Continued

Table: 344P *Continued*

	All Patients (N = 312)
Distribution of disease-free interval, mo,* n (%)	
<12	97 (31.6)
12-<24	11 (3.6)
24-<36	25 (8.1)
≥36	174 (56.7)
Number of present comorbidities by system organ class, median (minimum-maximum)	4 (0-27)
Musculoskeletal and connective tissue disorders, n (%)	245 (78.5)
Gastrointestinal disorders, n (%)	225 (72.1)
Metabolism and nutrition disorders, n (%)	190 (60.9)
Cardiac disorders, n (%)	49 (15.7)

*Disease-free interval was defined as the time from first diagnosis of breast cancer to onset of advanced/metastatic disease among patients with available initial breast cancer diagnosis dates and available date of first ABC diagnosis.

Conclusions: This is the first large, prospective multicenter study assessing real-world use of a CDK4/6 inhibitor. In the first 312-patient cohort, most were treated at community sites. A heterogeneous real-world population received PAL, including elderly, premenopausal, African-American, Latino/Hispanic, and male patients not commonly represented in clinical trials. Hormone partners received with PAL included steroidal and nonsteroidal aromatase inhibitors or fulvestrant, predominantly first-line.

Clinical trial identification: NCT03280303.

Editorial acknowledgement: Editorial support was provided by Anny Wu, PharmD, of Complete Healthcare Communications, LLC (West Chester, PA), a CHC Group company, and funded by Pfizer Inc.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: J.L. Blum: Steering committee: Pfizer Inc. M.A. Salkeni: Contracted research funding as study PI via author's institution: West Virginia University. J.J. Migas, J. Wang: Contracted research: Pfizer Inc. A. Bardia: Advisory board: Novartis, Pfizer Inc, Spectrum Pharma. G. Rocque: Steering committee: Pfizer Inc; Contracted research: Genentech, Carevive, Pack Health, Medscape. J.C. Cappelleri, G. Comstock, Y. Wang: Employee and stockholder: Pfizer Inc. D. Tripathy: Steering committee: Novartis, Pfizer Inc; Contracted research: Novartis, Pfizer Inc. All other authors have declared no conflicts of interest.

345P Everolimus-based therapy versus conventional therapy for refractory breast cancer patients with PI3K/AKT/mTOR mutations

Z. Chen[1], Y. Zheng[1], W. Cao[1], Y. Zhang[2], S. Cai[2], X. Shao[1], J. Huang[1], W. Ye[1], Y. Huang[1], Y. Yin[3], X. Wang[1]

[1]Department of Breast Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China, [2]The Medical Department, 3D Medicines Inc., Shanghai, China, [3]Department of Oncology, Jiangsu Province Hospital, Nanjing, China

Background: Molecular screening using next generation sequencing (NGS) with the aim of guiding therapy for patients with refractory cancer, is becoming increasingly more common in clinical practice. Given that tumors with alterations in PI3K/ATK/mTOR (PI3K) pathway exhibit sensitivity to mTOC1 inhibitor everolimus, everolimus is often off-label used to target PI3K pathway. However, efficacy of off-label-use of everolimus in refractory breast cancer is unknown. We conducted this retrospective study to assess the efficacy of molecular matched off-label use of everolimus for refractory breast cancer patients with mutations in PI3K pathway, compared with conventional therapy.

Methods: Patients with refractory metastatic breast cancer who received NGS with the aim of guiding therapy between 2015 and 2017, were screened for eligibility at two sites in China. Patients with mutations in PI3K pathway and treated with everolimus-based or conventional therapy were included. Everolimus was used outside its indications. The primary outcome was progression-free survival (PFS). Secondary outcomes were overall response rate (ORR), disease control rate (DCR) and safety profile.

Results: 33 patients with mutations in PI3K pathway were included in this analysis. 18 (54.5%) patients were hormone receptor positive and 14 (42.4%) patients were HER2 positive. 20 patients received everolimus-based therapy and 13 patients received conventional therapy. The PFS was shorter in everolimus group than conventional group (median, 2.05 vs 6.1 months; HR, 4.45; 95% CI, 1.64-12.10; P = 0.0016). ORR was 14.3% (2/14) in everolimus group and 23.1% (3/13) in conventional group (P = 0.648). DCR was 35.7% (5/14) in everolimus group and 100% (13/13) in conventional group (P = 0.001). The incidence of grade 3 or worse treatment-related adverse event was similar between groups (5 [38.5%] of 13 in everolimus group, 5 [25.0%] of 20 in conventional group, P = 0.393).

Conclusions: The off-label use of everolimus to target the PI3K/AKT/mTOR pathway is associated with poorer outcome in patients with refractory breast cancer. These data suggests that off-label use of everolimus to target PI3K/AKT/mTOR should not be encouraged.

Legal entity responsible for the study: Yongmei Yin, Xiaojia Wang.

Funding: National Natural Science Foundation of China.

Disclosure: All authors have declared no conflicts of interest.

346P Ribociclib (RIB) + fulvestrant (FUL) in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC): MONALEESA-3 biomarker analyses

P. Neven[1], K. Petrakova[2], G.V. Bianchi[3], L. De La Cruz Merino[4], G. Jerusalem[5], J.T. Beck[6], G.S. Sonke[7], S. Chia[8], S. Brucker[9], Y. Wang[10], W. He[11], K. Rodriguez Lorenc[12], F. Su[12], S-A. Im[13]

[1]Multidisciplinary Breast Center, Universitair Ziekenhuis Leuven, Leuven, Belgium, [2]Medical Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic, [3]Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [4]Clinical Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, [5]Medical Oncology, CHU Liege and Liege University, Liège, Belgium, [6]Medical Oncology and Hematology, Highlands Oncology Group, Fayetteville, AR, USA, [7]Department of Medical Oncology, Netherlands Cancer Institute/BOOG Study Center, Amsterdam, Netherlands, [8]Medical Oncology, BC Cancer Agency, Vancouver, BC, Canada, [9]Department of Gynaecology, Center for Women's Health, University of Tübingen, Tübingen, Germany, [10]Oncology, Novartis Pharma AG, Basel, Switzerland, [11]Oncology, Novartis Institutes for BioMedical Research, Cambridge, MA, USA, [12]Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [13]Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

Background: In the Phase III MONALEESA-3 study (NCT02422615), RIB + FUL significantly improved progression-free survival (PFS) vs placebo (PBO) + FUL in patients with HR+, HER2– ABC who received no or up to 1 line of prior endocrine therapy for ABC (hazard ratio 0.593; 95% confidence interval 0.480–0.732). Here we present PFS data by baseline tumor Ki67, total Rb, and p16 protein expression, and CCND1, CDKN2A, and ESR1 messenger RNA (mRNA) levels.

Methods: Postmenopausal women (N = 726) with HR+, HER2– ABC were randomized 2:1 to RIB (600 mg/day; 3 weeks on/1 week off) + FUL (500 mg) or PBO + FUL. The primary endpoint was PFS. PFS by biomarker expression was an exploratory endpoint. Baseline tumor tissue was evaluated for protein expression (immunohistochemistry) and gene expression (NanoString® nCounter Customized Panel). To assess correlations between protein/gene expression and PFS, patients were classified into prespecified low vs high expression subgroups; 14% of positively stained cells was used as a cutoff for Ki67, 10th percentile was used as a cutoff for total Rb, and median expression was used as a cutoff for all other proteins/genes.

Results: PFS hazard ratios for all biomarker subgroups favored RIB + FUL vs PBO + FUL (Table). Consistent RIB + FUL treatment benefit was seen regardless of Ki67 protein expression or CCND1 gene expression. A numerically greater PFS benefit was observed with RIB + FUL in patients with low vs high p16 protein expression and low vs high CDKN2A mRNA expression; a similar trend was observed in patients with low vs high ESR1 mRNA expression.

Conclusions: RIB + FUL significantly prolonged PFS vs PBO + FUL, with consistent treatment effects observed regardless of biomarker expression. There was a trend towards greater PFS benefit with RIB + FUL in patients with low vs high expression of p16 protein, and low vs high CDKN2A and ESR1 mRNA levels.

Clinical trial identification: NCT02422615 April 21, 2015.

Editorial acknowledgement: Editorial assistance was provided by Kate Gaffey PhD of ArticulateScience Ltd.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: K. Petrakova: Consulting/advisory role, speaker's bureau, travel/accommodation and expenses: Roche, Pfizer and Novartis during the conduct of the study. G. Jerusalem: Grants and personal fees from Novartis during the conduct of the study; Grants, personal fees and non-financial support: Novartis, Roche, BMS; Personal fees and non-financial support: Lilly; Personal fees: Celgene, Pfizer, Puma, Daiichi-Sankyo; Grants and personal fees: Amgen; Grants: MSD; Personal fees and non-financial support from AstraZeneca outside the submitted work. G.S. Sonke: Institutional reimbursement for patient accrual: Novartis during the conduct of the study; Institutional reimbursement for education and steering committee activities: Novartis; Institutional research support: Merck, AstraZeneca, and Roche, outside the submitted work. S. Chia: Honoraria and research funding: Novartis and Roche; Research funding: BMS and Genetech. W. He: Employment: Novartis. K. Rodriguez Lorenc, F. Su: Novartis Employee and owns stock: Novartis. S-A. Im: Advisory role: Novartis, during the conduct of the study; Grants: AstraZeneca; Advisory role: Hanmi, Roche and Pfizer, outside the submitted work. All other authors have declared no conflicts of interest.

Table: 346P

	RIB + FUL		PBO + FUL		Hazard ratio (95% confidence interval)
	Events, n/n	Median PFS, months	Events, n/n	Median PFS, months	
Ki67					
Low	55/118	19.4	43/68	14.5	0.612 (0.408–0.919)
High	95/208	19.1	56/93	12.3	0.637 (0.456–0.891)
Total Rb					
Low	8/32	Not reached	10/16	12.8	0.359 (0.130–0.988)
High	138/295	19.1	87/143	12.8	0.648 (0.495–0.850)
p16					
Low	66/161	22.1	57/83	11.9	0.449 (0.312–0.645)
High	76/151	16.6	41/67	12.8	0.719 (0.486–1.064)
CCND1					
Low	83/175	18.6	62/91	11.2	0.631 (0.453–0.880)
High	81/184	19.4	45/81	14.9	0.713 (0.494–1.028)
CDKN2A					
Low	73/177	20.6	56/89	11.0	0.527 (0.370–0.751)
High	91/182	16.4	51/83	14.5	0.802 (0.567–1.136)
ESR1					
Low	85/180	19.1	58/86	10.8	0.544 (0.386–0.765)
High	79/179	19.4	49/86	14.9	0.802 (0.560–1.149)

347P Potential survival gains from first-line (1L) systemic therapy advances in metastatic triple-negative breast cancer (mTNBC)

P. Bajaj[1], J.A. Roth[2], S.D. Sullivan[3], A. Stein[1], R. Mahtani[4], S.D. Ramsey[2]
[1]U.S. Medical Affairs, Genentech Inc. - Roche, South San Francisco, CA, USA, [2]Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]School of Pharmacy, University of Washington, Seattle, WA, USA, [4]Sylvester Comprehensive Cancer Center, University of Miami Health System, Deerfield Beach, FL, USA

Background: Approximately 15% of the 67,000 women diagnosed with metastatic breast cancer (mBC) annually in the U.S. have mTNBC. Few effective treatment options for mTNBC patients have been identified in the past decade & outcomes are poor vs. other mBC subtypes. The objectives of this study were to quantify overall survival (OS) gains in mTNBC from 2010-2015 & project the potential magnitude of OS gains from new therapies approved by 2020.

Methods: We created a simulation model to estimate OS in mTNBC cohorts diagnosed from 2010-2020. OS data were derived from mTNBC clinical trials & were extrapolated to a lifetime horizon by fitting parametric curves. The distribution of 1L regimens used in each diagnosis year came from the IPSOS Global Oncology Monitor - a commercial registry. We projected 2020 OS assuming that 50% of patients receive newly approved therapies (e.g. immunotherapy) & those therapies have an average OS hazard ratio (HR) of 0.7 vs. docetaxel. Scenarios explored alternative HRs of 0.6 & 0.8. We estimated 5-year OS, mean OS & population life year (LY) gains assuming static mTNBC incidence (10,050 cases/year).

Results: From 2010-2015, 5-year OS increased by 2.2% & mean OS increased 1.6 months. If new treatments meet projections for efficacy & market adoption, 5-year mTNBC OS could triple from 5.2% in 2010 to 15.6% in 2020. Over a lifetime horizon, mean per-patient OS could improve by 10.2 months (8,543 population LYs). The population survival gains from 2015-2020 (7,203 LYs) would be ~5-fold greater vs. gains from 2010-2015 (1,340 LYs). Scenarios with average new treatment HRs of 0.6 & 0.8 resulted in population survival gains of 10,902 LYs & 6,763 LYs vs. 2010.

Table: 347P

Diagnosis Year	5-Year OS (%)	Mean OS (Months)	Population LYs
2010	5.2	22.9	19,179
2015	7.4	24.5	20,519
2020 (Projected)	15.6	33.1	27,721

Conclusions: We report modest mTNBC survival gains from 2010 to 2015, but show that clinically meaningful gains could be achieved if new treatments in development achieve realistic levels of effectiveness & are widely adopted. There is high unmet need in mTNBC & these new treatments offer hope for improved future outcomes.

Legal entity responsible for the study: Genentech, Inc.
Funding: Genentech, Inc.

Disclosure: P. Bajaj A. Stein: Employee and stockholder: Genentech, Inc. / F. Hoffmann-La Roche AG. J.A. Roth: Consultant: Genentech; Research funding: Genentech. S.D. Sullivan: Research funding: Genentech, Inc. R. Mahtani: Advisor/consultant: Genentech and has received research support. S.D. Ramsey: Research funding from Genentech, Inc.

348P Economic evaluation of eribulin in the treatment of triple negative breast cancer in the United Kingdom

J. Wex[1], C. Bodnar[2], C. Simon[3], F. Fernandes[4], N. Tanova[1]
[1]HEMA, Amaris, London, UK, [2]Global Value and Access, Eisai Europe, Hatfield, UK, [3]Market Access, Eisai, Hatfield, UK, [4]Health Economics, Eisai, Hatfield, UK

Background: Eribulin is indicated in the European Union for patients with locally advanced or metastatic breast cancer after ≥1 prior chemotherapy for advanced disease, including an anthracycline and a taxane. The license is based on clinical trials which included patients with triple negative breast cancer (TNBC). We sought to evaluate clinical and cost-effectiveness of eribulin in this population using decision analytic modelling.

Methods: Data on OS, PFS and TTD from TNBC patients from two randomized open label studies of eribulin, 305 (NCT00388726) and 301 (NCT00337103), were pooled (N = 352). The comparators were TPC (any single-agent chemotherapy, hormonal or biological treatment; radiotherapy; or symptomatic treatment alone) (305) and capecitabine (301). A partitioned survival model developed for the National Institute for Health and Clinical Excellence submission based on pooled Kaplan-Meier data, accounting for tumour objective response and adverse events with health-state specific utilities mapped from QLQC30 data from study 301 was used. Lifetime horizon with discount rate of 3.5% for costs and quality-adjusted life years (QALYs) was applied. Threshold analysis was based on 2017 UK costs and reimbursement decision criteria.

Results: Use of eribulin versus the pooled comparator of capecitabine or TPC was associated with greater mean overall survival (16.00 vs 12.38 months) and progression-free survival (4.4 vs 3.6 months) with 0.3 life years (LYs) gained and 0.2 incremental QALYs. 77% of LYs and 75% of QALYs were gained in progressive disease. Using UK end of life criteria and considering the patient access scheme price, eribulin falls well within the cost-effectiveness threshold of £50,000/QALY and would be considered cost-effective in the UK setting. The results were sensitive to price of eribulin, utility in the progressive disease state, discount rates and drug administration costs.

Conclusions: Eribulin is cost-effective in the treatment of patients with TNBC after ≥1 prior chemotherapy for advanced disease, including an anthracycline and a taxane in the UK.

Legal entity responsible for the study: Amaris.
Funding: Has not received any funding.

Disclosure: J. Wex, N. Tanova: Research funding to the institution: Eisai. C. Bodnar, C. Simon, F. Fernandes: Employee: Eisai.

349P Use of bone-modifying agents (BMA) and osteonecrosis of the jaw (ONJ) among older patients with metastatic breast cancer (BC)

M. Chavez Mac Gregor[1], X. Lei[2], H. Zhao[2], C. van Poznak[3], S.H. Giordano[1]

[1]Breast Medical Oncology, Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Breast Medical Oncology, The University of Michigan, Ann Arbor, MI, USA

Background: BC patients who have evidence of bone metastases should be treated with BMAs in order to reduce skeletal related events. ONJ is a serious complication associated the use of BMAs. In this large population-based study we evaluate the patterns of use of BMAs and ONJ rates in a cohort of older BC patients.

Methods: Patients diagnosed with de novo metastatic BC between 2007-2013 were identified in the SEER-Medicare database. We identified the presence of bone metastases using specific PEDSF variables and claims. All patients were required to receive systemic anticancer therapy within one year of diagnosis. HCPCS codes were used to identify the use of BMAs within 1 year of cancer diagnosis, ONJ was identified using an established ICD-9 codes. Descriptive statistics and regression models were used.

Results: A total of 1,528 patients were included. The median age of the cohort was 74 yo. Within one year of diagnosis of bone metastases 71.1% of the patients received BMAs (68% bisphosphonates, 27% denosumab, 5% both). Older patients (OR = 0.64; 95%CI 0.46-0.89), those with more comorbidities (OR = 0.61; 95%CI 0.43-0.85) or with full/partial state buy-in (OR = 0.65; 95%CI 0.49-0.87) -surrogate for poverty- were less likely to receive BMAs. Nineteen cases of ONJ were identified, all of them occurred among BMAs-treated patients (1.7%), the 2-year and 4-year cumulative rates were 1.4% and 4.0%, respectively. Similar rates of ONJ were observed between patients treated with bisphosphonates and denosumab. Median duration of BMA therapy among patients who developed ONJ was 20 months (IQR 10-43). No clinical predictors of ONJ were identified.

Conclusions: In this large, nationally-representative cohort, the majority of the BC patients with evidence of bone metastases received treatment with BMA according to current guidelines. Similar rates of ONJ were observed among bisphosphonates and denosumab users. ONJ occurred in approximately 2% of this SEER-Medicare population of patients with BC and bone metastases treated with BMA. Our findings are of significant value since they reflect the patterns of care and complications associated with these commonly used agents in the general population.

Legal entity responsible for the study: Mariana Cgavez Mac Gregor.

Funding: CERCIT, Sudan G. Komen.

Disclosure: All authors have declared no conflicts of interest.

350P Liver surgery of breast cancer liver metastases: Rapid surgical decision after diagnosis does not negatively impact long-term results

V. Lucidi[1], G. Liberale[2], D. Germanova[3], M. Bez[1], V. Donckier[4]

[1]Digestive Surgery, Hepatobiliary Surgery & Liver Transplantation, Erasme University Hospital-(Universite Libre de Bruxelles), Brussels, Belgium, [2]Surgery, Institut Jules Bordet, Brussels, Belgium, [3]Digestive Surgery, Erasme University Hospital ULB, Brussels, Belgium, [4]Surgery, Institute Jules Bordet, Brussels, Belgium

Background: Surgery could be indicated in selected patients with breast cancer liver metastases (BCLM) but accurate identification of the candidates for surgery remains a challenge. We investigated if an observational period of time after the diagnosis of BCLM could improve the selection for surgery.

Methods: We performed a retrospective analysis of 72 consecutive patients operated for BCLM between 2000 and 2015. Clinicopathologic and outcome data were compared between 2 groups: Early surgery (ES), including patients operated for BCLM ≤12 months after liver metastases (LM) diagnosis, and late surgery (LS), including patients operated >12 months after diagnosis.

Results: Mean age was 48 years (28-74) at time of liver surgery. Median time between primary and LM diagnosis was 35 months (0-211) and median time between LM diagnosis and surgery was 12 months (0-134). Clinicopathologic characteristics were similar in ES (n = 37) and LS (n = 35) patients. In the whole population, 1, 3 and 5-years progression free (PFS) and overall (OS) survivals were respectively of 70%, 43%, 30% and 93%, 66%, 43%. In multivariate analysis, neither PFS nor OS differences were observed between ES and LS groups (PFS - HR = 1,13 p = 0,72 and OS - HR = 1,06, p = 0,85 for LS), only primary tumor estrogen receptor positivity had a positive impact for OS (HR = 0,48 p = 0,05).

Conclusions: No difference in survival was observed between patients operated rapidly for BCLM as compared with patients operated after observational period, suggesting that it is not necessary to postpone the surgery in patients with resectable LM.

Legal entity responsible for the study: Hôpital Erasme ULB.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

351P Impact of breast cancer molecular subtypes on the occurrence, kinetics and prognosis of central nervous system metastases in a large multicenter cohort

W. Jacot[1], G. Louvel[2], A. Darlix[1], J. Fraisse[3], E. Brain[4], M. Debled[5], M.A. Mouret Reynier[6], A. Goncalves[7], F. Dalenc[8], P. Augereau[9], J-M. Ferrero[10], C. Levy[11], J-D. Fumet[12], C. Jouannaud[13], C. Veyret[14], V. Dieras[15], M. Robain[16], C. Courtinard[16], D. Pasquier[17], T. Bachelot[18]

[1]Medical Oncology, ICM Regional Cancer Institute of Montpellier, Montpellier, France, [2]Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [3]Biometrics Unit, ICM Regional Cancer Institute of Montpellier, Montpellier, France, [4]Department of Medical Oncology, Institut Curie, Paris & Saint-Cloud, France, [5]Department of Medical Oncology, Institute Bergonié, Bordeaux, France, [6]Department of Medical Oncology, Centre Jean Perrin, Clermont-Ferrand, France, [7]Department of Medical Oncology, Institute Paoli Calmettes, Marseille, France, [8]Department of Medical Oncology, Centre Claudius-Regaud - IUCT Oncopole, Toulouse, France, [9]Department of Medical Oncology, Institut de Cancérologie de l'Ouest, Angers, France, [10]Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France, [11]Department of Medical Oncology, Centre Francois Baclesse, Caen, France, [12]Department of Medical Oncology, Centre Georges-François Leclerc, Dijon, France, [13]Department of Medical Oncology, Institut Jean Godinot, Reims, France, [14]Department of Medical Oncology, Centre Henri Becquerel, Rouen, France, [15]Medical Oncology Department, Centre Eugène Marquis, Rennes, France, [16]Department of Research and Development, UNICANCER, Paris, France, [17]Academic Department of Radiation Oncology, Centre Oscar Lambret, Lille, France, [18]Department of Medical Oncology, Centre Léon Bérard, Lyon, France

Background: Metastatic breast cancer (MBC) behavior differs depending on the molecular subtype based on hormone receptors (HR) and HER2 statuses. We aimed at evaluating the kinetics of central nervous system metastases (CNSM) occurrence, and the prognosis after CNSM, according to the molecular subtype.

Methods: Retrospective analysis of 16703 MBC patients from the French Epidemiological Strategy and Medical Economics (ESME) database involving 18 specialized cancer centers (NCT03275311) (2008-2014 database). The time between stage IV and CNSM diagnosis (CNSM-free survival CNSMFS) and between CNSM diagnosis and death from any cause (overall survival OS) were estimated with the Kaplan-Meier method and compared with the log-rank test.

Results: Median follow-up was 42.8 months. Among the selected patients, 64.1% of patients had HR+/HER2-, 11.0% HER2+/HR+, 7.5% HER2+/HR- and 17.4% triple negative (TN, HR-/HER2-) MBC. Median age at MBC diagnosis was 61.2. 4118 patients (24.6%) were diagnosed with CNSM at initial diagnosis of primary tumor or during their MBC follow-up: 18.7%, 34.9%, 49.2% and 38.0% of patients with HR+/HER2-, HER2+/HR+, HER2+/HR- and TN tumors, respectively. Median age at CNSM diagnosis was 58.1 overall, 54.1 for TN patients and 59.9 for HER2+ patients ($p < 0.0001$). 1200 patients (7.2%) had CNSM at the time of stage IV diagnosis, while 2918 developed CNSM during the course of MBC, with a median CNSMFS of 17.0 months (95% CI 16.5-17.9). The molecular subtype was independently associated with CNSMFS: HER2-/HR+ NE (95%CI 91.1NE), HER2+/HR+ 61.7 (95%CI 51.7-74.1), HER2+/HR- 24.9 (95%CI 22.7-28.9) and TN 29.9 months (95%CI 27.0-33.1) ($p < 0.001$). With a 30 months median follow-up, median OS after CNSM diagnosis was 7.9 months (95% CI 7.2-8.4): 7.1 months for HR+/HER2-, 18.9 months for HER2+/HR+, 13.1 months for HER2+/HR- and 4.4 months for TN ($p < 0.0001$). These differences were significant when assessed in multivariate analysis ($p < 0.0001$ for HER2+/HR+, HER2+/HR- and TN tumors compared with HER2/ HR+ tumors).

Conclusions: We found that the breast cancer molecular subtype strongly impacts the occurrence, kinetics and prognosis of CNSM in MBC patients.

Legal entity responsible for the study: UNICANCER.

Funding: Pierre Fabre, Pfizer, AstraZeneca and MSD.

Disclosure: All authors have declared no conflicts of interest.

352P Features associated with long-term survival in metastatic breast cancer

N. Klar[1], M. Rosenzweig[2], B. Diergaarde[3], A.M. Brufsky[4]

[1]Department of Medicine, UPMC Presbyterian Hospital, Pittsburgh, PA, USA, [2]School of Nursing, University of Pittsburgh, Pittsburgh, PA, USA, [3]Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA, [4]Division of Hematology/ Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA

Background: 5-10% of women with metastatic breast cancer (MBC) survive ≥5 years. Predictors of long-term survival are not clearly elucidated. We used data from 122 long-term MBC survivors (≥5-year survival from date of MBC diagnosis) and 191 short-term MBC survivors (≤2-year survival from date from MBC diagnosis) to identify clinico-pathologic and socioeconomic features associated with MBC survival.

Methods: Women initially diagnosed with breast cancer (BC) in or after 1999, and diagnosed with MBC at Magee Women's Cancer Program of UPMC were included (N = 313). Data abstracted from medical records included: stage at initial BC diagnosis, body mass index (BMI), Charlson Comorbidity Index (CCI), age, menopausal status at initial BC diagnosis, tumor receptor status at initial BC diagnosis, site of initial metastases, time between initial diagnosis and MBC, household income, race, employment status, and partner status. Differences between groups were assessed using t-tests and

Chi-square or Fisher's exact tests. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariate logistic regression models.

Results: Long-term survivors were significantly ($P < 0.05$) younger, had more ER positive, PR positive, and Her2 positive disease, lower CCI, more often premenopausal at initial diagnosis, lower rates of visceral metastases, higher household income, and more often partnered than short-term survivors. Long-term term survivors were also significantly more often diagnosed with de novo MBC compared to short-term survivors. The association with long-term survival remained significant after adjustment for age, tumor receptor status, and CCI (OR: 3.0, 95% CI 1.6-5.4). Time interval between initial diagnosis and MBC, BMI, race, and employment status were not associated with survival.

Conclusions: Diagnosis of de novo MBC, ER-, PR- and/or Her2-positive primary tumor, higher household income, younger age, lower CCI, premenopausal status, and having a partner are associated with long-term survival after diagnosis of MBC. This is one of the first studies to show a survival benefit in MBC for patients with de novo MBC, positive partner status and higher household income.

Legal entity responsible for the study: Magee Women's Breast Program.

Funding: Has not received any funding.

Disclosure: A.M. Brufsky: Consulting fees: Roche. All other authors have declared no conflicts of interest.

353P Physical activity and lifestyle in women with metastatic breast cancer: The ABLE study

B. Fervers[1], L. Delrieu[1], O. Pérol[1], O. Febvey-Combes[2], A. Dufresne[3], T. Bachelot[3], P. Heudel[4], O. Tredan[3], M. Touillaud[1], V. Pialoux[5]

[1]Cancer Environnement, Centre Léon Bérard, Lyon, France, [2]Département de la Recherche Clinique et de l'Innovation, Centre Léon Bérard, Lyon, France, [3]Département d'Oncologie Médicale, Centre Léon Bérard, Lyon, France, [4]Centre Léon Bérard, Lyon, France, [5]Laboratoire Inter-Universitaire de Biologie de la Motricité, Université Claude Bernard Lyon, Villeurbanne, France

Background: About 5% of breast cancers are metastatic (MBC) at diagnosis and 20-30% of localized breast cancer become secondarily metastatic. Patients suffer from many detrimental symptoms related to metastasis and treatments. Only four intervention studies worldwide have focused on physical activity (PA) interventions in MBC patients. The ABLE study is designed to assess the feasibility of a 6-month PA intervention in MBC patients and the effects of PA on physical, biological, psychological and clinical parameters.

Methods: A cohort of 50 newly diagnosed MBC patients have been recruited in an unsupervised and personalized 6-month PA program. At baseline and 6 months, we assessed anthropometrics, functional tests, biological parameters (inflammation, oxidative stress), questionnaires-based PA, quality of life, & fatigue, and tumor progression. Patients have worn a PA tracker which served both as a tool to record their own behaviour and maintain exercise adherence.

Results: The recruitment rate was at 94%. At baseline, participants' age was 54.7 years (SD 10.4), BMI was 25.9kg/m^2 (5.7). Significant increase in distance during 6MWT (10.0%), extension force of the quadriceps (20.3%) and significant decrease of weight (2.0%), BMI (2.3%) and hip circumference (2.4%) were observed after the completion of the program. Mean walking steps during 6 months were 4799 per day.

Conclusions: The high recruitment rate shows the willingness of MBC patients to participate in this type of program. Preliminary data confirmed the need and desire of a PA intervention in the MBC population. This unsupervised PA program may encourage patients to maintain a long term physically active lifestyle.

Clinical trial identification: NCT03148886.

Legal entity responsible for the study: Centre Léon Bérard.

Funding: Cancéropole Lyon Auvergne Rhône Alpes, National Cancer League, Odyssea and Activ'RA.

Disclosure: All authors have declared no conflicts of interest.

355P Establishment and validation of M1 stage subdivisions for patients with de novo metastatic breast cancer: A population-based study

C. Lin, J. Wu, L. Zhu

Comprehensive Breast Health Center, Shanghai Ruijin Hospital, Shanghai Jiao Tong University, College of Medicine, Shanghai, China

Background: Patients with metastatic breast cancer (MBC) is a heterogeneous group with different survival outcomes. The current "catch-all" M1 category of breast cancer cannot be used for accurate prognosis prediction.

Methods: Patients with de novo MBC were identified using the Surveillance, Epidemiology, and End Results (SEER) database and divided randomly into the training and validation sets. The Fine and Gray's competing risks model was developed to identify the variables associated with increased breast cancer-specific death (BCSD) in the training set. Cumulative incidence curves were estimated and compared using Gray's test. And the M1 subdivisions system was established based on the independent prognostic factors for BCSD.

Results: Multivariate analysis showed the involvement of brain or liver and the number of metastatic organs were independent prognostic factors for BCSD. Therefore, we subdivided the M1 stage into three categories: M1a, involvement of single organ but no brain or liver; M1b, liver metastasis only or involvement of multiple organs but no brain or liver; M1c, involvement of multiple organs including liver but no brain, or brain involvement with or without liver, irrespective of the number of metastatic organs (M1b vs M1a, subdistribution hazard ratio [SHR] 1.45, 95% CI 1.28 - 1.65; M1c vs M1a, SHR 2.47, 95% CI 2.22 - 2.75; M1c vs M1b, SHR 1.67, 95% CI 1.47 - 1.90). The dose-response risk estimation was also observed in the validation and whole sets. Primary tumor surgery decreased from 43.2% in 2010 to 29.8% in 2014, with similar patterns seen in all M1 subdivisions. And patients of M1a benefited most from primary tumor surgery (M1a: SHR 0.55, 95% CI 0.49 - 0.60; M1b: SHR 0.71, 95% CI 0.60 - 0.82; M1c: SHR 0.63, 95% CI 0.55 - 0.72) in the adjusted competing risks model. Three-year cancer-specific mortality cumulative rates.

Table: 355P

	Training set		Validation set		Whole set	
M1 subdivision	Incidence rate (%)	95% CI (%)	Incidence rate (%)	95% CI (%)	Incidence rate (%)	95% CI (%)
M1a	42.4	39.8 - 44.9	44.1	41.6 - 46.7	43.2	41.4 - 45.1
M1b	53.7	49.1 - 58.0	50.6	46.3 - 54.8	52.1	48.9 - 55.1
M1c	72.1	68.3 - 75.6	70.4	66.4 - 74.0	71.3	68.6 - 73.8
P	< .001		< .001		< .001	

Conclusions: The M1 subdivisions system can better guide the prognosis prediction and treatment planning in patients with de novo MBC.

Legal entity responsible for the study: Ethics Committee, Shanghai Ruijin Hospital, Shanghai Jiao Tong University, College of Medicine, Shanghai, CN.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

356P A prospective observational study of mobile application-based patient-reported outcomes (PRO) in advanced breast cancer: Interim baseline data from the MADELINE study

D. Odom[1], D. Mitra[2], K. Hollis[3], D. Richardson[3], J.A. Kaye[4], L. McRoy[5]

[1]Biostatistics, RTI Health Solutions, Research Triangle Park, NC, USA, [2]Patient Health & Impact, Pfizer Inc, New York, NY, USA, [3]Surveys and Observational Studies, RTI Health Solutions, Research Triangle Park, NC, USA, [4]Pharmacoepidemiology and Risk Management, RTI Health Solutions, Research Triangle Park, NC, USA, [5]US Medical Affairs, Pfizer Inc, New York, NY, USA

Background: MADELINE is a multicenter study enrolling women with advanced/metastatic breast cancer (ABC/MBC) receiving palbociclib in combination with an aromatase inhibitor (AI) as initial endocrine therapy or fulvestrant after progression on prior endocrine therapy according to the FDA-approved indication for palbociclib (Group 1) or approved therapies for ABC/MBC other than palbociclib (Group 2). A novel mobile application was developed to collect real-time PRO data to assess patient (pt) functioning and quality of life through daily, weekly, and monthly questionnaires for 6 months. Patient demographic and clinical information was recorded in an electronic case report form at baseline and for the planned 6-month follow-up.

Methods: Patients were administered the 12-Item Short Form Health Survey (SF-12) and the Center for Epidemiologic Studies Depression Scale (CES-D-10) at baseline. An analysis of baseline data as of March 1, 2018, on Group 1 pts with baseline mobile app and electronic case report form data was performed.

Results: Thirteen sites contributed 50 pts for this baseline analysis. Mean (SD) age was 58.6 (11.48); 86% were white. The most common metastatic sites were bone (54%) and lymph nodes (32%). ECOG performance status was 0, 1, and 2 in 61%, 24%, and 2% of pts, respectively. At enrollment, 27 pts (54%) initiated palbociclib plus AI, and 23 (46%) initiated palbociclib plus fulvestrant. There were no substantial differences between these palbociclib subgroups on SF-12 domain scores or CES-D-10 score; overall cohort scores are shown in the table.

Conclusions: This initial analysis describes the current population of palbociclib-treated pts in the MADELINE study. Recruitment and data collection are ongoing with plans for 30 total sites and up to 250 patients, with final results expected August 2019.

Table: 356P

Measure Mean (SD)	Group 1 (N = 50)
SF-12	
General Health	46.7 (9.51)
Physical Functioning	45.4 (11.07)
Role Physical	44.3 (11.46)
Bodily Pain	45.1 (12.96)
Vitality	45.3 (10.06)
Social Functioning	47.2 (10.83)
Role Emotional	47.3 (9.76)
Mental Health	48.8 (10.73)
Physical Component Summary	44.4 (11.65)
Mental Component Summary	48.7 (10.53)
CES-D-10	7.5 (4.95)

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: D. Odom, K. Hollis, D. Richardson, J.A. Kaye: Employee: RTI Health Solutions, who were paid consultants to Pfizer in connection with the development of this abstract. D. Mitra, L. McRoy: Employment and stock ownership: Pfizer.

357P Stereotactic radiosurgery (SRS) for brain metastases (BM) from breast cancer (BC): A single centre experience of factors influencing survival

T. Wilson[1], T. Robinson[1], C. Macfarlane[2], T. Spencer[3], C. Herbert[3], J. Braybrooke[1]

[1]Medical Oncology, University Hospitals Bristol NHS Trust Bristol Haematology and Oncology Centre, Bristol, UK, [2]Oncology, University Hospital Southampton NHS Foundation Trust, Southampton, UK, [3]Clinical Oncology, University Hospitals Bristol NHS Trust Bristol Haematology and Oncology Centre, Bristol, UK

Background: BM occur in up to 30% of patients with BC. SRS can be considered as an alternative to surgery or whole brain radiotherapy for control of single or multiple metastases. Factors that could predict overall survival (OS) and guide treatment choice have not been clearly defined.

Methods: Data for consecutive patients with BC treated with SRS between November 2013 and August 2017 in a single tertiary referral centre were collected to assess factors that might predict survival. T-tests, Kaplan Meier and log-rank methods were used for statistical analysis.

Results: 93 patients (pts) received SRS, of whom 32 were alive when data was censored on 1/2/18. The median overall survival (OS) post SRS was 14.0 mths (95% C.I +/- 2.4mths) with a significant correlation between age and OS (53 pts $\leq$60yr, OS = 18.1mths; 43pts >60y OS = 10.3mths, r=-0.21, p = 0.04). There were 31 ER+/HER2- pts (OS 15.2mths), 14 ER+/HER2+ pts (OS 31.9mths), 30 ER-/HER2+ pts (OS 22.8mths) and 16 Triple negative (TN) pts (OS 8.5mths). OS was significantly better for pts with HER2+ disease (p = 0.0018) with the poorest survival in pts with TN cancer (p = <0.0001). 39pts had 1 lesion treated (OS 16.2mths), 35pts had 2-5 lesions treated (OS 9.7mths), 19 pts had $\geq$6 lesions (OS 19.2mths). Whilst the number of lesions treated did not correlate with OS (r=-0.095, p = 0.37) a larger volume of tumour treated (>10cm^3) was associated with worse survival (r=-0.253, p = 0.01). At the time of SRS 17pts had no other systemic disease (OS 13.7mths). When present, control of systemic disease outside the brain was associated with improved OS (36 pts stable systemic disease OS = 20mths, 32 pts progressive systemic disease (PSD) OS = 9.7mths; p = 0.0013). 49 pts had known disease status at death, 17 had PSD, 16 had progressive CNS disease (PCD), 13 had PSD + PCD and 3 had no progression.

Conclusions: Age, receptor status, control of systemic disease, total tumour volume treated, but not the number of lesions appears to influence survival following SRS treatment of BM in BC. Our results are consistent with other series with worse outcomes seen in older patients and those with TN cancers. In addition to treating BM, control of systemic disease outside the brain remains important in prolonging survival.

Legal entity responsible for the study: Jeremy Braybrooke.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

358P Prolonged overall survival for patients with bone-only metastases at presentation of metastatic breast cancer

E. Curtit[1], F. Bazan[1], L. Chaigneau[1], G. Mouillet[1], E. Dobi[1], L. Mansi[1], N. Meneveau[1], M-J. Paillard[1], G. Meynard[1], E. Klajer[1], C. Villanueva[2], P. Montcuquet[1], X. Pivot[3], L. Cals[4]

[1]Medical Oncology, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [2]Medical Oncology, Centre de Cancérologie du Grand Montpellier, Montpellier, France, [3]Medical Oncology, Centre Paul Strauss Centre de Lutte contre le Cancer, Strasbourg, France, [4]Medical Oncology, CH Mende, Mende, France

Background: More than 50% of metastatic breast cancer patients experience bone metastases over the course of disease and around 15% of cases have metastases confined to the skeleton at metastatic presentation. The aim of this study was to access the overall survival of breast cancer patients with bone-only metastases at presentation.

Methods: Among 907 patients, we identified from our prospective computerized database 123 patients with bone-only metastases at diagnosis of metastatic breast cancer. We retrospectively collected data from the patients' files.

Results: The median overall survival was 8,3 years (CI 95% 6,7-10,3) and 73% and 41% of patients were alive at 5 and 10 years, respectively. No multivariate model with factors identified at presentation was able to predict overall survival length. Sixty per cent of patients developed visceral metastases over the time and the median interval between the diagnosis of bone metastases and the occurrence of visceral metastases was 28 months (4 - 193). In multivariate analysis, negative progesterone receptor status was associated with the occurrence of visceral metastasis (HR = 2,4; p = 0,03). Eleven per cent of patients had a solitary bone metastasis; 67% of patients developed axial metastases and 41% long bone metastases.

Conclusions: Breast cancer patients with bone-only metastases at presentation of metastatic disease might form a distinct clinical entity among metastatic breast cancer patients with a favorable prognosis and a prolonged overall survival. No prognostic factors identified at the presentation of the disease were able to predict very long survivors. Further investigations on these tumors biology and clinical trials dedicated to this population are required.

Legal entity responsible for the study: CHRU Besançon.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

359P Surgery of the primary tumor for de novo metastatic breast cancer: The controversy continues

B. López de San Vicente, E. Galve Calvo, A. Zumarraga, F. Pikab ea, J.F. Arango Arteaga, M. López Santillan, C. Figaredo, M.A. Sala Gonzalez, M. Nuño Escolastico, P. Novas Vidal, J. Legaspi, P. Martinez del Prado

Medical Oncology, Hospital Universitario Basurto, Bilbao, Spain

Background: De novo metastatic breast cancer (dnMBC) represents 6–10% of breast cancer. Due to its incurability, dnMBC is generally treated with systemic therapies to achieve disease control and reduce tumor-related symptoms. The need for radical locoregional treatment and its consequent benefit in this setting remains still controversial. Meta-analysis of retrospective studies and prospective randomized studies did not report a clear survival benefit. The aim of this study was to analyze the impact of surgery to primary tumor (PT) in patients (pts) presenting with dnMBC.

Methods: Between Feb 2006-Oct 2015 we performed a retrospective chart review to 129 consecutive pts who attended our hospital with dnMBC. Descriptive, Kaplan-Meier and Cox regression analyses were carried out using SPSS version 23.0.

Results: A total of 129 pts. were analyzed. Median age was 68 years (range: 20-95), 59 pts (46%) had single organ metastasis, and their distribution according to the predominant site of disease was: skin/soft tissue 42 pts (33%), bone 87 pts (67%) and visceral 85 pts (66%). Surgery (S) of the PT was done in 32 pts (25%), 24 was radical procedures, 8 palliative and besides, 27 pts underwent axillary dissection. Initial S treatment was the choice for 29 pts. In the S group single organ disease was present in 66% vs 39% non-S group. Metastatic sites were: 50% vs 71% visceral, 44% vs 21% with bone metastasis in the S vs non-S group respectively. With a median follow-up of 2 years (SD 2.20), the 5-yr overall survival (OS) was 11.64% in the entire de novo MBC population, with a median OS of 36 m in the S-group vs 21 m. in the non-S-group (HR 1.46 p = 0.081). Subgroup analyses did not show a benefit of PT surgery in OS regardless of the number of metastasis and site of disease, and BC subtypes. The multi-adjusted HR for surgery was 0.14 (p = 0.188). The multivariate Cox regression analysis model included the site of disease (p = 0.971), the histopathologic grade (p = 0.876) and the hormone receptor status (p = 0.003).

Conclusions: In our series, surgical treatment of the primary tumor in patients with de novo metastatic breast cancer did not show a benefit in overall survival. Results of ongoing randomized trials are needed.

Legal entity responsible for the study: Medical Oncology Service, Basurto University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

361TiP A phase III study comparing trastuzumab emtansine with trastuzumab, pertuzumab, and docetaxel in elderly patients with advanced stage HER2-positive breast cancer (JCOG1607 HERB TEA study)

A. Shimomura[1], K. Tamura[2], T. Mizutani[3], T. Shibata[3], F. Hara[4], T. Fujisawa[5], N. Niikura[6], T. Hojo[7], C. Kambayashi[8], S. Saji[9], N. Masuda[10], M. Sawaki[11], N. Yamamoto[12], F. Nagashima[13], T. Shien[14], H. Iwata[15]

[1]Breast and Medical Oncology / Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [3]JCOG Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Breast Oncology, NHO Shikoku Cancer Center, Matsuyama, Japan, [5]Breast Oncology, Gunma Prefectural Cancer Center, Gunma, Japan, [6]Department of Breast and Endocrine Surgery, Tokai University School of Medicine Isehara Campus, Isehara, Japan, [7]Department of Breast Surgery, National Cancer Center Hospital East, Chiba, Japan, [8]Department of Breast Surgery, Niigata Cancer Center, Niigata, Japan, [9]Department of Medical Oncology, Fukushima Medical University, Fukushima, Fukushima, Japan, [10]Department of Surgery, Breast Oncology, National Hospital Organization Osaka National Hospital, Osaka, Japan, [11]Department of Breast Oncology, Aichi Cancer Center Hospital, Aichi, Japan, [12]Division of Breast Surgery, Chiba Cancer Center, Chiba, Japan, [13]Department of Medical Oncologyy, Kyorin university Hospital, Tokyo, Japan, [14]Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan, [15]Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Background: Systemic chemotherapy with anti-HER2 therapy is the standard of care for HER2-positive advanced breast cancer. Patient outcomes have improved remarkably with the use of novel anti-HER2 drugs, including trastuzumab (H), pertuzumab (P), and trastuzumab emtansine (T-DM1). The combination treatment comprising H, P, and docetaxel (D) (HPD) is highly recommended as the 1st-line treatment for patients with HER2-positive advanced breast cancer. In contrast, for elderly patients over 65 years of age, this regimen seems to be intolerable mentally and physically, and impairs their quality of life. A new standard treatment with less toxicity and non-inferior efficacy for elderly patients is needed.

Trial design: We have planned a randomized, multicenter, open-label, phase III trial to confirm the non-inferiority of T-DM1 compared to HPD in terms of overall survival (OS) in elderly patients with HER2-positive advanced breast cancer. The eligibility criteria are as follows: 1) histologically proven HER2-positive breast cancer with metastatic disease 2) age 65-74 years with a performance status (PS) score 0-2, or 75-79 years with a PS score 0-1, and 3) no anti-HER2 therapy with chemotherapy for breast cancer, excluding peri-operative adjuvant therapy. Patients will be randomized to receive either HPD (H 6 mg/kg, P 420 mg/body, and D 60 mg/m^2) or T-DM1 3.6 mg/kg every 3 weeks. The dose up of D (75 mg/m^2) from the second cycle is defined based on the data regarding safety during the first cycle. The primary endpoint is OS. The secondary endpoints are progression-free survival, response rate, adverse events, breast cancer-related death, and deterioration of activities of daily living. The trial has been designed to achieve 70% power to confirm non-inferiority of T-DM1 compared with HPD at a one-sided alpha of 5% with a non-inferiority margin of 1.3 in terms of hazard ratio. With a median OS of 30 months in both arms, 6 years of accrual, and 5 years of follow up, 312 pts are required, and the planned sample size is 330. The study commenced in January 2018.Clinical trial information: UMIN000030783.

Clinical trial identification: UMIN000030783.

Legal entity responsible for the study: Hiroji Iwata.

Funding: Japan Agency for Medical Research and Development.

Disclosure: N. Niikura: Research fund: Chugai Pharmaceutical CO., Ltd. S. Saji: Honoraria for lecture: Eisai, Chugai and Pfizer; Research grant: Taiho and Chugai. N. Masuda: Honoraria: Chugai, AstraZeneca, Pfizer and Takeda; Research funding: Chugai, AstraZeneca, Kyowa-kirin, MSD, Novartis, Pfizer Eli-Lilly and Daiichi-Sankyo. F. Nagashima: Research funding: Taiho, Ono, Oncotherapy, Merck, Zeria, Lilly Japan, Takeda, Chugai, Yakult, Sumitomo Dainippon, Daiichi Sankyo, Shionogi, Novartis, J-Pharma, Bristol-Myers Squibb, Kyowa Hakko Kirin, Mochida, Astellas, Bayer, MSD, Eisai, Janssen. H. Iwata: Honoraria: Chugai, Daiichi Sankyo, AstraZeneca, Pfizer; Consultant: Chugai, Daiichi Sankyo, Kyowa Hakko Kirin, Lilly, Novartis, AstraZeneca, Pfizer; Received research funding: Chugai, MSD, Kyowa Hkao Kirin, GSK, Daiichi Sankyo, Chugai, Lilly, Novartis, Bayer and Pfizer. All other authors have declared no conflicts of interest.

362TiP ATTAIN: Phase III study of etirinotecan pegol (EP) vs treatment of physician's choice (TPC) in patients (pts) with metastatic breast cancer (MBC) who have stable brain metastases (BM) previously treated with an anthracycline, a taxane, and capecitabine (ATC)

D. Tripathy[1], S.M. Tolaney[2], A.D. Seidman[3], C.K. Anders[4], N.K. Ibrahim[1], H.S. Rugo[5], C.J. Twelves[6], V. Dieras[7], V. Müller[8], A.L. Hannah[9], M.A. Tagliaferri[10], J. Cortes Castan[11]

[1]Department of Breast Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA, [2]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [3]Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [4]UNC Breast Center, University of North Carolina, Chapel Hill, NC, USA, [5]Breast Cancer Center, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [6]Oncology and Clinical Research, St. James's University Hospital Leeds, Leeds, UK, [7]Department of Medical Oncology, Institut Curie, Paris, Paris, France, [8]Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany, [9]Consultant, Consultant, Sebastapol, CA, USA, [10]Clinical Development, Nektar Therapeutics, San Francisco, CA, USA, [11]Breast Cancer Program, Vall d'Hebron University Hospital, Barcelona, Spain

Background: EP is a next-generation topoisomerase I inhibitor-polymer conjugate that provides continuous exposure to SN-38, the active metabolite of irinotecan. A BM mouse model showed high penetration and retention of SN-38 in CNS lesions, resulting in decreased size of CNS lesions and improved survival at concentrations achieved at the recommended dose in pts (Adkins BMC Cancer 2015). Although a phase 3 trial (BEACON) of EP vs TPC in 852 pts with advanced BC did not meet its primary endpoint of overall survival (OS) (HR 0.87; $P = 0.08$), a pre-planned subset analysis of 67 pts with stable BM showed improved OS (HR 0.51 [95% CI 0.30-0.86]; $P < 0.01$) (Perez Lancet Oncol 2015). The current phase 3 trial (ATTAIN) was designed to further study this subpopulation of pts.

Trial design: Pts with MBC with locally treated stable BM will be randomized 1:1 to EP or TPC in an open-label phase 3 study. Eligibility includes: ECOG PS 0 or 1; adequate organ function; prior ATC therapy (any setting); $\geq$1 prior cytotoxic regimen for pts with triple negative MBC; $\geq$2 prior cytotoxic regimens for pts with HR+ or HER2+ BC (pts with HR+/HER2+ BC must have received prior hormone therapy/HER2 targeted therapy); prior definitive local therapy of BM (whole brain radiation [RT], stereotactic RT or surgical resection as single-agent or combination); and stable signs/symptoms of BM with steroids (ie, unchanged or decreasing $\geq$7 days prior to randomization). Primary endpoint is OS. Key secondary endpoints are ORR and PFS by RECIST v1.1 and RANO-BM, CBR (ORR+SD $\geq$ 6 months) and QoL. Pts randomized to TPC will receive 1 of 7 IV agents. Pts are stratified by region, PS and receptor status. An independent data monitoring committee will assess interim data and determine final number of events needed to provide 80% conditional power to detect a statistically significant improvement in OS based on the promising zone adaptive design (Mehta & Pocock, 2011). Up to 220 pts will be randomized. PK sampling and UGT1A1 testing will be performed in the EP arm; plasma ctDNA will be assessed for predictive markers of efficacy.

Clinical trial identification: NCT02915744.

Legal entity responsible for the study: Nektar Therapeutics, San Francisco, CA.

Funding: Nektar Therapeutics, San Francisco, CA.

Disclosure: D. Tripathy: Consulting or advisory role: Novartis, Nektar, Pfizer, Puma Biotechnology; Travel, Accommodations, Expenses: Novartis; Research funding: Genentech/Roche (to institution), Novartis (to institution). S.M. Tolaney: Consulting or advisory role: Novartis, Pfizer, Merck, Lilly, Nanostring Technologies AstraZeneca, Puma Biotechnology, Genentech; Research funding (to institution): Genentech/Roche, Merck, Exelixis, Pfizer, Lilly, Novartis, Bristol-Myers Squibb; Research funding (to author): Eisai. A.D. Seidman: Honoraria: Eisai, Genentech, Genomic Health, Novartis; Consulting or advisory role: Nektar, Eisai; Speaker's bureau: Eisai, Genentech, Genomic Health, Novartis; Research funding: Bayer, Novartis. C.K. Anders: Consulting or advisory role: Sanofi, Novartis, Merrimack, Genentech/Roche, to-BBB technologies BV, Lilly, Nektar, Kadmon, Angiochem Patents, royalties, other intellectual property: Up to Date.com, Jones and Bartlell; Research funding (to institution): Sanofi, Novartis, to-BBB technologies BV, Puma Biotechnology, Angiochem, Merrimack, Lilly, Merck, Cascadian Therapeutics, Nektar, Tesaro. N.K. Ibrahim: Speakers' bureau: Celgene, Roche, Novartis; Travel, accommodations, expenses: Roche, Novartis; Honoraria: Celgene, Roche, Novartis; Research funding (to institution): GenomeDx, Newlink Genetics, Archer Biosciences. H.S. Rugo: Consulting or advisory role: Amgen; Speakers' bureau: Genomic Health; Travel, accommodations, expenses: Novartis, Roche/Genentech, OBI Pharma, Pfizer, Puma Biotechnology, Mylan; Honoraria: Genomic Health; Research funding (to institution): Plexxikon, Macrogenics, OBI Pharma, Eisai, Pfizer, Novartis, Lilly, Genentech, Merck, GTx, Incyte, Immunomedics. C.J. Twelves: Honoraria: Daiichi Sankyo, Eisai, Nektar. V. Dieras: Consulting or advisory role: Abbvie, Novartis, Pfizer, Roche/Genentech, Lilly Pharma; Speakers' bureau: Novartis, Pfizer, Roche; Travel, accommodations, expenses: Novartis, Pfizer, Roche. V. Müller: Consulting or advisory role: AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Nektar, Roche/Genentech, Novartis; Travel, accommodations, expenses: Pfizer, Roche Pharma AG. A.L. Hannah: Leadership: NeoGenomics Laboratories; Stock ownership interests: NeoGenomics Laboratories Consulting; Advisory role: Nektar, Pfizer, BeiGene. M.A. Tagliaferri: Employment: Nektar Leadership, Nektar Stock; Ownership interests: Nektar Consulting or advisory role (immediate family member): Bluebird Bio, Nektar Patents, royalties, other intellectual property: Nektar; Travel, accommodations, expenses: Nektar; Travel, accommodations, expenses (an immediate family member): Bluebird Bio, Nektar. J. Cortes Castan: Stock and other ownership interests: MedSIR; Honoraria: Celgene, Eisai, Novartis, Pfizer, Roche; Consulting or advisory role: AstraZeneca, Biothera, Celgene, Cellestia Biotech, Roche.

363TiP Phase Ib/IIa study of RX-5902, a novel orally bioavailable inhibitor of phosphorylated P68, which prevents nuclear β-catenin translocation in patients with triple negative breast cancer

J.R. Diamond[1], E. Andreopoulou[2], A.M. Favret[3], R. Nanda[4], C. Peterson[5], E. Benaim[5]
[1]Medical Oncology, University of Colorado Cancer Center Anschutz Cancer Pavilion, Aurora, CO, USA, [2]Medical Oncology, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY, USA, [3]Oncology, Virginia Cancer Specialists, Fairfax, VA, USA, [4]Oncology, University of Chicago, Chicago, IL, USA, [5]Clinical Operations, Rexahn Pharmaceuticals, Inc, Rockville, MD, USA

Background: RX5902 is an oral anti-tumor and immune modulating drug targeting the phosphorylated form of p68 (also known as DDX5), a member of the DEAD box family of RNA helicases. Phosphorylated p68 may play a vital role in cell proliferation and tumor/cancer progression by affecting elements in the Wnt Canonical pathway.

Trial design: This study is conducted as a phase 1b/2a with a 2-stage design. In stage 2 of the phase 2a study, eligible subjects (aged $\geq$ 18 years) are those diagnosed with triple negative breast cancer, refractory intolerant or ineligible to receive approved standard therapies. There is no limit on the number of prior therapies. Subjects need to have measurable or evaluable disease per RECIST ver 1.1, ECOG performance of 0 or 1 and normal organ function. Use of potent inhibitors or inducers of CYP3A4/3A5, within 14 days of planned study treatment, are excluded. Eligible subjects, who have been fasting, will receive oral RX-5902 at 250 mg administered 5 times per week followed by 2 days off for 4 weeks in each cycle. Treatment will continue for 6 or more cycles, or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or decision to discontinue. Primary endpoint is progression free survival (by RECIST v1.1); secondary end points include safety, overall response rate, time to progression and duration of response (by RECIST v1.1), duration of response. adverse events will be graded per NCI CTCAE v4.0. Response will be assessed every 8 weeks. Exploratory endpoints include biochemical levels of drug targets. Approximately 40 evaluable subjects will be enrolled in stage 2 of the phase 2.

Clinical trial identification: NCT02003092.

Legal entity responsible for the study: Rexahn Pharmaceuticals Inc.

Funding: Rexahn Pharmaceuticals, Inc.

Disclosure: C. Peterson, E. Benaim: Employee: Rexahn Pharmaceuticals. All other authors have declared no conflicts of interest.

364TiP Anti-hormonal maintenance treatment with or without the CDK4/6 inhibitor ribociclib after first line chemotherapy in hormone receptor positive/HER2 negative metastatic breast cancer: A phase II trial (AMICA) GBG 97

T. Decker[1], C. Denkert[2], K. Lübbe[3], V. Müller[4], C. Mundhenke[5], J. Furlanetto[6], M. Schmidt[7], M. Thill[8], V. Tierbach[9], F. Seither[10], S. Loibl[6]
[1]Hämatologie, Onkologie, Ravensburg, Germany, [2]Institute of Pathology, Charite Berlin Mitte, Berlin, Germany, [3]Onkologie, Diakovere gGmbH, Hannover, Germany, [4]Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany, [5]Klinik für Gynäkologie und Geburtshilfe, Universität Kiel, Kiel, Germany, [6]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [7]Johannes Gutenberg-Universität Mainz, Mainz, Germany, [8]Gynäkologie, Kliniken Markus-Krankenhaus, Agaplesion, Frankfurt am Main, Germany, [9]Project Management, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [10]Statistic, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany

Background: Although longer duration of chemotherapy (CT) is associated with longer progression-free survival (PFS) and overall survival (OS) in patients with metastatic breast cancer (MBC), the duration of CT is usually dictated by toxicities and patients and physicians preferences, resulting in treatment durations of less than 6 months. Therefore, well tolerated maintenance treatments with the potential to prolong PFS and OS are needed.

Trial design: AMICA is a multicentre, prospectively, randomized, open-label, controlled phase II study. Patients with hormone receptor (HR)+/HER2- MBC achieving stable disease or tumor response after at least 4 cycles of first-line CT at the discretion of the investigator (e.g. taxanes, capecitabine, vinorelbine, anthracyclines) will be eligible to be randomized 2:1 to receive maintenance endocrine therapy (ET) per investigator's choice either with or without the CDK4/6 inhibitor ribociclib. Patients might have received up to one prior line of ET. Maintenance ET could have already been started up to 6 weeks before randomization, but after achievement of stable disease or tumor response. Life-expectacy of $>$ 6 months is required. In both study arms, treatment will be given until disease progression, unacceptable toxicity, or withdrawal of consent. Primary objective is to evaluate the impact of a maintenance ET after first-line CT with or without ribociclib on PFS. Secondary objectives are OS, clinical benefit rate, safety, compliance and patient reported outcomes. Biomarkers predicting response to CDK inhibition and ET in formalin-fixed paraffin-embedded metastatic tissue and blood as well as the role of mutations in ctDNA will be analysed. Overall, 150 patients will be recruited. The study is conducted in 20-30 sites in Germany. One patient has been recruited so far.

Clinical trial identification: AMICA, GBG 97.

Legal entity responsible for the study: GBG Forschungs GmbH.

Funding: Novartis.

Disclosure: C. Denkert: Personal fees: Teva, Novartis, Pfizer, Roche, Amgen, MSD Oncology; Other: Sividon Diagnostics, outside the submitted work. K. Lübbe: Consulting or advisory role: Roche and Novartis. V. Müller: Honoraria: Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Pfizer, Novartis, Roche, Teva; Consolting or advisory role: Hexal, Roche, Pfizer, Amgen, Daiichi Sankyo, Nektar, EISAI; Travel accommodation: Roche, Pfizer. M. Schmidt: Honoraria: Roche, Novartis, Pfizer; Consulting or advisor role: Roche, Novartis, Pfizer; Speakers' bureau: Roche, Novartis, Pfizer; Travel accommodations: Roche, Pfizer. M. Thill: Travel reimbursement, Consulting, Honoraria: Amgen, AstraZeneca, Celgene, Eisai, Genomic Health, Lilly, Myriad, Neodynamics, Novartis, Pfizer, pfm Medical, Roche, RTI Surgical, SurgicEye, Teva; Writing assistance: Roche and Celgene; Research funding: Genomic Health. S. Loibl: Grants for Institution: AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, Teva, Vifor during the conduct of the study as well as outside the submitted work. All other authors have declared no conflicts of interest.

365TiP SAMANTHA: A European registry study to prospectively observe treatment patterns and outcomes in participants with HER2-positive unresectable locally advanced (LA) or metastatic breast cancer (mBC)

G.G. Steger[1], F. Puglisi[2], C. Timcheva[3], L. Costa[4], M. Casa-Nova[5], D. Hitzl[6], B. Dampier[7], N. Lindegger[8]
[1]Department of Internal Medicine I, Division of Oncology and Hematology, Medizinische Universität Wien, Vienna, Austria, [2]Department of Clinical Oncology, IRCCS CRO di Aviano, National Cancer Institute, Aviano, Italy, [3]Clinic of Medical Oncology, MHAT for Women Health Nadezhda OOD, Sofia, Bulgaria, [4]Oncology Division, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lissabon, Portugal, [5]Medical Oncology, Hospital Beatriz Angelo-Loures, Loures, Portugal, [6]Medical Affairs, Roche Austria GmbH, Vienna, Austria, [7]Medical Affairs, Clinical Research Consulting, Vienna, Austria, [8]Global Product Development, F. Hoffmann-La Roche AG - Switzerland, Basel, Switzerland

Background: Numerous treatment options are available to patients with HER2-positive (HER2+) breast cancer. The used drugs as well as the sequence in which they are used may vary between countries. Frequently used in unresectable LA/mBC is trastuzumab, usually proposed in various combinations, as well as pertuzumab, trastuzumab-emtasine, and lapatinib. Only limited data are available on the treatment patterns used in clinical practice. This study is part of a global umbrella study and will meet the need for real world data on treatment patterns and outcomes in HER2+ unresectable LA or mBC. A descriptive analysis may identify possible associations between patient characteristics, treatments and outcomes. The study will collect data for up to 8 years, thus as new treatments become available, the study will also offer a unique opportunity to gain insight into evolving treatment options.

Trial design: SAMANTHA is a prospective, multicenter non-interventional post authorization safety study designed to observe anti-cancer treatment regimens and clinical outcomes in participants with HER2+ unresectable LA/mBC for up to 8 years. Diagnosis of unresectable LA or mBC can be up to 6 months old prior to registry enrollment. Enrolled participants will receive treatment and clinical assessments for their HER2+ unresectable LA/mBC as determined by their treating physician, according to the standard of care and routine clinical practice at each site. Primary outcome measures are progression-free survival per anti-cancer treatment regimens assessed according to site-/country-specific medical practice and percentage of participants by different anti-cancer treatment regimens and treatment sequences. Secondary outcome measures include overall survival, duration of response per anti-cancer treatment regimens, percentage of participants with best overall response of complete response or partial response per anti-cancer treatment and total number of treatment regimens received by participants.

Clinical trial identification: NCT02913456, EUPAS22426, MO39146.

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: G.G. Steger: Honoraria and travel support: Roche Austria. F. Puglisi: Compensation for an advisory board: Roche. C. Timcheva: Travel support: Roche Bulgaria. L. Costa: Honoraria and travel support: Roche Portugal. D. Hitzl: Employee: Roche Austria. B. Dampier: Fees for services: Roche Austria. N. Lindegger: Employee: F.Hoffmann-La Roche. All other authors have declared no conflicts of interest.

366TiP The NAME trial: A direct comparison of oral navelbine given either classic or metronomic in metastatic HER2 neg breast cancer

S.T. Langkjer[1], J. Kenholm[2], J.D. Jensen[3], K. Wedervang[4], A.T. Brixen[5], M. Grunnet[6], L. Stenbygaard[7], H. Danø[8], V. Glavicic[9], E.H. Jacobsen[10], A.S. Brems-Eskildsen[11], H.L. Kruse[12], T. Dongsgaard[13], J. Neimann[12], J. Geisler[14]

[1]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [2]Deparment of Oncology, Regionshospitalet Herning, Herning, Denmark, [3]Oncology, Odense University Hospital, Odense, Denmark, [4]Oncology, Sønderborg Sygehus, Sønderborg, Denmark, [5]Oncology, Herlev Hospital, Herlev, Denmark, [6]Oncology, Rigshospitalet, Copenhagen, Denmark, [7]Oncology, Aalborg Sygehus Syd, Aalborg, Denmark, [8]Oncology, Hilleroed Hospital, Hilleroed, Denmark, [9]Oncology, Naestved, Naestved, Denmark, [10]Oncology, Sydvestjysk Sygehus Esbjerg, Esbjerg, Denmark, [11]Oncology, Aarhus University Hospital, Aarhus, Denmark, [12]Deparment of Oncology, Aarhus University Hospital, Aarhus, Denmark, [13]Oncology, Regionshospitalet Herning, Herning, Denmark, [14]Deparment of Oncology, Ankerhus University Hospital, Oslo, Norway

Background: Navebine is an antineplastic agent that has shown afficacy in the treatment of a variety of solid tumors, including breast cancer. The drug can be given intriavenously, but also as oral tablet treatment. Preclinical studies, as well as clinical observations, suggest that the administration of small, frequent doses of chemotherapy (metronomic dosing) has an effect, not only on cancer cells, but also on endothelialcells in the tumor vasculature. By giving smaller, but more frekvent doses of the drug, higher dose intensity, without corresponding side effects, is optained. Whether treatment under the metronomic principle is superior to conventional treatment, has not yet been validated in the clinic, so this study is hoped to clarify this.

Trial design: This is a investigator-initated, prospective randomized fase II, non-blinded multinational, multicentre study running in Denmark and Norway. 200 women diagnosed with HER2 neg metastatic breast cancer will be enroled. Patients are randomized to either: Arm A Clasical treatment: Navelbine Oral: Navelbine Oral[a]: 60 mg/m^2 day 1, day 8 (and day 15), every three weeks for the first cycle. Hereafter 80 mg/m^2 day 1 and day 8, every three weeks for de following cycles. Or Arm B Metronomic treatment: Navelbine Oral[a]: with 3 week cycles of daily doses of 30 mg. (Patients with body surface $\leq$ 1,54 m^2 or 65 Years or more start on 20 mg daily.) Treatment is given first or second line (chemotherapy). The primary Objectives is to evaluate the Disease Control Rate (CR + PR + SD, SD > 3 months) in the two arms. Secondary Objectives are to compare the duration of Disease Control, TTP, RR, DR and OS and side effects for the two regimens. Also Evaluation of the Global Health Status/QoL, on the basis of the EORTC QOL C30 questionnaire is made. Finally a translational study to explore the potential of biomarkers during metronomic therapy is performed.The patients will be treated until progression or to high toxicity, or until the patient wishes discontinuation.

Clinical trial identification: EudraCT: 2016-002165-63. Health Board no: 2017040059. Approved by Research Ethics Commitee and Data Protection Agency June 2017.

Legal entity responsible for the study: Sven Tyge Langkjer.

Funding: The study is an investigator-initiated study, but financially supported by the pharmaceutical company Pierre Fabre.

Disclosure: All authors have declared no conflicts of interest.

367TiP LUCY: A phase IIIb, real-world study of olaparib in HER2-negative metastatic breast cancer patients with a BRCA mutation

K.A. Gelmon[1], G.P. Walker[2], G.V. Fisher[2], S.C. McCutcheon[2]

[1]British Columbia Cancer Agency, Vancouver, BC, Canada, [2]AstraZeneca, Cambridge, UK

Background: The Phase III OlympiAD trial (NCT02000622) showed a significant improvement in progression-free survival (PFS) in favour of olaparib vs physician's choice chemotherapy in patients with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm). In January 2018, the US FDA expanded the approved use of olaparib to treat patients with HER2-negative mBC and a gBRCAm. LUCY (NCT03286842) has been initiated to evaluate the clinical effectiveness of olaparib in these patients in a real-world setting, and has been expanded to include a cohort of patients with somatic BRCA mutations (sBRCAm).

Trial design: LUCY is an open-label, single-arm, multicentre, international Phase IIIb trial. Patients with HER2-negative mBC and a deleterious BRCAm (gBRCAm or sBRCAm), who have received treatment with taxane or anthracycline in either the adjuvant or metastatic setting, and $\leq$2 prior lines of chemotherapy for metastatic disease, will be enrolled. Patients will be treated with open-label olaparib tablets (300 mg twice daily) until disease progression, unacceptable toxicity, or other discontinuation criteria. For gBRCAm patients (Cohort 1), the primary objective is to evaluate the clinical effectiveness of olaparib via investigator-assessed PFS (radiological, symptomatic, or clear progression of non-measurable disease); secondary objectives include overall survival, time to second progression, and clinical response rate. These primary and secondary objectives will be exploratory in sBRCAm patients (Cohort 2), and PFS will be assessed by RECIST 1.1.

An additional key exploratory objective will be 24-week disease control rate in the subset of all patients with adequately treated, stable brain metastases at baseline. Safety and tolerability will be described. Initial screening across ~170 sites in 16 countries will be conducted to identify a target sample of 250 patients with gBRCAm and 20 patients with sBRCAm. The first subject was enrolled in Q1 2018.

Clinical trial identification: NCT03286842.

Editorial acknowledgement: Stephen Paterson, Mudskipper Business Ltd.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: K.A. Gelmon: Consulting or advisory role: AstraZeneca, Eli Lilly, Merck, and Pfizer; Expert opinion: Genentech. G.P. Walker: Contracted services and stockholder; AstraZeneca. G.V. Fisher, S.C. McCutcheon: Employee and stockholder; AstraZeneca.

368TiP START: A randomized phase II study in patients with triple negative, androgen receptor positive locally recurrent (unresectable) or metastatic breast cancer treated with darolutamide or capecitabine (UCBG-306)

H. Bonnefoi[1], C. Levy[2], G. MacGrogan[3], T. Grellety[4], B. Asselain[5], M. Pulido[6], S. Everhard[7], J. Lemonnier[8], A. Gonçalves[9]

[1]Medical Oncology, Institute Bergonié, Bordeaux, France, [2]Department of Medical Oncology, Centre Francois Baclesse, Caen, France, [3]Department of Pathology, Institute Bergonié, Bordeaux, France, [4]Medical Oncology, Institute Bergonié, Bordeaux, France, [5]UCBG, UNICANCER, Paris, France, [6]Epidemiological and Clinical Research Unit and INSERM CIC1401, Institute Bergonié, Bordeaux, France, [7]R&D, UCBG, UNICANCER, Paris, France, [8]R&D, UCBG, UNICANCER, Paris, France, [9]Department of Medical Oncology, Institute Paoli Calmettes, Marseille, France

Background: Up to 36% of triple-negative breast cancer (TNBC) are androgen receptor (AR)-positive ($\geq$ 10% by immuno-histochemistry, IHC). When these tumours metastasise, several clinical trials assessing antagonists of the AR or androgen synthesis suppressor showed promising clinical benefit rates (CBR). Darolutamide is a novel, effective and well tolerated AR antagonist tested in prostate cancer clinical trials. Thus we aim to assess clinical activity and safety of darolutamide in AR-positive TNBC.

Trial design: This is an open-label, multicenter, randomized, two-arm non-comparative phase II trial (NCT03383679). Women with locally recurrent (unresectable) or metastatic and centrally confirmed AR-positive TNBC are eligible. Patients should be chemotherapy naïve or have received a maximum of one line of chemotherapy for advanced disease. Eligible patients are randomized (2:1) between darolutamide experimental arm (600 mg twice daily) and capecitabine control arm (according to each center policy, minimum 1000 mg/m2 twice daily, 2 weeks on and 1 week off). Randomization (minimization) is stratified by number of previous lines of chemotherapy (0 versus 1). In each arm, the primary endpoint is the clinical benefit rate (CBR) at 16 weeks, defined as complete response, partial response or stable disease as per RECIST 1.1 criteria. Tumour biopsies and sequential circulating tumour DNA are collected as part of a translational research program. A total of 90 patients will be randomized.The first patient was included in March 2018. As of May 2018, 3 patients have been screened and 1 patient has been randomized.

Clinical trial identification: NCT03383679.

Legal entity responsible for the study: UNICANCER.

Funding: Bayer.

Disclosure: All authors have declared no conflicts of interest.

369TiP PATINA: A randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + Anti-HER2 therapy + endocrine therapy (ET) vs. anti-HER2 therapy + ET after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer (MBC)

S. Loibl[1], O. Metzger[2], S.J. Mandrekar[3], C. Mundhenke[4], S. Seiler[5], P. Valagussa[6], A. DeMichele[7], E. Lim[8], D. Tripathy[9], E.P. Winer[10], C. Huang[11], L. Carey[12], P. Francis[13], K.D. Miller[14], M.P. Goetz[3], A. Prat[15], S. Loi[16], I. Krop[2], L. Gianni[17], E.M. Ciruelos[18]

[1]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [2]Alliance Foundation for Clinical Trials in Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [3]Alliance Foundation for Clinical Trials in Oncology, Mayo Clinic, Rochester, NY, USA, [4]German Breast Group, Universitätsklinikum Schleswig-Holstein, Kiel, Germany, [5]Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [6]Fondazione Michelangelo, Fondazione Michelangelo, Milan, Italy, [7]PrECOG, University of Pennsylvania-Perelman Center for Advanced Medicine, Philadelphia, PA, USA, [8]Australia & New Zealand Breast Cancer Trials Group, Garvan Institute, Darlinghurst, Australia, [9]Alliance Foundation for Clinical Trials in Oncology, MD Anderson Cancer Center, Houston, TX, USA, [10]Alliance Foundation for Clinical Trials in Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [11]Pfizer Oncology, New York, NY, USA, [12]Alliance Foundation for Clinical Trials in Oncology, University of North Carolina - Chapel Hill, Chapel Hill, NC, USA, [13]Australia & New Zealand Breast Cancer Trials Group, Peter MacCallum Cancer Center, Melbourne, Australia, [14]PrECOG, Indiana University Simon Cancer Center, Indianapolis, IN, USA, [15]SOLTI, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [16]Australia & New Zealand Breast Cancer Trials Group, Peter MacCallum Cancer Center, Translational Breast Cancer Genomics Lab, Melbourne, Australia, [17]Fondazione Michelangelo, IRCCS San Raffaele, Medical Oncology, Milan, Italy, [18]SOLTI, Hospital Universitario 12 de Octubre, Madrid, Spain

Background: Pre-clinical data showed the role of CDK 4/6 inhibition in HER2+ disease. Results from phase 2 clinical trials point to synergistic antitumor activity and potential efficacy of palbociclib when given in combination with anti-HER2 therapy (tx), particularly in HR+/HER2+ breast cancer. The aim of PATINA is to evaluate the efficacy and safety of the addition of palbociclib to anti-HER2 tx and ET maintenance after induction tx in the 1st line setting for HR+/HER2+ MBC.

Trial design: The PATINA trial (AFT-38/NCT02947685) is a pivotal, open-label, international, phase III study. The trial is open to patients (pts) with histologically confirmed HR+/HER2+ MBC provided they are without evidence of disease progression by local assessment after induction tx. Following 4-8 cycles of chemotherapy (taxane or vinorelbine) with anti-HER2 tx for MBC, pts will be randomized 1:1 to standard anti-HER2 tx (trastuzumab +/- pertuzumab) in combination with ET with or without palbociclib until disease progression. ET options are either an aromatase inhibitor or fulvestrant. Premenopausal women must receive LHRH agonist. Total planned accrual is 496 pts. Primary objective is to demonstrate that the combination of palbociclib with anti-HER2 tx plus ET is superior to anti-HER2 tx plus ET alone in prolonging progression-free survival (PFS). Key secondary objectives are measures of tumor control, overall survival, safety and quality of life. The main translational science objective is to compare PFS estimates according to PIK3CA mutation status. All pts approached to participate in PATINA will be asked to share remaining biospecimens with the Mastering Breast Cancer Initiative. This initiative was created in order to understand the natural history of MBC and how it envolves over time with the aim to develop new treatments for this patient population. Recruitment has started in 07/2017 and is expected to take place across approximately 130 sites in Australia, Germany, Italy, New Zealand, Spain, and the US.

Clinical trial identification: AFT-38/NCT02947685.

Legal entity responsible for the study: Alliance Foundation Trials (AFT) in collaboration with GBG Forschungs GmbH.

Funding: The study is sponsored by Alliance Foundation Trials (AFT) and financially supported by Pfizer.

Disclosure: S. Loibl: Grants: AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, Teva, Vifor during the conduct of the study as well as outside the submitted work. D. Tripathy: Personal fees: Pfizer, during the conduct of the study. C. Huang: Other: Pfizer , during the conduct of the study. M.P. Goetz: Other: Biovica, Novartis, Sermonix, Genomic Health; Grants and other: Lilly; Grants: Pfizer, outside the submitted work. S. Loi: Consultant (not compensated): Seattle Genetics, Pfizer, Novartis, BMS, Merck and Roche-Genentech. All other authors have declared no conflicts of interest.

370TiP A phase Ib, multicenter, open-label study of the antibody-drug conjugate trastuzumab deruxtecan (DS-8201a) combination with nivolumab for advanced HER2-expressing breast or urothelial cancer

S.A. Hurvitz[1], M.D. Galsky[2], J. Shahidi[3], G. Zhang[4], S. Raza[3], A. Necchi[5]

[1]Department of Medicine, UCLA Medical Center, Los Angeles, CA, USA, [2]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Clinical Development, Daiichi Sankyo Inc., Basking Ridge, NJ, USA, [4]Biostatistics and Data Management, Daiichi Sankyo Inc., Basking Ridge, NJ, USA, [5]Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: DS-8201a is a novel antibody-drug conjugate comprised of a humanized HER2 antibody attached by a cleavable peptide-based linker to a topoisomerase I inhibitor; characterized by a high drug-to-antibody ratio of about 8. In an ongoing phase 1 trial, DS-8201a showed high and durable responses across multiple tumors, with a confirmed objective response rate (ORR) of 61.4% in previously T-DM1-treated HER2-positive (IHC 3+ or IHC2+ and ISH+) breast cancer (BC) and 31.6% in HER2 low-expressing (IHC 2+/1+ and ISH–) BC (Oct 2017 cutoff; Modi et al, SABCS 2017). Nivolumab, an anti-PD-1 antibody, is FDA-approved for metastatic urothelial carcinoma (UC) after platinum failure. A xenograft model of HER2-expressing cancer showed significantly increased survival with the combination of DS-8201a with an anti-PD-1 antibody vs either treatment alone (Iwata et al, ASCO 2017).

Trial design: This phase 1b, multicenter, open-label study will assess the combination of DS-8201a with nivolumab in previously chemotherapy-treated HER2-expressing advanced BC or UC. Previous treatment with anti-PD-1/PD-L1 therapy is an exclusion criterion. A dose escalation (part 1) will identify the recommended dose for expansion (RDE), and dose expansion (part 2) will evaluate efficacy and safety/tolerability of the DS-8201a RDE combination with nivolumab (360 mg IV; q3wk). Part 1 is a 3 + 3+3 design with 3 dose cohorts of DS-8201a (3.2, 5.4, and 6.4 mg/kg q3wk); enrollment will start at 3.2 mg/kg. Following RDE determination, enrollment in part 2 will open (Table); estimated total enrollment is 99–117. ORR is the primary efficacy endpoint; secondary endpoints include overall survival, disease control rate, duration of response, progression-free survival, time to response based on central review, and safety/tolerability. The study is open for enrollment as of May 2018.

Table: 370TiP

Part 2 Cohorts

Cohort	Cancer Type	HER2 Status	Approximate Enrollment
1	BC	HER2-positive (IHC 3+ or ISH+)	30
2	BC	HER2 low-expressing (IHC 2+/1+ and ISH–)	15
3	UC	HER2 high-expressing (IHC 3+/2+)	30
4	UC	HER2 low-expressing (IHC 1+)	15

Clinical trial identification: NCT03523572.

Editorial acknowledgement: Medical writing and editorial support was provided by Stefan Kolata, PhD of AlphaBioCom, LLC (King of Prussia, PA).

Legal entity responsible for the study: Daiichi Sankyo, Inc.

Funding: Daiichi Sankyo, Inc.

Disclosure: S.A. Hurvitz: Grants: Amgen, Bayer, BI Pharma, Genentech, GSK, Lilly, Novartis, Pfizer, Roche, PUMA, Merrimack, Medivation, Dignitana, OBI Pharma, Biomarin, Cacadian, Lilly, Novartis, OBI Pharma, Bayer. M.D. Galsky: Consultancy fees: Genetech, Merck, Novartis, Astellas, AstraZeneca, and BMS; Stock/stock options: Dual Therapeutics. J. Shahidi, G. Zhang, S. Raza: Full time employee: Daiichi Sankyo, Inc. A. Necchi: Personal fees: Roche, Janssen; Grants and personal fees: Merck, AstraZeneca.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii122–viii132, 2018
doi:10.1093/annonc/mdy273

CNS TUMOURS

371O Intra-CSF liposomal cytarabine plus systemic therapy as initial treatment of breast cancer leptomeningeal metastasis: A randomised, open-label trial

E. Le Rhun[1], A. Mailliez[1], J. Wallet[2], I. Rodrigues[1], T. Boulanger[3], I. Desmoulins[4], J. Barriere[5], M. Fabbro[6], S. Taillibert[7], C. Andre[8], M.C. Le Deley[2], M. Weller[9], J.M. Bonneterre[10]

[1]*Breast Cancer Unit, Oscar Lambret Center, Lille, France,* [2]*Department of Biostatistics, Oscar Lambret Center, Lille, France,* [3]*Department of Radiology, Oscar Lambret Center, Lille, France,* [4]*Department of Medical Oncology, Centre Georges-François Leclerc (Dijon), Dijon, France,* [5]*Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France,* [6]*Department of Medical Oncology, ICM Regional Cancer Institute of Montpellier, Montpellier, France,* [7]*Neuro-Oncology, Pitié-Salpétrière Hospital, Paris, France,* [8]*Department of Pathology, Oscar Lambret Center, Lille, France,* [9]*Neurology, University Hospital and University of Zurich, Zurich, Switzerland,* [10]*Breast Cancer Unit, Centre Oscar Lambret, Lille, France*

372O Mutational and inflammatory microenvironment characteristics in primary and matched local recurrent non-small cell lung cancer brain metastases

A.S. Berghoff[1], B. Erguener[2], M.R. Schuster[2], U. Rajky[1], G. Ricken[3], J.M. Frischer[4], B. Gatterbauer[4], C. Marosi[5], K. Dieckmann[6], G. Widhalm[4], C. Bock[2], M. Preusser[7]

[1]*Department of Medicine 1, Medical University of Vienna, Vienna, Austria,* [2]*Austrian Academy of Sciences, CeMM Research Center for Molecular Medicine, Vienna, Austria,* [3]*Institute of Neurology, Medical University of Vienna, Vienna, Austria,* [4]*Department of Neurosurgery, Medical University of Vienna, Vienna, Austria,* [5]*Department of Medicine I - Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria,* [6]*Department of Radiotherapy, Medical University of Vienna, Vienna, Austria,* [7]*Department of Medicine I, Vienna General Hospital (AKH) - Medizinische Universität Wien, Vienna, Austria*

373O Results of phase II trial of SL-701, a novel immunotherapy targeting IL-13Ra2, EphA2, and survivin, in adults with second-line recurrent glioblastoma (GBM)

D. Peereboom[1], L.B. Nabors[2], P. Kumthekar[3], M. Badruddoja[4], K. Fink[5], F. Lieberman[6], S. Phuphanich[7], E. Dunbar[8], T. Walbert[9], D. Schiff[10], D.D. Tran[11], L.S. Ashby[12], N. Butowski[13], F. Iwamoto[14], R. Lindsay[15], J. Bullington[16], M. Schulder[17], J. Sherman[18], C. Brooks[19], D. Reardon[20]

[1]*Brain Tumor and Neuro-Oncology Center, Cleveland Clinic Foundation, Cleveland, OH, USA,* [2]*Neuro-Oncology, University of Alabama Comprehensive Cancer Center, Birmingham, AL, USA,* [3]*Department of Neurology and Department of Medicine, The Ken &Roth Davee, Chicago, IL, USA,* [4]*Neuro-Oncology, Center for Neurosciences, Tucson, AZ, USA,* [5]*Neuro-Oncology, Baylor Scott&White Neuro-Oncology Associates, Dallas, TX, USA,* [6]*Division of Hematology/Oncology, University of Pittsburgh, Pittsburgh, PA, USA,* [7]*Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA,* [8]*Piedmont Brain Tumor Center, Piedmont Helathcare, Atlanta, GA, USA,* [9]*Neuro-Oncology, Henry Ford Health System, Detroit, MI, USA,* [10]*Neurology, University of Virginia School of Medicine, Charlottesville, VA, USA,* [11]*Department of Neurosurgery, University of Florida, Gainesville, FL, USA,* [12]*Neuro-Oncology, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA,* [13]*Neurological Surgery, UCSF, San Francisco, CA, USA,* [14]*Neuro-Oncology, Columbia University Medical Center, New York, NY, USA,* [15]*R&D, Stemline Therapeutics, New York, NY, USA,* [16]*Clinical, Stemline Therapeutics, New York, NY, USA,* [17]*Neuro-Oncology, North Shore University Hospital, Manhasset, NY, USA,* [18]*Neurosurgery, George Washington University, Washington, DC, USA,* [19]*R&D, Stemline Therapeutics, New York, NY, USA,* [20]*Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*

374O Mismatch repair deficiency (MMRd) in glioma patients (PTS): Frequency and correlation with clinical, histological and molecular characteristics

G. Lombardi[1], M. Caccese[1], M. Simonelli[2], M. Fassan[3], P. Persico[4], E. Lorenzi[4], R. Bertorelle[5], M.P. Gardiman[3], L. Bellu[6], A. Pambuku[1], A. Santoro[2], V. Zagonel[1]

[1]Department of Clinical and Experimental Oncology, Veneto Institute of Oncology, IOV – IRCCS, Padua, Italy, [2]Department of Biomedical Sciences, Humanitas University and Humanitas Cancer Center, Rozzano, Italy, [3]Surgical Pathology Unit, Department of Medicine (DIMED), University Hospital Padua, Padua, Italy, [4]Humanitas Cancer Center, Humanitas Clinical and Research Hospital, Rozzano, Italy, [5]Immunology and Molecular Oncology Unit, Veneto Institute of Oncology, IOV – IRCCS, Padua, Italy, [6]Radiation Therapy and Nuclear Medicine Unit, Veneto Institute of Oncology, IOV – IRCCS, Padua, Italy

375O Radiological phenotyping of IDH mutation status in gliomas using dynamic susceptibility contrast perfusion-weighted MRI

D. Roettger[1], E. Sanverdi[2], C. Sudre[2], S. Brandner[2], V. Katsaros[2], S. Bisdas[2]

[1]R&D, Image Analysis Ltd, London, UK, [2]Institute of Neurology, University College London, London, UK

376PD Impact of a molecular prescreening program (MPP) in the management of patients with non-glioblastoma brain tumors

J.C. Benítez Montañez[1], M. Vieito Villar[2], C. Hierro[2], M. Gonzalez Rodriguez[2], I. Matos[2], I. Braña Garcia[2], C. Suarez Rodriguez[2], E.A. Martinez Saez[3], M.C. Perez-Gago[2], R. Morales-Barrera[2], C. Ortiz[2], C. Suarez[2], X. Maldonado[4], F. Martinez-Ricarte[5], C. Auger[6], A. Azaro[2], R. Dienstmann[7], J. Carles[2], E. Garralda[2]

[1]Medical Oncology, Hospital Mutua de Terrassa, Terrassa, Spain, [2]Oncology, Vall đHebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [3]Pathology, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Radiation Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain, [6]Radiology, Hospital Vall d'Hebron, Barcelona, Spain, [7]Oncology Data Science, Vall d'Hebron University Hospital, Barcelona, Spain

377PD **Multiplex digital PCR for the diagnostic of pilocytic astrocytoma and glioneuronal tumors**

F. Fina[1], D. Henaff[2], A. Bresson[2], V. Juline[2], A. Romain[1], C. Carole[3], D. Figarella-Branger[1]

[1]Service d'Anatomie Pathologique et Neuropathologie, APHM, Marseille, France, [2]R&D, ID solutions, Grabels, France, [3]CNRS, INP, Inst Neurophysiopathol, Aix-Marseille University, Marseille, France

378PD **Hypothyroidism is associated with improved survival prognosis in patients with newly diagnosed brain metastases**

C. Wippel[1], A.M. Starzer[1], A.S.S. Berghoff[2], E. Bergen[1], P. Wolf[3], G. Widhalm[4], J.M. Frischer[4], B. Gatterbauer[4], C. Marosi[1], K. Dieckmann[5], R. Bartsch[1], M. Preusser[6]

[1]Department of Medicine I - Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria, [2]Department of Medicine I, Medical University of Vienna, Vienna, Austria, [3]Department of Medicine III, Medical University of Vienna, Vienna, Austria, [4]Department of Neurosurgery, Medical University of Vienna, Vienna, Austria, [5]Department of Radiotherapy, Medical University of Vienna, Vienna, Austria, [6]Department of Medicine I, Vienna General Hospital (AKH) - Medizinische Universität Wien, Vienna, Austria

379PD **Androgen receptor expression in breast cancer brain metastases**

E.S. Bergen[1], A.S.S. Berghoff[1], U. Rajky[1], M. Rudas[2], Z. Bago-Horvath[2], R. Exner[3], K. Dieckmann[4], G. Widhalm[5], M.I. Gnant[3], C.C. Zielinski[6], G.G. Steger[1], M. Preusser[1], R. Bartsch[1]

[1]Department of Medicine 1, Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria, [2]Department o Pathology, Medical University of Vienna, Vienna, Austria, [3]Department of Surgery, Medical University of Vienna, Vienna, Austria, [4]Department of Radiotherapy, Medical University of Vienna, Vienna, Austria, [5]Department of Neurosurgery, Medical University of Vienna, Vienna, Austria, [6]Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

380PD **Understanding biological activity, tumor response and pseudoprogression in a phase-IIb study of MDNA55 in adults with recurrent or progressive glioblastoma (GB)**

M.F. Bexon[1], A. Achrol[2], K. Bankiewicz[3], A. Brenner[4], N. Butowski[5], S. Kesari[6], F. Merchant[7], R. Merchant[7], D. Randazzo[8], M. Vogelbaum[9], M. Zabek[10], J. Sampson[8]

[1]Medical, Medicenna BioPharma, Houston, TX, USA, [2]Neurovascular Surgery, Pacific Neurosciences Institute, Santa Monica, CA, USA, [3]Department of Neurological Surgery, UCSF, San Francisco, CA, USA, [4]Medical Oncology, University of Texas Health San Antonio, San Antonio, TX, USA, [5]Neurological Surgery, UCSF, San Francisco, CA, USA, [6]Department of Translational Neurosciences and Neurotherapeutics, Pacific Neurosciences Institute, Santa Monica, CA, USA, [7]Clinical, Medicenna BioPharma, Houston, TX, USA, [8]Department of Neurosurgery, Duke University Medical Center, Durham, NC, USA, [9]Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA, [10]Neurovascular Surgery, Mazovian Brodnowski Hospital, Warsaw, Poland

381PD Comprehensive geriatric assessment (CGA) for outcome prediction in elderly patients (PTS) with glioblastoma (GBM): A mono-institutional experience

G. Lombardi[1], E. Bergo[1], L. Bellu[2], M. Caccese[3], A. Lettiero[1], G. Tierno[1], A. Pambuku[1], A. Brunello[1], V. Zagonel[1]

[1]Medical Oncology 1, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy, [2]Radiotherapy, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy, [3]Medical Oncology, University of Verona, AOUI Verona, Verona, Italy

382PD Second-line treatment of bevacizumab plus lomustine versus bevacizumab plus irinotecan in patients with recurrent glioblastoma

J. Simões, N.T. Tavares, C. Borges, S. Meireles, C. Fernandes, A. Costa, C. Caeiro, M. Damasceno

Medical Oncology Department, Centro Hospitalar de São João, Porto, Portugal

383P Worldwide trends in survival from adult glioma 2000-2014 (CONCORD-3): Impact of morphology

F. Girardi, V. Di Carlo, A. Bonaventure, C. Allemani, M.P. Coleman, CONCORD Working Group

Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

Background: The CONCORD programme initiated world-wide surveillance of trends in population-based cancer survival in 2015. The third cycle (CONCORD-3) covered 18 cancers, including brain tumours. Data for 656,659 adults (15-99 years) diagnosed with a brain tumour were provided by 286 registries in 59 countries. For adults diagnosed during 2010-2014, 5-year net survival from all brain tumours combined varied between 15% and 42%. We will present detailed comparison of survival trends for gliomas defined by anatomic location, morphology and WHO grade.

Methods: We will present the numbers of adults diagnosed with a glioma and the subtype distribution by continent. We will estimate net survival up to 5 years, using the unbiased Pohar Perme estimator. Net survival is the probability that patients survive their cancer until a given time since diagnosis, after controlling for competing risks of death (background mortality) by age, sex, country and calendar year.

Results: Data were obtained for 545,184 adults. Glioblastoma was the most common morphology (57%). Astrocytic, oligodendroglial and oligo-astrocytic tumours specified as WHO grade I-III made up 21% of all gliomas, while glioma not otherwise specified (NOS) and astrocytoma NOS made up 15%. Rarer tumours, such as oligodendroglioma, fibrillary astrocytoma, pilocytic astrocytoma, mixed glioma, anaplastic oligodendroglioma and anaplastic astrocytoma made up less than 10% of gliomas in all continents. The frequency of glioblastoma was 58% or higher in Europe, North America and Oceania, 53% in Africa and around 45% in Asia and Central and South America. The frequency of astrocytoma NOS was lowest in Europe, North America and Oceania (below 9%) and highest in Central and South America (22%).

Conclusions: The distribution of gliomas varies around the world. The differential was the frequency of unspecified morphologies, which may be partly attributable to diagnostic capacity. We will assess the extent to which disparities in morphology contribute to worldwide variation in survival from adult brain tumours. When comprehensive survival analyses are available, this project is expected to become the reference for international comparison of brain tumour survival, to help inform national cancer control plans.

Legal entity responsible for the study: London School of Hygiene and Tropical Medicine.

Funding: Children with Cancer UK.

Disclosure: All authors have declared no conflicts of interest.

384P Clinical characteristics of 3,030 glioblastoma multiforme (GBM) patients in high, upper middle and lower middle economic regions based on real-world data (RWD)

L.M. Mitrofan[1], M.R. Krukas-Hampel[2], L.A. Mendoza[3]

[1]Real World Evidence Solutions, Oncology, IQVIA, Paris, France, [2]Consulting Services, IQVIA Global Consulting Services, New York, NY, USA, [3]Medical Strategy & Science, Oncology-Hematology, IQVIA, Prague, Czech Republic

Background: GBM is the most common and aggressive primary brain tumor in adults. This study investigated RWD-based differences among 3,030 GBM patients stratified by three economic regions.

Methods: The analysis was based on IQVIA syndicated cross-sectional surveys, collecting anonymized patient-level data between January 2016 and September 2017 in different countries, grouped into three economically different regions. Region 1 (high): EU5 (France, Germany, Italy, UK, Spain), Canada, Australia; Region 2 (upper middle): Korea, China, Taiwan; Region 3 (lower middle): Brazil, Mexico.

Results: The percentage of patients aged >65 years was 23.9 % for region 1, 6.33 % for region 2 and 13.62 % for region 3, confirming younger GBM population in region 2. The age difference among the regions was statistically significant ($P < 0.0001$). The incidence of male (65 %) and female (35 %) patients was homogenous across all regions. Region 1 showed the highest testing rate (60 %) for MGMT promoter methylation and region 3 the lowest (33 %). EGFR mutation was not studied in more than 50 % of patients across the regions. However, in overall tested population, the EGFR VIII mutations varied: 39 %, 90 %, and 73 % for regions 1, 2 and 3, respectively. Concerning drug treatment options, temozolomide was the leading therapy (> 90 %) in all three regions, regardless of MGMT and EGFR status. The highest percentage (35 %) for cognitive impairment studied by MMSE (Mini Mental State Examination) was found in region 2, followed by 25 % and 22 % in regions 1 and 3, respectively. We did not find any differences in Performance Status or comorbidities among the regions, with no reported comorbidities in > 60 % of patients.

Conclusions: This multi-variable analysis from RWD shows differences in clinical characteristics (i.e., age, biomarkers and MMSE), which may be taken into consideration in the design of GBM global studies. To our best knowledge, this study was based on the largest GBM database ever published.

Legal entity responsible for the study: IQVIA.

Funding: IQVIA.

Disclosure: All authors have declared no conflicts of interest.

385P Radiotherapy versus combined radiochemotherapy for unresectable glioblastoma: A SEER based analysis

M.H. Osman

Faculty of Medicine, Zagazig University, Zagazig, Egypt

Background: Glioblastoma (GBM) is the most common type of malignant primary brain tumors originating from glial cells. GBM is an aggressive and extremely invasive tumor with a very poor prognosis and median survival of 12.1-14.6 months. Surgery is a corner stone in the treatment of GBM. However, resection may be inapplicable for lesions located in eloquent gray matter such as brainstem, basal ganglia or thalamus. For unresectable tumors, treatment varies from short-course radiotherapy to extended-course radiotherapy and even combined radiochemotherapy. In this study, we compare radiotherapy alone with combined radiochemotherapy to determine patients' survival with both treatments.

Methods: To identify patients with unresectable GBM, the Surveillance, Epidemiology and End Results database (SEER) of the National Cancer Institute was searched. Patients with an initial diagnosis of GBM between 2004 and 2013 were identified and their clinical characteristics were extracted from records for analysis.

Results: A total number of 2562 patients with unresectable GBM was identified with a median age of 63 years and a median survival of 6 months. The most common sites for tumor was frontal lobe (23.2%) and overlapping lesion of brain (21.1%). Out of total, 548 (21.4%) with a median age of 69 years received radiotherapy alone and 2014 (78.6%) with a median age of 61 years received combined radiochemotherapy. Survival analysis showed that patients who received combined radiochemotherapy had better survival compared to whom received radiotherapy alone with 1-year relative survival of 32.3% and 11.5% and 2-year relative survival of 11.1% and 3.5% for combined radiochemotherapy group and radiotherapy alone group, respectively (p-value < 0.001).

Conclusions: The prognosis of patients with unresectable GBM is still very poor. Combined radiochemotherapy showed a significant better survival compared to radiotherapy alone.

Legal entity responsible for the study: Mohamed H. Osman.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

386P Clinical characteristics of glioblastoma multiforme (GBM) patients who reached 400 days post diagnostic from a retrospective real-world data

L.M. Mitrofan[1], M.R. Krukas-Hampel[2], L.A. Mendoza[3]

[1]Real World Evidence Solutions, Oncology, IQVIA, Paris, France, [2]Consulting Services, IQVIA Global Consulting Services, New York, NY, USA, [3]Medical Strategy & Science, Oncology-Hematology, IQVIA, Prague, Czech Republic

Background: GBM is the most common and aggressive primary CNS malignancy with a median survival of 12-14 months. Less than 3% of GBM patients survive three years. Understanding the clinical profile along with the predictors for Long Term Survivors is of outstanding importance.

Methods: This study used IQVIA syndicated cross sectional surveys analysing retrospectively anonymized live patient-level data between January 2016 and September 2017 from EU5, Canada, Australia, Korea, China, Taiwan, Brazil and Mexico. We characterized patients who achieved at least 400 days (group 400) between their diagnosis and the start date of their latest therapy at the time they were surveyed. 370 patients correspond to group 400 from the collected population of 3,036. Due to methodological limitations for data collection, we will mainly focus our analysis on the clinical profile of group 400 without fully comparing them with the rest of the population.

Results: Majority of patients in group 400 are relapsed (92.4%) with a mean of 791.7 $\pm$780.6 days from diagnosis to relapse date ($N = 342$). 38% of patients are having an ECOG more than 2 at the moment of their current therapy and 67% have no comorbidities. The time to first chemotherapy has a mean value of 293.3 $\pm$795.1 days) and the time to first surgery is 33.7 $\pm$250.5 days. 57.0% of patients had one surgery with 70.8% of these patients having a total resection for their last surgery. In addition, the age of the patients was below 45 years for 33% for group 400 versus 20% for the bellow 400, which indicate a higher number of young patients in the group 400. We identified that Ratio male/female is relatively homogenous across both groups. The expression of mutant EGFRvIII was significantly lower (4.59%) in the 400 group compared with 16.84% in the bellow 400 group ($P<.0001$). MGMT promoter methylation was not significantly different ($P = 0.3711$).

Conclusions: GBM patients who reach 400 days between their diagnosis and the start date of last therapy are in majority patients who had relapsed and more likely to be younger, and show a lower percentage of non-mutated EGFRvIII. Of outmost clinical interest, it would be to predict what patients would pass from below 400 group to 400 days group.

Legal entity responsible for the study: IQVIA.

Funding: IQVIA.

Disclosure: All authors have declared no conflicts of interest.

387P Corticosteroids administration as a prognostic factor in glioblastoma patients: An Egyptian experience

K. Abdel Karim, M.R. Kelany, O. Abdelrahman, A.M. El-Adawy

Clinical Oncology Department, Ain Shams University, Faculty of Medicine, Cairo, Egypt

Background: Glioblastoma multiform (GBM) is the most common primary malignant brain tumors. Standard management is maximal safe resection followed by concurrent chemoradiotherapy then adjuvant chemotherapy with temozolomide TMZ. Management of GBM patients also involves medical treatment containing corticosteroids that might have direct effects on tumor cell proliferation and apoptosis. We aimed at discussing the clinical relation between corticosteroids usage in GBM patients, overall survival OS, and progression free survival PFS, according to the records from Clinical Oncology Department, Ain Shams University, Cairo, Egypt.

Methods: Retrospective analysis was performed on 66 adult patients diagnosed with GBM by surgery or imaging criteria between January 2014 and December 2016. Data analysis was performed on October 2017 to assess the relation between corticosteroid dependence (defined as the failure to withdraw the corticosteroids after their initiation during the treatment with radiotherapy and TMZ) with OS and PFS. Patients were arranged in 2 arms according to steroid dependency. Arm (A) was steroid dependent (34 patients) and arm (B) was steroid non-dependent (32 patients).

Results: The median age of the entire cohort was 52.8 years (Range 25-72) with male predominance (68.1%) and 72.7 % of the patients received radiotherapy as their main treatment. 59.1 % of the whole cohort were treated by standard radiotherapy regimen of 60 Gy, while 13.6 % were treated by hypo-fractionation radiotherapy with total dose of 45 Gy. 62.1 % of the patients received TMZ concurrently with radiotherapy. Corticosteroids dependency was statistically significantly correlated to both OS with a median of 2.5 months in the corticosteroids dependent group vs. 13.1 months in the corticosteroids non-dependent group ($p < 0.001$), and also to PFS with a median of 2.3 in the corticosteroids dependent group vs. 9.4 months in the corticosteroid non-dependent group ($p = 0.035$).

Conclusions: This study from an Egyptian center shows that dependence on corticosteroids during the course of treatment of GBM patients may affect survival. Larger multicentric studies are needed to elaborate the influence of corticosteroids on the disease course.

Legal entity responsible for the study: Clinical Oncology Department, Ain Shams University, Cairo, Egypt.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

388P Impaired survival in resected glioblastoma multiforme patients treated with early chemoradiation

L.P. del Carpio[1], P. Gomila[1], S.D. Camacho[1], S. Moron[1], M. Riudavets[1], C. Molto[1], A. Bujosa[1], M. Borrell[1], R. Teres[1], B. Martin[1], P. Gallardo[1], E. Acosta[2], L. Tilea[2], A. Soto[2], C. De Quintana[3], J. Craven-Bartle[2], A. Gallardo[4], B. Gomez[5], S. Bonilla[5], O. Gallego[1]

[1]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2]Radiation Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]Neurosurgery, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [4]Pathology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [5]Neuroradiology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Background: The best time to initiate concurrent chemoradioation (ChRT) with temozolamide after surgery in glioblastoma multiform (GBM) patients has not been clearly established. Our aim was to investigate whether survival is influenced by the time to ChRT in patients with different types of surgery.

Methods: We conducted a retrospective study of all the patients treated in our centre from January 2005 to December 2017, with a histological diagnosed GBM, which underwent surgery and completed concurrent ChRT with temozolamide. The time to ChRT was grouped in 4 quartiles, and early ChRT was defined as happening during the first quartile. Surgery type was divided into resection (R) and biopsy (B). Survival at 12 months (OS12m), median progression free survival (mPFS) and overall survival (mOS) were calculated. Other relevant clinical factors were also analyzed.

Results: From a total of 160 patients, 119 who completed ChRT were included. The median time to ChRT was 37 days, (Q1=26, Q2=37, Q3=45); 35 (30%) received early ChRT (≤26 days). Patients who underwent R were 101 (85%) and 18 (15%) B. The mean age was 62y, 94 patients (79%) had PS 0-1, MGMT methylation was positive in 23 (19%). There were no significant differences between groups regarding Age, PS and MGMT status; but more patients treated with B received early ChRT (31% vs 8%). The OS12m was shorter for patients who underwent R and received early vs no-early ChRT (35% vs 73%, p = 0.002). No differences in OS12m were found for B patients (0% vs 18%, p = 0.4) according to time to ChRT. For patients who received early ChRT, the mOS was similar despite surgery type (9.9, 95% CI 9.6 – 11 vs 12.9, 95% CI 6.5 – 19.3, p = 0.8, for R and B, respectively). But for patients who did not receive early ChRT, longer survival was achieved in the R vs B subgroup (16.2, 95%CI 14.1 – 17.8 vs 11.1, 95% CI 4.5 – 17.7, p = 0.024, for R and B, respectively) and resection type remained significant in the multivariate analysis (HR = 1.2, p = 0.02).

Conclusions: We have found that patients with GBM who underwent resection had a worse prognosis if they received early chemoradiation (≤ 26 days). No differences were found for biopsied patients. A no-early chemoradation approach for patients who underwent resection may be safe. Prospective studies are encouraged.

Legal entity responsible for the study: Hospital de la Santa Creu i Sant Pau.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

389P Bevacizumab-induced hypertension correlation with survival in recurrent glioblastoma multiforme

N.T. Tavares, J. Simões, C. Borges, S. Meireles, A. Costa, C. Fernandes, C. Caeiro, M. Damasceno

Serviço de Oncologia Médica, Centro Hospitalar de São João, EPE, Porto, Portugal

Background: Patients with Glioblastoma multiforme (GBM) have a poor prognosis and therapeutic options are scarce after recurrence. Bevacizumab (Bv) is approved for use in this setting with proven benefits in progression-free survival (PFS) but not in overall survival (OS). Arterial hypertension (HT), a well described side effect of Bv, has been proposed as a predictive marker of clinical response in GBM as well as in other neoplasms, though conflicting data is available. This study tried to evaluate the prognostic impact of HT and other factors in recurrent GBM.

Methods: Retrospective cohort of adult patients with recurrent GBM treated with a combination of Bv + Irinotecan (BvI) or Lomustine (BvL) between 01/01/2009 and 31/12/2017. Clinical records were analysed. Bv-induced HT was defined as a single evaluation ≥140/90 mmHg during first 3 months of treatment or the need to initiate or increase dose of antihypertensive drugs. OS and PFS were estimated by Kaplan-Meier method and multivariate analysis according to Cox regression; a significant level of 0.05 was chosen to assess the statistical significance.

Results: 120 patients were included with male gender predominance (64.2%) and a median age at Bv onsent of 58.7 (27-78 yo). All patients were treated in first line with surgery (complete resection: 61.7%; partial resection: 38.3%) and Stupp protocol. BvI was used in 70.8% (n = 85) and BvL in 29.2% (n = 35) patients. Bv-induced HT was found in 29% of patients (n = 29) and proteinuria (PU) in 15% (n = 18). Median PFS was 4.4 months (mo) (CI 95% 3.5-5.4) and median OS was 7.8 mo (CI 95% 6.8-87). In multivariate analysis (Table), both HT and PU had an impact in PFS. OS was significantly prolonged in patients with HT and in those without corticosteroids (CCS) at Bv.

Table: 389P

		PFS (mo)	HR (CI 95%)	OS (mo)	HR (CI 95%)
HT	Yes	9.1	HR 1.825	14	HR 2.726
	No	4.1	(1.136-2.931), p = 0.013	7.8	(1.325-5.608), p = 0.006
PU	Yes	6.1	HR 2.341	-	-
	No	3.9	(1.282-4.275), p = 0.006	-	
CCS at Bv onset	Yes	-	-	6.9	HR 2.022
	No	-		13.4	(1.059-3.860), p = 0.033

Conclusions: In recurrent GBM patients treated with Bv combinations, HT was significantly related with prolonged PFS and OS. PU and the need for CCS also showed a significant prognostic impact.

Legal entity responsible for the study: Serviço de Oncologia Médica - Centro Hospitalar de São João, EPE.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

390P +405C>G polymorphism of VEGF in randomly selected GBM patients

I. Djan[1], M. Djan[2], N. Vucinic[3], B. Nikolin[4], S. Salma[4], S. Lucic[5], N. Vuckovic[6], M. Lucic[7]

[1]Department of Radiotherapy, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia, [2]Department of Biology and Ecology, University of Novi Sad Faculty of Sciences, Novi Sad, Serbia, [3]Department of Pharmacy, University of Novi Sad Faculty of Medicine, Novi Sad, Serbia, [4]Department of Medical Oncology, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia, [5]Department of Nuclear Medicine, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia, [6]Department of Pathology, University of Novi Sad Faculty of Medicine, Novi Sad, Serbia, [7]Diagnostic Imaging Center, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia

Background: Vascular endothelial growth factor (VEGF) is a glycoprotein growth factor specific for vascular endothelial cells, responsible for angiogenesis. So far, 44 SNPs with clinical relevance have been detected (ClinVar NCBI database) and the majority of those are associated with cancers of colon and others solid tumors. The aim of this study was to assess the distribution of + 405C>G VEGF gene polymorphism in patients diagnosed with glioblastoma and to test association with the overall survival.

Methods: Tissue paraffin-embedded samples were subjected to molecular analyses and VEGF polymorphism detection retrieved from 66 patients diagnosed for glioblastoma. VEGF genotypes at position <G405C were detected using allele-specific PCR, followed by RFLP-PCR with 2U of BsmFI (Fermentas, Lithuania). The results were analyzed using SPSS Statistics 17.0 software.

Results: The most frequent allele (SNP variant) was G (72.58%) (Table). No statistically significant differences were observed in a pairwise genotype groups comparison for overall survival (OS). Between-group variance is negative (-3,840), indicating no differences in mean OS among genotypes. ANOVA also did not show any statistically significant variance among groups (F = 0.124; p = 0.879).

Table: 390P Descriptive statistics for overall survival in three genotypes of VEGF gene

Genotype	N	Mean OS	SD	SE	CI (95%)	
					lower	upper
CC	9	10.56	8.918	2.973	3.70	17.41
CG	32	11.00	9.449	1.670	7.59	14.41
GG	21	12.10	8.420	1.837	8.26	15.93
Total	62	11.31	8.910	1.132	9.04	13.57

N – number of patients; OS – overall survival in months; SD – standard deviation; SE – standard error; CI – confidence interval; min – minimum in months; max – maximum in month

Conclusions: Even though no significant difference in overall survival in GBM patients regarding the examined polymorphism of VEGF gene was found, it was also shown that genotype GG has one month longer overall survival in the examined patients group. It

is probable that random selection of patients regardless of applied treatment, or without treatment, and ECOG 1-4 requires larger number of patients to be included in order to provide final proof whether this polymorphism has any effect on overall survival.

Legal entity responsible for the study: Milos Lucic.

Funding: Provincial Secretariat for High Education and Science of Vojvodina Province.

Disclosure: All authors have declared no conflicts of interest.

391P Expression and clinical prognostic role of ZWINT in glioma: Analysis based on data-mining and integration of gene databases

Z. Mengxian

Cancer Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Human ZW10 interacting kinetochore protein (ZWINT) gene plays critical roles in mitotic cycle maintenance and is known to be linked with poor clinical prognosis in various tumors. However, the clinical significance of ZWINT in glioma has not yet been understood. The purpose of this study was to determine the expression profile and functions of ZWINT in glioma, to confirm its prognostic value.

Methods: The gene expression and clinical information profile were downloaded from The Cancer Genome Atlas (TCGA) dataset and a statistical analysis was made. We probed the edgeR and gplots packages in the R language to identify differentially expressed genes (DEGs). The Kaplan–Meier plotter online tool was used to study the association of ZWINT expression and overall survival (OS) of glioma patients. Immunohistochemistry (IHC) and quantitative RT-PCR were performed to evaluate protein and mRNA expression levels of ZWINT. ZWINT-siRNA was transfected into U251 and U87 glioma cells to inhibit the expression of ZWINT. Then, the effects of ZWINT silencing on glioma cell lines proliferation, invasion and apoptosis were determined by the Celigo assay, MTT assay, transwell assay, Annexin V FACS assay and Caspase-3/7 assay in vitro. Functional and pathway enrichment analysis were performed for DEGs using the DAVID database. Protein–protein interaction (PPI) network analysis was established by STRING and visualized by Cytoscape.

Results: Integrated analysis revealed that ZWINT protein and mRNA expression were significantly upregulated in glioma versus normal tissues, its expression was positively correlated with the patient age, poor pathological grade, and conferred poor prognosis. Knockdown of ZWINT expression inhibited the proliferation and invasion of U251 and U87 cells, and apoptosis was distinctly increased following ZWINT-siRNA infection. 20 hub genes and a significant module showed that the DEGs were principally related to cell division, and mitotic cell cycle.

Conclusions: Our preliminary study highlighted that the expression of ZWINT is upregulated in glioma, which is correlated with poor prognosis. ZWINT silencing can effectively inhibit proliferation, induce apoptosis and suppress migration and invasion during human glioma development, which may provide a new promising tumor-specific therapeutic combination hub genes target for anti-mitosis agents.

Legal entity responsible for the study: Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Funding: China National Natural Fund Project (NO.81272780).

Disclosure: The author has declared no conflicts of interest.

392P Lipid peroxidation and cognitive impairment in patients with brain cancers

S. Kim[1], S. Kim[2]

[1]College of Nrusing, Keimyung University, Daegu, Republic of Korea, [2]Public Health Center, Uijeongbu City Hall, Uijeongbu City, Republic of Korea

Background: The prevalence of cognitive impairment is known to be high, but the knowledge of its correlates with lipid peroxidation is limited. The mechanisms responsible for the development of cognitive impairment have been discussed widely, and emerging evidence suggests a significant role of lipid peroxidation as well as vascular inflammation as main contributors to cognitive impairment. We aimed to explore the relationship between lipid peroxidation and the presence of cognitive impairment in patients with brain cancers during cancer-related therapy.

Methods: 58 first-ever brain cancer patients without previous cognitive impairment were consecutively enrolled in the current study. The levels of lipid peroxidation were evaluated by looking at the total cholesterol (TC) to high-density lipoprotein (HDL)-cholesterol (TC/HDL-c), low-density lipoprotein (LDL)-cholesterol to HDL-cholesterol (LDL-c/HDL-c), and triglycerides to HDL-cholesterol (TG/HDL-c) at the same time as performing a cognitive impairment test. The lipid peroxidation was measured at two times, within 24 h after admission and 3 months after recieving cancer-related therapy. Cognition function was evaluated by the Mini-Mental State Examination (MMSE) at the same time as lipid peroxidation evaluation.

Results: In this study, all patients were homogeneous in terms of general characteristics, tumor histology types, severity, and location. The patients were classified as cognitively impaired (n = 15, 25.9%) or non-cognitively impaired (n = 43, 74.1%) at 3 month after recieving cancer-related therapy. At admission time, the serum levels of lipid peroxidation were normal values in all patients but the levels were increased at 3 months after brain cancer onset in cognitively impaired groups. The level of lipid peroxidation was significantly different both with and without cognitive impairment groups at 3 months after brain cancer onset ($p < 0.001$). There was no significant difference between the two groups in tumor histology types, severity, and location.

Conclusions: Lipid peroxidation will need to be considered as a potential indicator for the management of cognitive impairment in early brain cancer stages.

Legal entity responsible for the study: Kim Sanghee.

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP; Ministry of Science, ICT & Future Planning) (No. NRF-2017R1C1B5016280).

Disclosure: All authors have declared no conflicts of interest.

393P FAT1 on YAP1-TEAD1 interaction augments oncogenic potential of GBM cells

Y. Gupta[1], S.S. Shivajirao[1], K. Irshad[1], B. Dikshit[1], T. Srivastava[2], P.P. Chattopadhyay[1], S. Sinha[1], K. Chosdol[1]

[1]Biochemistry, AIIMS, New Delhi, India, [2]Genetics, University of Delhi, New Delhi, India

Background: Glioblastoma (GBM) is a lethal brain tumor arising from supporting cells of the brain. We have recognized the oncogenic role of FAT1 gene in GBM, regulating inflammatory and hypoxic microenvironment of the tumor as well as migratory/invasive properties of tumor cells. In *Drosophila*, fat, the ortholog of FAT1, is known to regulate the Salvador-Warts-Hippo (SWH) pathway, but its role in human is not clear. Here, we have analyzed the effect of FAT1 on SWH pathway in glioma.

Methods: Glioma cell lines (U87MG, U373, A172, GOS3 and SW1088) were transfected with FAT1 specific siRNA/control siRNA and the expression of SWH pathway molecules was analysed by qPCR/western blot. Protein-protein interactions were analyzed by co-immunoprecipitation (Co-IP) after over-expression of YAP1 (wild-type and mutated) and TEAD1 with and without FAT1 knockdown.

Results: The mRNA expression of FAT1 and SWH pathway molecules (MST1, LATS1, LATS2, YAP1 and TEAD1) was highest in U87MG cells followed by A172, U373MG and GOS3. After FAT1 knockdown, the mRNA expression of MST1 and BIRC2 were significantly decreased with no change in the levels of LATS1, LATS2, YAP1, TEAD1 and BIRC5. At protein level, increased YAP1 and phospho-YAP1 was observed after FAT1 knockdown with increased total as well as phospho-YAP1 in the cytoplasmic extract as compared to the nuclear extract. There was significant reduction in the interaction between YAP1 and TEAD1 in siFAT1 treated cells compared with siControl treated cells.

Conclusions: On FAT1 knockdown, we found (i) increased YAP1 protein level, which could be by increasing the protein stability as no change was observed at the mRNA level, (ii) increased phospho-YAP1 level as it relieves the inhibitory effect on YAP1 phosphorylation, (iii) it affects the sub-cellular localization of YAP1 by retaining YAP1 in the cytosol and thereby, (iv) decrease in the YAP1:TEAD1 interaction with decreased expression of their target gene, Birc2. This finding of the effect of FAT1 on YAP1 in GBM is novel with features pointing towards the oncogenic role of FAT1 by regulating YAP1 sub-cellular localization and co-transcriptional activity independent of SWH pathway.

Legal entity responsible for the study: All India Institute of Medical Sciences, New Delhi.

Funding: All India Institute of Medical Sciences, New Delhi.

Disclosure: All authors have declared no conflicts of interest.

394P Extracts of *Cerbera manghas L.* effectively inhibit the growth of glioblastoma cells and their stemloids

Y-J. Lai, J-C. Tsai, W-S. Liu, H-I. Lam

Department of Life Science, National Taiwan Normal University, Taipei, Taiwan

Background: Glioblastoma multiforme (GBM) is the grade IV glioma and the most common adult primary brain tumor. It is notorious for its heterogeneity, invasiveness and resistance to chemo- and radiotherapies. These characteristics make it a highly recurrent malignant disease with poor prognosis. The potential new target for intervention in GBM is its cancer stem cells (GSCs).

Methods: To identify an improved treatment by targeting GSCs, we screened 400 botanical extracts for their effects on cytotoxicity and colony formation ability in GBM cell lines and tumorspheres.

Results: We identified the extracts of *Cerbera manghas* L. as being effective inhibitors of the growth and migration of GBM cell lines and its tumorspheres. We further demonstrated that neriifolin was one of the active principles. Neriifolin effectively inhibits the growth of $CD133^+$-GBM tumorspheres and their colony formation. The extracts of *Cerbera* and neriifolin both reduced AKT activation and caused cell cycle G1 arrest while reducing the protein level of the stem cell marker Sox2. Furthermore, higher doses of these treatments induced apoptosis of tumorspheres. In the mouse

xenotransplantation model, neriifolin inhibited the growth of $CD133^{+}$-GBM tumorsphere-derived tumors in vivo.

Conclusions: In summary, neriifolin obtained from extracts of *C. manghas* may serve as a drug lead compound for GBM therapies.

Editorial acknowledgement: Louise T. Chow.

Legal entity responsible for the study: Department of life Science, National Taiwan Normal University.

Funding: Ministry of Science and Technology, Taiwan, ROC.

Disclosure: All authors have declared no conflicts of interest.

395P Contrast enhancement in low grade gliomas: A classic prognostic factor in the molecular age

F. Castet[1], E. Alanya[2], M. Gil-Gil[1], N. Vidal[3], C. Izquierdo[4], C. Mesia[1], J. Bruna[5]

[1]Medical Oncology, Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain, [2]Medical Oncology and Radiotherapy, Edgardo Rebagliati Martins National Hospital - EsSalud, Lima, Peru, [3]Anatomia Patològica, Hospital Universitari de Bellvitge, Hospitalet De Llobregat, Spain, [4]Service de Neuro-Oncologie, Hospices Civils de Lyon, Groupe Hospitalier Est, Lyon, France, [5]Neurology, Hospital Universitari de Bellvitge, Hospitalet De Llobregat, Spain

Background: Contrast enhancement (CE) is described in 10-60% of low grade gliomas (LGG). Its prognostic significance is controversial, and its correlation with IDH mutations and 1p/19q codeletion is unknown. The aim of this study is to investigate whether CE is associated with molecular characteristics of LGG and elucidate its prognostic value.

Methods: All confirmed histological cases of LGG diagnosed in a single institution between years 2000-2016 were retrospectively reviewed (n = 104). Clinical, radiological and molecular factors were collected. Spinal and brainstem localization, only-biopsied tumours with ring-like enhancement and incomplete medical records were excluded. 1p/19 codeletion analysis was performed by FISH, IDH was performed by immunohistochemistry. IDH wild-type tumours were confirmed with qPCR. Overall survival (OS) was estimated by Kaplan-Meier method.

Results: We included 89 patients, with a median follow-up of 73.3 months. Mean age was 41.6 years, and 65.2% were male. CE was present on 25.8% of preoperative MRI, and 25.3% of patients were considered high-risk according to Pignatti score. Most were astrocytomas (67.4%) and 84.4% were surgically removed. IDH mutation was found in 66.7% of tumour samples, and 17.9% had a 1p/19q codeletion. No differences were observed amongst CE and non-CE groups, apart from age (46.6 vs 39.9 years, respectively; $p = 0.041$). IDH mutation ($p = 0.776$) and 1p/19q codeletion ($p = 0.512$) were evenly distributed. On univariate analysis, size >6cm ($p = 0.002$), CE ($p = 0.026$), extent of resection ($p = 0.008$), Pignatti score ($p = 0.002$) and IDH mutation ($p = 0.003$) were significantly associated to OS. On multivariate analysis, only CE ($p = 0.009$) and IDH status ($p = 0.005$) were independently associated to OS.

Conclusions: CE in LGG provides complementary and independent prognostic information to IDH and 1p/19q codeletion. Its contribution to treatment decisions requires further exploration in larger prospective cohort studies.

Legal entity responsible for the study: Unidad de Neuro-Oncología, Institut Català d'Oncologia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

396P Can diffusion tensor MR imaging identify glioma IDH mutation status?

S. Bisdas[1], J. Yuan[2], L. Mancini[2], D. Roettger[3]

[1]Institute of Neurology, University College London, London, UK, [2]Department of Neuroradiology, University College London Hospitals NHS Trust, London, UK, [3]R&D, Image Analysis Ltd, London, UK

Background: The isocitrate dehydrogenase (IDH) mutation status is a recognized molecular biomarker for glioma stratification. In addition, glioma clinical management benefits from advanced MRI sequences including diffusion tensor imaging (DTI). For first time, we investigated the diagnostic power of DTI to characterize gliomas with respect to IDH mutation status.

Methods: This retrospective study examines the accuracy of DTI for staging of IDH mutant (98) and wild-type (67) gliomas in a treatment-naïve setting. The tumour was manually segmented in the MRI and two DTI-derived parameters, namely fractional anisotropy (FA) and mean diffusivity (MD) values were calculated and plotted as histograms. Thresholds for the optimal diagnostic performance in terms of IDH mutation were sought in selected histogram parameters of FA and MD maps using parametric and non-parametric tests as well as receiver operating characteristic curve analysis.

Results: Significantly higher MD median values and significantly lower FA median values were observed in the IDH mutant compared with the wild-type group. As follows, the median MD value was defined as a robust predictor for IDH mutation status [area under the curve (AUC) = 0.82]. The developed logistic regression model included the top 5 correlating histogram parameters and the patient age. The assessment using the parameter combination reached better performance (AUC=0.85) compared with the prediction using parameter of the median MD value alone.

Conclusions: MR imaging DTI-derived metrics (MD and FA values) in combination with demographic information has the potential to non-invasively predict molecular stratification of gliomas.

Legal entity responsible for the study: University College London.

Funding: Has not received any funding.

Disclosure: D. Roettger: Head of Scientific and Medical Affairs: IAG. All other authors have declared no conflicts of interest.

397P Comparative assessment of orthotopic brain tumor growth using bioluminescence and magnetic resonance imaging

Y. Tsvetkova[1], C. Green[2], G. Schuetz[2], J. Hoffmann[3], D. Zopf[1], P. Lejeune[1]

[1]Drug Discovery, Oncology, Bayer AG, Berlin, Germany, [2]MR & CT Contrast Media Research, Bayer AG, Berlin, Germany, [3]Experimental Pharmacology & Oncology, EPO Berlin-Buch GmbH, Berlin, Germany

Background: Small-animal tumor models are essential for developing translational therapeutic strategies in oncology research. Intracranial brain tumor models are of high clinical relevance, since they closely resemble the tumorigenesis in humans. The use of such models, however, requires the application of imaging methods to quantitatively assess tumor growth and therapy efficacy. The objective of this study was to evaluate intracranial tumor growth and treatment response in mouse models using magnetic resonance imaging (MRI) and bioluminescence imaging (BLI). Further aim was to establish correlation between tumor volume and bioluminescence signal and compare the imaging modalities in terms of accuracy and efficiency.

Methods: Three groups (untreated, vehicle and Temozolomide-treated group) of ten mice each were implanted intracranially using stereotactic device with U87 glioma cells expressing firefly luciferase. Two cycles of temozolomide at 50 mg/kg 5days on/9days off were administered orally by gavage. The mice were imaged using bioluminescence and MR (preclinical 4.7 T MR scanner) once per week.

Results: The data showed that both imaging methods can efficiently measure tumor growth and therapy response but significantly differ in their throughput and type of information. MRI offers detailed tumor localization and 3D volumetric measurements, but has limited capacity to assess early tumor growth. BLI identifies tumors early but not tumor localization, precluding discrimination of intraventricular and extracranial tumor growth. Tumor volume determined with MRI and BLI signal intensity showed a strong linear correlation (r = 0.918).

Conclusions: BLI appears a reliable technique to evaluate intracranial tumor growth in mouse models. Adding MR scans to longitudinal BLI improves assessment of tumor properties such as volume, location, hemorrhage and necrosis. Other intracranial tumor xenografts, with varying characteristics, i.e. diffuse growth, are being analyzed to improve assessment of both imaging modalities.

Legal entity responsible for the study: Bayer AG.

Funding: Bayer AG.

Disclosure: All authors have declared no conflicts of interest.

398P Radiologically evident treatment effects in patients with glioblastoma (GBM) and its clinical implications

H.K. Gan[1], C. Murone[1], M. Wong[2], G. Fitt[3], E. Kennedy[4], D. Maag[4], K. Aldape[5]

[1]Medical Oncology, Olivia Newton-John Cancer Research Institute/ Austin Health, Heidelberg, Australia, [2]Medicine, Sydney Medical School, The University of Sydney, Sydney, Australia, [3]Radiology, Austin Health and Olivia Newton-John Cancer Research Institute, Austin Hospital, Heidelberg, Melbourne, Australia, [4]Oncology Development, AbbVie Inc USA, North Chicago, IL, USA, [5]Department of Pathology, Toronto General Hospital/Research Institute (UHN), Toronto, ON, Canada

Background: GBM is the most common primary brain tumor. Survival is poor with standard surgery followed by radiotherapy (RT) and temozolomide (TMZ). Pseudoprogression on MRI is well described post-RT, particularly within the first 3 months, and confounds response assessment. Whilst not previously described for drug treatment alone, anecdotal cases were described in a Phase 1 study of depatuxizumab mafodotin (depatux-m). Depatux-m is an antibody-drug conjugate, comprised of a tumor-specific anti-EGFR antibody linked to a microtubule cytotoxin, monomethyl auristatin F, that demonstrated promising antitumor activity in adult GBM pts with EGFR-amplified tumors. This exploratory study will determine if depatux-m exhibits radiologically evident treatment effects in pts with GBM, i.e. drug induced pseudoprogression.

Methods: This non-interventional study enrolls pts with GBM who underwent tumor debulking surgery after MRI evidence suggested treatment failure in Phase 1-3 depatux-m trials. Pts had received depatux-m alone or in combination with TMZ. Resected tumor tissue is formalin-fixed, paraffin-embedded and centrally reviewed. Radiographic assessments were collected per original study protocol (typically q8 wks), or as clinically indicated, and centrally reviewed. Clinical response is evaluated by RANO criteria. This study will assess correlation between radiographic and histologic evidence of disease progression after depatux-m treatment. Exploratory endpoints are progression-free survival and overall survival.

Results: As of April 2018, 7 pts with recurrent GBM were enrolled at 2 sites in Australia. All pts completed RT at a minimum of 11 months (range 11-26) prior to re-resection. 4 pts had histological confirmation of recurrence prior to treatment.

Conclusions: Histology showed that 57% (4/7) of pts with disease progression by RANO criteria after depatux-m, with or without TMZ, had predominantly treatment effect per local pathologist assessment. Central review indicated that of these 4 pts, 2 pts were ≥75% necrotic and 2 showed complete absence of tumour. 2 pts had histological confirmation of recurrence prior to treatment. Cases and associated clinical impact are presented.

Editorial acknowledgement: Medical writing support was provided by Ana Mrejeru, Ph.D., of AbbVie.

Legal entity responsible for the study: AbbVie Inc.

Funding: AbbVie Inc.

Disclosure: H.K. Gan: Consulting/advisory role: AbbVie; Speakers' bureau: Ignyta, Bristol-Myers Squibb; Research funding: AbbVie; Travel, accommodations, expenses: Ignyta. E. Kennedy, D. Maag: Employee and stock: AbbVie. All other authors have declared no conflicts of interest.

399P Melanoma with brain metastases: Experience of immunotherapy in a single center

D.R. Naskhletashvili[1], L.V. Demidov[2], A.H. Bekyashev[1], V.A. Aloshin[1], E.V. Prozorenko[1]

[1]Neurooncology, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [2]Biotherapy, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation

Background: The effectiveness of conventional chemotherapy (temozolomide, fotemustine, lomustine) alone and its combinations with radiation therapy in patients with melanoma with cerebral metastases does not exceed 7-10%, There is no significant impact on overall survival, which is 2-4 month. Research of immunotherapy (nivolumab, ipilimumab, pembrolizumab) is relevant in melanoma patients with brain metastases in the absence of mutations of the BRAF, or in the case of the progression of the disease while therapy BRAF inhibitors in patients with mutations of the BRAF.

Methods: The effect of the various schemes immunotherapy was evaluated in 22 patients with melanoma with brain metastases in Russian N.N. Blokhin Cancer Research Center. Patients received the following treatment options: nivolumab (6 patients), ipilimumab (11 patients), nivolumab + ipilimumab (2 patients), pembrolizumab (3 patients). The immunotherapy was combined with whole brain irradiation in 1 patient (4,5%), in 11 patients (50,0%) – in combination with stereotactic radiotherapy/radiosurgery.

Results: Complete regression of brain metastases was achieved in 3 patients (13,6%), partial regression in 2 (9,1%), stabilization in 11 (50,0%). Thus, the tumor control in the brain was observed in 16 patients (72,7%). In 22 patients (100,0%) were also established metastases in other sites (extracranial lesions). Complete regression of metastases in extracranial lesions was achieved in 4 patients (18,2%), partial regression – in 2 (9,1%), stabilization in 13 (59,1%). The median time to disease progression was 5,0 months. The median survival of patients was 10,0 months.

Conclusions: The preliminary results of our study show that the application of immunotherapy, including the combination with local control of metastases in the brain in patients with melanoma with brain metastases provides control over the disease in most patients and has a significant advantage with a group of historical control (chemotherapy ± whole brain irradiation).

Legal entity responsible for the study: Russian N.N. Blokhin Cancer Research Center.

Funding: Russian N.N. Blokhin Cancer Research Center.

Disclosure: All authors have declared no conflicts of interest.

400P Systemic management of malignant meningioma: A comparative survival and molecular marker analysis between ocreotide in combination with everolimus compared to sunitinib

A.F. Cardona Zorrilla[1], A. Ruiz-Patiño[1], O. Arrieta[2], L. Zatarain-Barron[2], F. Hakim[3], E. Jimenez[3], J.A. Mejia[3], F. Ramon[3], N. Useche[4], S. Bermudez[4], D. Pineda[5], H. Cifuentes[5], L.L. Rojas[6], L.E. Pino Villareal[7], C. Balana[8]

[1]Translational Research, Foundation for Clinical and Applied Cancer Research, Bogotá, Colombia, [2]Thoracic Oncology, Instituto Nacional de Cancerologia, Mexico City, Mexico, [3]Neurosurgery, Fundacion Santa Fe de Bogotá, Bogotá, Colombia, [4]Neuroradiology, Fundacion Santa Fe de Bogotá, Bogotá, Colombia, [5]Neuroradiology, Clinica Del Country, Bogotá, Colombia, [6]Clinical Oncology, Clinica Colsanitas, Bogotá, Colombia, [7]Clinical Oncology, Fundacion Santa Fe de Bogotá, Bogotá, Colombia, [8]Neuro-Oncology Section, Oncology Department, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain

Background: Anaplastic and atypical recurrent meningioma constitute a rare pathology with very few available effective systemic treatments.

Methods: A comprehensive analysis of 31 patients with atypical (WHO II) or anaplastic meningiomas (WHO III) that were recurrent and refractory to radiotherapy was conducted in two reference centers of Colombia. Only patients who had received some systemic treatment (sunitinib, everolimus/octeotride and bevacizumab) and had a complete follow-up were included. Overall survival (OS), progression free survival and toxicities were evaluated. Additionally, tissue samples were examined for PDGFRa and VEGFR2 and its expression was correlated with outcomes.

Results: Twenty two patients (72%) were females with a median age of 55 years (SD ± 15.3). The most prevalent histology was anaplastic meningioma in 20 patients (65%) with 48% of patients suffering from three previous relapses before the start of systemic treatment. A total of 14 patients received combination therapy with octeotride/everolimus, 11 received sunitinib and the remaining 6 other second line agents. Median OS was 37.3 months (95%CI 28.5-42.1) and the PFS during the treatment with everolimus/octeotride (EO) and sunitinib (Su) was 12.1 months (95%CI 9.2-21.1) and 9.1 months (95%CI 6.8-16.8); $p = 0.43$), respectively. The OS of the group treated with the EO→Su→Bev sequence ($1^{st}/2^{nd}/3^{rd}$ line) was 6.5 months longer than the Su→EO→Bev sequence, a finding that was not significant (36.0 vs. 29.5 months; $p = 0.349$). When analyzing molecular markers, the positive PDGFRa and negative VEGFR2 expression were associated with longer survival both in OS and PFS.

Conclusions: Sunitinib and ocreotide/everolimus have similar efficacy and safety in the systemic management of refractory meningioma. VEGFR2 and PDGFRa expression are strongly associated with major survival endpoints.

Legal entity responsible for the study: Foundation for Clinical and Applied Cancer Research – FICMAC

Funding: Supported by the Foundation for Clinical and Applied Cancer Research - FICMAC (Bogotá Colombia) research grant 011-2017SD.

Disclosure: All authors have declared no conflicts of interest.

401P Impact of postoperative residual tumor and meningeal dissemination in adult medulloblastoma: A retrospective analysis

R. Barreto, P.A.H. Viveiros, M.C. Mesquita, V.M. Santos, O. Feher

Oncologia Clínica, ICESP - Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

Background: Medulloblastoma (MB) is the most common central nervous system (CNS) malignant tumor in children and reaches its peak in the first decade of life. In adults, MB is very rare, comprising less the 1% of total CNS tumors. Although molecular subtypes are well defined, the impact of other prognostic variables, such as postoperative residual tumor (PRT) and the presence of neuroaxis dissemination (NAD) are controversial.

Methods: We performed a retrospective analysis in consecutive adult patients with MB treated at Instituto do Câncer do Estado de São Paulo from 2008 to 2016. Patients data on tumor histology, ECOG-PS at diagnosis, low/high-risk clinical classification (according to tumor size, metastasis, NAD and PRT) and adjuvant radiotherapy (RT) or chemotherapy (CT) were reviewed through medical records.

Results: Thirty-eight patients were included. Median age was 28,8 years-old (18,3 to 40,8) and patients were followed-up for a median of 5,28 years. Five patients died during follow-up, all cancer related, and 8 had progression events. All patients were submitted to surgical resection; 15 were considered high-risk patients; 34 were submitted to RT and 23 to CT in addition to RT. The most common RT regimen was 36Gy on neuroaxis and 18Gy boost on the posterior fossa (67%) and the most common CT protocol was a combination of lomustine, vincristine and cisplatin (39%). The two most common histological subtypes were classical (19), followed by desmoplastic (14). Fifteen patients were considered high-risk. On univariate analysis, the presence of PRT ($p < 0,0001$) and NAD ($p = 0,008$) had a negative impact on survival. Cox proportional-hazards regression for multivariate analysis confirmed the detrimental impact of PRT, while NAD had a marginal effect.

Conclusions: Medulloblastoma seems to bear a general favorable prognosis among adults. The presence of postoperative residual tumor, and perhaps neuroaxis dissemination, seem to impact negatively survival.

Legal entity responsible for the study: Olavo Feher.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

402P Adult medulloblastoma: An oncology radiation therapy department experience with 22 cases

M. Kallel[1], Z. Fessi[1], W. Siala[1], W. mnejja[1], N. Fourati[1], H. daoud[1], T. Boudawara[2], Z. Boudawara[1], M. Frikha[3], J. Daoud[1]

[1]Radiation Oncology, Habib Bourguiba Hospital Institute - Sfax, Sfax, Tunisia, [2]Pathology, Hopital Habib Bourguiba - Sfax University, Sfax, Tunisia, [3]Medical Oncology, Habib Bourguiba Hospital Insitute - Sfax, Sfax, Tunisia

Background: Medulloblastoma is the most common central nervous system tumor in children. However, the occurrence in adults is rare and accounts for about 1% - 2%. The objective of this study is to define the clinical characteristic of this entity and therapeutic results.

Methods: We retrospectively evaluated the treatment data of 22 adult patients (≥18 years) treated for medulloblatoma from 1993 to 2013 in our department. Median follow up was 161.5 months [58; 296 months].

Results: Male female ratio was 2.14 :1. Median age was 25 years [18 ; 57]. Eight patients (36%) had cerebellar hemispheric tumors, nine cases (41%) occur in the vermis and five patients (23%) had an hemispheric-vermian localisation. Twenty one patients (95%) underwent macroscopically total exicision. Sixteen patients (73%) had classic form; five patients had desmoplastic (23%) type and one patient had extensive nodularity type. Patients were stratified into standard and high risk in 14 and 5 cases respectively. The risk couldn't be identified for 3 patients. Among patients in the high-risk group, four received a cisplatin/etoposide chemotherapy before radiation. All patients had craniospinal radiotherapy. The mean interval between surgery and the begining of radiation therapy was 107 days. Craniospinal dose range between 30Gy and 36Gy. The dose in the posterior fossa was respectively 54Gy and 64Gy in 18 (82%) and 4 (18%) cases. The 5 year overall survival was 63%.

Conclusions: There are differences between pediatric and adult patients with medulloblastoma in terms of clinical and pathological characteristic. Ultimately, prospective trials including adult patient with medulloblastoma are needed to optimize the management of this rare and complex disease.

Legal entity responsible for the study: Kallel Mouna.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

403P Pineal parenchymal tumors: Patterns of care from a tertiary cancer centre in India

B. Devnani[1], S. Gupta[1], H. Kp[1], P.K. Julka[2], G.K. Rath[3]

[1]Radiation Oncology, All India Institute of Medical Sciences, Delhi, India, [2]Radiotherapy and Oncology, All India Institute of Medical Sciences, Delhi, India, [3]Radiation Oncology, B.R. Ambedkar Institute Rotary Cancer Hospital (AIMS), New Delhi, India

Background: The aim of this study is to report clinical features and treatment outcome of pineal parenchymal tumors (PPTs).

Methods: Between 2006-2017, medical records of 34 patients of PPTs were analyzed to study patterns of care of patients who received adjuvant radiotherapy (RT) with or without chemotherapy (CT) following surgery. Overall survival (OS) and progression-free survival (PFS) were analyzed by Kaplan- Meier method.

Results: According to WHO classification, the study comprises of 19 pineoblastomas (PB), 11 pineal parenchymal tumors of intermediate differentiation (PPTID) and 4 pineocytomas (PC). Median age at presentation was 10, 26 and 30 years, respectively. Headache was commonest symptom (77%) followed by visual disturbance. 59% underwent surgical resection and 41% had biopsy only. Median MIB labelling index of PPTIDs was 6%, whereas it was 35% in PB and 2% in PC. Spinal drop metastasis was present in 8 patients with PB and 3 patients with PPTIDs. All PBs and PPTIDs with spinal drop metastasis (2) received cranio-spinal irradiation (CSI) and adjuvant CT. The rest of the PPTIDs and PC received focal RT to the brain. The commonest regimen was a combination of carboplatin and etoposide (CE), used in 6 (32 %) PB. CE with vincristine and IT-MTX was given in patients who developed drop metastasis subsequently. At a median follow-up of 16 months, 9 (47%) patients of PB and 3 (27%) of PPTID developed recurrence in cranio-spinal axis. 5 year progression-free survival was 41%, 62% and 75%, respectively. Median overall survival (OS) was 27, 50, 18 months, and 5 year OS was 38%, 47% and 75%, respectively.

Conclusions: PPTs reflect a broad spectrum of malignant potential and prognosis. PB is an aggressive tumor and requires adjuvant CSI and CT following surgery. PPTIDs are relatively rare and require meticulous pretreatment evaluation of neuraxis and knowledge of pathological factors for management. Multi-institutional cooperation in the form of prospective studies is recommended in view of rarity of tumor.

Legal entity responsible for the study: AIIMS, New Delhi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

404P Advantages of next-generation sequencing in revealing low-level somatic mosaicism in blood samples of retinoblastoma patients

E.A. Alekseeva[1], V.M. Kozlova[2], T.L. Ushakova[2], A.S. Tanas[1], O.V. Babenko[1], T.P. Kazubskaya[2], V.V. Strelnikov[1], D.V. Zaletaev[3]

[1]Laboratory of Epigenetics, Research Centre for Medical Genetics, Moscow, Russian Federation, [2]Institute of Pediatric Oncology, N. N. Blokhin Science Medical Research Center of Oncology, Moscow, Russian Federation, [3]Laboratory of Medical Genetics, Sechenov First Moscow State Medical University, Moscow, Russian Federation

Background: Retinoblastoma (RB) is an embryonic malignant tumor of retina caused by inactivation of both alleles of the RB1 tumor suppressor gene. Identifying low-level mosaic mutations in RB1 gene in blood samples is challenging. Mosaic mutations arise in early embryogenesis and require high-resolution techniques for detection. In approximately 10% of families, the initial RB1 mutation is mosaic. The ability to identify RB1 mosaicism is important for genetic counseling because mosaicism increases the risk for developing RB in the other eye, second cancers and transmitting the mutation to progeny.

Methods: Using NGS we have evaluated the spectrum and frequency of RB1 mutations mosaicism in peripheral blood of 120 patients with sporadic RB (82 unilateral and 38 bilateral).

Results: In 5,8% (7/120) of patients a low-level mosaic mutation was found. The spectrum of identified mosaic RB1 mutations, the degree of mosaicism and clinical characteristics are shown in the table. Additionally, we analyzed the Sanger sequencing data from 72 blood samples from patients with sporadic RB (48 unilateral and 24 bilateral), performed earlier in our laboratory, and have not identified mosaic cases.

Table: 404P The spectrum of identified mosaic RB1 mutations

Sample	Form (uni/bi-lateral)	Age of onset	Mosaic mutation	Degree of mosaicism,%	Mutation in relatives
RB1	Uni-	6 mo	c.C1363T (14ex)	C:80, T:20	Negative
RB2	Uni-	1yr 8 mo	c.C1363T (14ex)	C:74, T:26	Negative
RB3	Bi-	3 weeks	c.2326delC (23ex)	wt:80, del:20	Negative
RB4	Uni-	3 yr	c.C958T (10ex)	C:80, T:20	Negative
RB5	Uni-	3 mo	c.C751T (8ex)	C:84, T:16	Negative
RB6	Uni-	1 yr 8 mo	c.1215 + 1G-A (12ex)	G:87, A:13	Negative
RB7	Uni-	8 mo	c.C1735T (18ex)	C:79, T:21	Negative
RB8	No symptoms	No	c.887delT (9ex)	wt:85, del:15	Positive bilateral daughter

Conclusions: NGS is an efficient method for detecting low-level mosaic mutations in blood samples from RB patients. Clinically, RB1 mosaicism is variable, it can manifest as a bilateral or a unilateral form with early or late onset, or without disease, which make the diagnosis even more difficult.

Legal entity responsible for the study: FASO Russia.

Funding: The research was carried out within the State assignment of FASO Russia.

Disclosure: All authors have declared no conflicts of interest.

405TiP Avelumab in newly diagnosed glioblastoma multiforme: The SEJ study

F.H. Jacques[1], G. Nicholas[2], I. Lorimer[3]

[1]Neurology, Clinique Neuro-Outaouais, Gatineau, QC, Canada, [2]Oncology, Ottawa Hospital General campus, Ottawa, ON, Canada, [3]Cancer Therapeutics Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada

Background: Patients with Glioblastoma Multiforme (GBM) despite standard therapy have a dismal prognosis and thus represent a significant unmet medical need. GBM has well documented systemic and local immunosuppressive mechanisms to escape immune surveillance and grow. GBM tumor cells as well as the microglia within it have a high incidence of PD-L1 surface expression which makes it more susceptible to anti-PD-L1 antagonism and ADCC through avelumab therapy. Combination of avelumab with other anticancer therapies have been shown safe and perhaps synergistic. A clinical trial looking at adding avelumab to standard therapy in patients with GBM is therefore indicated.

Trial design: This is a single center, phase 2, open label, open-ended add-on, single dose study of 52 weeks duration in patients receiving standard therapy for newly diagnosed GBM. In total 30 patients who meet the entry criteria will be entered into the study within 3 weeks of finishing their last day of combined radiotherapy/temozolomide. Avelumab will be initiated concurrently with the initiation of the first 5 day, monthly cycle of temozolomide and continued for a total of 52 weeks. The study will consist of 3 different phases: Combination Phase a Monotherapy Phase and an Extended Safety Follow-up Phase.

Clinical trial identification: NCT03047473.

Legal entity responsible for the study: Clinique Neuro-Outaouais.

Funding: Study is funded by an unrestricted grant from Merck Serono.

Disclosure: All authors have declared no conflicts of interest.

406TiP Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable high-grade gliomas patients: OLA-TMZ-RTE-01

D. Stefan[1], P. Lesueur[1], J. Lequesne[2], E. Coquan[3], P.E. Brachet[3], L. Castera[4], N. Goardon[4], J. Lacroix[5], M. Lange[2], A. Capel[2], B. Andre[6], J-M. Grellard[2], B. Clarisse[7]

[1]Radiotherapy Department, Centre Francois Baclesse, Caen, France, [2]Clinical Research Department, Centre Francois Baclesse, Caen, France, [3]Oncology Department, Centre Francois Baclesse, Caen, France, [4]Biology and Genetic Department, Centre Francois Baclesse, Caen, France, [5]Radiology Department, Centre Francois Baclesse, Caen, France, [6]Informatics Department, Centre Francois Baclesse, Caen, France, [7]Clinical Research, Centre Francois Baclesse, Caen, France

Background: The Stupp protocol is the standard treatment of glioblastoma multiform (GBM). The non-dividing nature of normal brain cells is an opportunity to enhance the therapeutic ratio by combining radiation with inhibitors of replication-specific DNA repair pathways such PARP inhibitors as olaparib. PARP inhibition also increases cellular sensitivity to radiation and may be higher in tumor than in normal tissue. Progress in technical imaging and intensity-modulated-radiotherapy (IMRT) techniques provide new possibilities for sparing healthy tissues. We propose a phase 1/2a trial to assess the safety and efficacy of Olaparib combined with TMZ plus fractionated IMRT as a first line treatment in unresectable GBM patients (pts).

Trial design: Based on the Stupp phase 2 design, 2 treatment periods are considered. The radiotherapy (RT) period occurs after the last surgery: the pt receives IMRT, daily TMZ during IMRT and olaparib, given at the same dose until 4 weeks after the end of IMRT. For the maintenance (MT) period, the pt receives TMZ (days 1-5 every 28 days, for 6 cycles) plus olaparib (at the MT dose level up to disease progression or unacceptable toxicity). The phase 1 includes 2 consecutive dose escalations to separate both periods for DLT (Dose Limiting Toxicities) assessment. First 15 pts will receive olaparib only during the RT period to determine the MTD1 (Maximum-Tolerated Dose) among 7 dose levels, by assessing DLT on this period. Next 15 pts will all receive MTD1 during the RT period, and a new dose-escalation will determine MTD2 ($\leq$MTD1) during the MT period, assessing DLT from the first 2 cycles. For phase 2a, IMRT and TMZ are given according to the Stupp protocol. Olaparib is given at the MTD1 during the RT period and at the MTD2 during the MT period. Brain disease is assessed using RANO criteria. The trial includes ancillary studies on tumor biopsies, spectro-MRI and neurocognitive and quality of life assessment. Up to 79 pts will be enrolled: 30 pts in the phase 1 and 49 pts in the phase 2a (Case&Morgan two-stage design). This trial (NCT03212742) is granted by the French Cancer Institute and Health Ministry (PHRC-K15-135) and Astra-Zeneca for olaparib provision. First pt was enrolled on Oct 2017.

Legal entity responsible for the study: Comprehensive Cancer Centre François Baclesse.

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.

407TiP Phase II open-label, global study evaluating dabrafenib in combination with trametinib in pediatric patients with BRAF V600–mutant high-grade glioma (HGG) or low-grade glioma (LGG)

D. Hargrave[1], O. Witt[2], K. Cohen[3], R. Packer[4], A. Lissat[5], U. Kordes[6], T.W. Laetsch[7], L. Hoffman[8], A. Lassaletta[9], N.U. Gerber[10], S. Gilheeney[11], S. Holm[12], C. Kramm[13], D. Sumerauer[14], C. Reitmann[15], M.W. Russo[16], E. Bouffet[17]

[1]Haematology and Oncology Department, Great Ormond Street Hospital for Children, London, UK, [2]KiTZ Clinical Trial Unit, CCU Pediatric Oncology and Department of Pediatric Oncology, Hopp Children's Cancer Center at the NCT Heidelberg, Heidelberg, Germany, [3]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD, USA, [4]Center for Neuroscience and Behavioral Medicine, Children's National Health System, Washington, DC, USA, [5]Department of Pediatrics, Charité – Universitätsmedizin Berlin, Berlin, Germany, [6]Department of Pediatric Hematology and Oncology, University Medical Center Eppendorf, Hamburg, Germany, [7]Department of Pediatrics, The University of Texas Southwestern Medical Center and Children's Health, Dallas, TX, USA, [8]Pediatric Hematology / Oncology Department, Children's Hospital Colorado, Aurora, CO, USA, [9]Pediatric Hematology / Oncology Department, Hospital Infantil Universitario Niño Jesus, Madrid, Spain, [10]Early Phase Clinical Trials Unit, Department of Oncology, University Children's Hospital, Zurich, Switzerland, [11]Department of Pediatric Neuro-Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [12]Division of Pediatric Oncology, Karolinska Institutet, Stockholm, Sweden, [13]Division of Pediatric Hematology and Oncology, University of Goettingen, Goettingen, Germany, [14]Department of Paediatric Haematology and Oncology, Faculty Hospital Motol, Prague, Czech Republic, [15]Global Development Operations Trial Management, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [16]Global Drug Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [17]Division of Haematology/Oncology, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Background: Activation of the MAPK pathway via the BRAF V600 mutation has been observed in several tumors. This mutation is observed in a subset of pediatric brain tumors, including HGG and LGG for which limited therapeutic options are currently available. In a phase I/II clinical trial of pediatric patients (pts) with recurrent or refractory BRAF V600–mutant relapsed tumors, the BRAF inhibitor dabrafenib demonstrated its efficacy, including complete responses, in pediatric pts with HGG and LGG. As the combination of dabrafenib plus the MEK inhibitor trametinib has resulted in improved efficacy in multiple adult BRAF V600–mutant tumors, including melanoma and non-small cell lung cancer, this combination warrants further investigation in pediatric pts with gliomas bearing the same mutation.

Trial design: This global, open-label, phase II study (NCT02684058) will evaluate the anti-tumor activity of the combination of dabrafenib plus trametinib in 2 pediatric glioma cohorts recruiting from up to 70 sites across 17 countries. The single-arm BRAF V600–mutated HGG cohort of approximately 40 pts (aged $\geq$ 6 and $<$ 18 y) with relapsed or refractory disease will be treated with dabrafenib twice daily (BID) plus trametinib once daily (QD) based on age and weight. The primary endpoint for this cohort is overall response rate (ORR) per investigator's assessment according to Response Assessment in Neuro-Oncology (RANO) criteria. The BRAF V600–mutated LGG cohort of approximately 102 chemotherapy-naive pts (aged $\geq$ 6 and $<$ 18 y) with unresectable disease will be randomized 2:1 to receive either dabrafenib (BID) plus trametinib (QD) or carboplatin plus vincristine. The primary endpoint for the LGG cohort is ORR per independent assessment according to RANO criteria. Pt crossover from the chemotherapy arm to the experimental arm will be allowed after independent confirmation of radiologic disease progression. Key secondary endpoints for both cohorts include duration of response, progression-free survival, time to response, clinical benefit rate, overall survival, and safety/tolerability.

Clinical trial identification: NCT02684058.

Editorial acknowledgement: Medical writing assistance was provided by William Fazzone, PhD (ArticulateScience LLC), funded by Novartis Pharmaceuticals Corporation.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: D. Hargrave: Consultancy: Novartis. O. Witt: Membership on board of directors or advisory committees: Novartis; Study committee on selumetinib trial: AzstraZeneca. K. Cohen: Research Funding: Novartis; Membership on board of directors or advisory committees: Novartis. T.W. Laetsch: Consultancy: Novartis, Loxo Oncology, Bayer; Research funding: Pfizer. A. Lassaletta: Consultancy: Shire, Clinigen. C. Kramm: Research funding: Novartis, Eisai, Boehringer Ingelheim, Merck. C. Reitmann, M.W. Russo: Employment: Novartis; E. Bouffet: Research funding to institution: Roche, Bristol-Myers Squibb.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii133–viii148, 2018
doi:10.1093/annonc/mdy279

DEVELOPMENTAL THERAPEUTICS

408O Sitravatinib demonstrates activity in patients with novel genetic alterations that inactivate CBL

L. Bazhenova[1], R.D. Carvajal[2], B.C. Cho[3], K. Eaton[4], S. Goel[5], R.S. Heist[6], M. Ingham[2], D. Wang[7], T. Werner[8], S. Neuteboom[9], D. Potvin[10], I. Chen[11], J. Christensen[12], R. Chao[11], A. Alva[13]

[1]Medicine, Moores UCSD Cancer Center, La Jolla, CA, USA, [2]Medical Oncology, Columbia University Medical Center, New York, NY, USA, [3]Medical Oncology, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea, [4]Medical Oncology, University of Washington Medical Center, Seattle, WA, USA, [5]Medical Oncology, Montefiore Medical Center (East Campus) - Medical Park at Eastchester Albert Einstein Cancer Center, Bronx, NY, USA, [6]Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA, [7]Medical Oncology, Henry Ford Hospital, Detroit, MI, USA, [8]Medical Oncology, Huntsman Cancer Institute, Salt Lake City, UT, USA, [9]Clinical Science, Mirati Therapeutics, Inc., San Diego, CA, USA, [10]Biostatistics, Mirati Therapeutics, Inc., San Diego, CA, USA, [11]Medical Oncology, Mirati Therapeutics, Inc., San Diego, CA, USA, [12]Translational Research, Mirati Therapeutics, Inc., San Diego, CA, USA, [13]Medical Oncology, Cancer Center, University of Michigan, Ann Arbor, MI, USA

409O Larotrectinib efficacy and safety in TRK fusion cancer: An expanded clinical dataset showing consistency in an age and tumor agnostic approach

U.N. Lassen[1], C.M. Albert[2], S. Kummar[3], C.M. van Tilburg[4], S.G. Dubois[5], B. Geoerger[6], L. Mascarenhas[7], N. Federman[8], R.J. Schilder[9], F. Doz[10], J.D. Berlin[11], D-Y. Oh[12], S.S. Bielack[13], R. McDermott[14], D.S. Tan[15], S. Cruickshank[16], N.C. Ku[16], M.C. Cox[16], A. Drilon[17], D.S. Hong[18]

[1]Finsen Center, Department of Oncology, Phase 1 Unit, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [2]Pediatric Oncology, Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Medical Oncology, Stanford Cancer Institute, Stanford University, Stanford, CA, USA, [4]Pediatric Oncology, Hopp Children's Cancer Center at the NCT Heidelberg (KiTZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany, [5]Pediatric Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA, [6]Department of Pediatric and Adolescent Oncology, Institut Gustave Roussy, Villejuif, France, [7]Oncology, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, [8]Pediatric Oncology, University of California, Los Angeles, CA, USA, [9]Medical Oncology, Thomas Jefferson University, Philadelphia, PA, USA, [10]Pediatric Oncology, Institut Curie and University Paris Descartes, Paris, France, [11]Medicine, Vanderbilt Ingram Cancer Center, Nashville, TN, USA, [12]Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea, [13]Pediatric Oncology, Klinikum Stuttgart - Olgahospital, Stuttgart, Germany, [14]Medical Oncology, AMNCH Adelaide and Meath Hospital, Dublin, Ireland, [15]Medical Oncology, National Cancer Center, Singapore, [16]Clinical Development, Loxo Oncology, South San Francisco, CA, USA, [17]Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [18]Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

410O **First-in-human, first-in-class study of the CD44v6 inhibitor AMC303 as monotherapy in patients with advanced epithelial tumors**

E. Calvo[1], P.G. Aftimos[2], A. Azaro[3], M.J. de Miguel[4], C. Jungels[5], J. Zeron-Medina Cuairan[6], P.G. Nuciforo[7], P. Ehmer[8], A. Martin[9], H.K. Bender[10], K. Dembowsky[10]

[1]START Phase I, Hospital Madrid Norte San Chinarro Centro Integral Oncologico Clara Campal, Madrid, Spain, [2]Phase I Unit, Institute Jules Bordet, Brussels, Belgium, [3]Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Start-Madrid Phase 1 Unit, Hospital Madrid Norte San Chinarro Centro Integral Oncologico Clara Campal, Madrid, Spain, [5]Medical Oncology, Institute Jules Bordet, Brussels, Belgium, [6]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [7]Molecular Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [8]Clinical Pharmacokinetics, Pharmacelsus GmbH, Saarbrücken, Germany, [9]Research, Amcure GmbH, Eggenstein-Leopoldshafen, Germany, [10]Clinical Development, Amcure GmbH, Eggenstein-Leopoldshafen, Germany

411O **Initial results from a phase I/IIa trial evaluating BMS-986158, an inhibitor of the bromodomain and extra-terminal (BET) proteins, in patients (pts) with advanced cancer**

J. Hilton[1], M.C. Cristea[2], M. Voskoboynik[3], S. Postel-Vinay[4], W. Edenfield[5], A. Gavai[6], S. Wee[6], N. Srivastava[6], A. Klippel[6], D. Jackson[6], A. Apfel[6], S.D. Chasalow[6], D. Williams[6], M. Donovan[6], B. Fischer[6], S. Khaldoyanidi[6], J.R. Diamond[7]

[1]Division of Medical Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, ON, Canada, [2]Department of Medical Oncology & Therapeutics Research, City Of Hope National Medical Center, Duarte, CA, USA, [3]Department of Oncology, Nucleus Network, Monash University, Victoria, Australia, [4]Department of Drug Development, Institut de Cancérologie Gustave Roussy, Villejuif, France, [5]Internal Medicine, GHS Cancer Institute, Greenville Health System, Greenville, SC, USA, [6]Immuno-Oncology, Bristol-Myers Squibb, Princeton, NJ, USA, [7]Division of Medical Oncology, University of Colorado School of Medicine, Aurora, CO, USA

412PD **Clinical activity, safety, and PK/PD from a phase I study of RO6874281, a fibroblast activation protein (FAP) targeted interleukin-2 variant (IL-2v)**

I. Melero[1], E. Castanon Alvarez[2], M. Mau-Sorensen[3], U.N. Lassen[4], M.P. Lolkema[5], D.G. Robbrecht[6], C.A. Gomez-Roca[7], J. Martin-Liberal[8], J. Tabernero[9], W. Ros[10], S. Ahmed[11], N. Isambert[12], H. Piper Lepoutre[13], C. Boetsch[14], J. Charo[15], S. Evers[16], V. Teichgräber[15], J.H.M. Schellens[17]

[1]Laboratory of Immunology, Clinica Universitaria de Navarra, Pamplona, Spain, [2]Medical Oncology, Clinica Universitaria de Navarra, Pamplona, Spain, [3]SKACCD - Rigshospitalet, Copenhagen, Denmark, [4]Finsen Center, Department of Oncology, Phase 1 Unit, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [5]Medical Oncology, Erasmus University Medical Center, Rotterdam, Netherlands, [6]Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, [7]Medical Oncology & Clinical Research, Institut Universitaire du Cancer - Toulouse- Oncopole, Toulouse, Haute-Garonne, France, [8]Oncology, Vall dHebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [9]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [10]Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands, [11]Leicester Cancer Research Centre, University Hospitals of Leicester NHS Trust Leicester Royal Infirmary, Leicester, UK, [12]Medical Oncology, Centre Georges-François Leclerc, Dijon, France, [13]Safety Sciences, Roche Innovation Center Basel, Basel, Switzerland, [14]Pharmaceutical Sciences, Roche Innovation Center Basel, Basel, Switzerland, [15]Translational Medicine Oncology, Roche Innovation Center Zurich, Schlieren, Switzerland, [16]Oncology DTA, Roche Innovation Center Basel, Basel, Switzerland, [17]Division of Clinical Pharmacology, Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands

413PD **Phase I clinical and translational evaluation of AZD6738 in combination with durvalumab in patients (pts) with lung or head and neck carcinoma**

M. Krebs[1], J. Lopez[2], A. El-Khoueiry[3], Y-J. Bang[4], S. Postel-Vinay[5], W. Abidah[6], S-A. Im[7], L.T. Khoja[8], N. Standifer[9], G.N. Jones[10], P. Marco-Casanova[10], P. Frewer[11], A. Berges[12], A. Cheung[12], C. Stephens[8], B. Felicetti[8], E. Dean[8], A. Pierce[10], S. Hollingsworth[13]

[1]Phase I Unit, The Christie NHS Foundation Trust, Manchester, UK, [2]Phase I Unit, The Royal Marsden Hospital, London, UK, [3]Medical Oncology, Norris Cancer Centre, Los Angeles, CA, US, [4]Internal Medicine (Medical Oncology), Seoul National University Hospital, Seoul, Republic of Korea, [5]Drug Development Department, Institute Gustave Roussy, Paris, France, [6]Medical Oncology, Memorial Sloan Kettering Hospital, New York, NY, USA, [7]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [8]Early Clinical Development, IMED Biotech Unit, AstraZeneca UK, Cambridge, UK, [9]Clinical Immunology & Bioanalysis, Medimmune plc, San Francisco, CA, USA, [10]Translational Science, IMED Biotech Unit, AstraZeneca UK, Cambridge, UK, [11]Early Clinical Biometrics, ECD, IMED Biotech Unit, AstraZeneca UK, Cambridge, UK, [12]Quantitative Clinical Pharmacology, Early Clinical Development, IMED Biotech Unit, AstraZeneca UK, Cambridge, UK, [13]Oncology, IMED Biotech Unit, AstraZeneca UK, Cambridge, UK

414PD **Phase I study of the CTLA-4 inhibitor MK-1308 in combination with pembrolizumab in patients with advanced solid tumors**

B.C. Cho[1], R. Perets[2], J. Bar[3], M-J. Ahn[4], D-W. Kim[5], K. Yoh[6], A. Nagrial[7], D.R. Spigel[8], D.H. Lee[9], M. Gutierrez[10], D. Kotasek[11], S. Siddiqi[12], A. Chain[12], B.D. Butts[12], Y. Zhang[12], X. Li[12], J. Cyrus[12], A. Tse[12], R.A. Altura[12], D. Rasco[13]

[1]Medical Oncology, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea, [2]Oncology, Rambam Medical Center, Haifa, Israel, [3]Institute of Oncology, Sheba Medical Center at Tel HaShomer, Ramat Gan, Israel, [4]Hematology and Oncology, Samsung Medical Center, Sungkyunkwan University of Medicine, Seoul, Republic of Korea, [5]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [6]Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [7]Blacktown Cancer and Hematology Center, Blacktown Hospital and University of Sydney, Sydney, Australia, [8]Medical Oncology, Sarah Cannon Research Institute, Nashville, TN, USA, [9]Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, [10]Oncology Research, Hackensack University Medical Center, Hackensack, NJ, USA, [11]Medical Oncology, Adelaide Cancer Centre, Adelaide, Australia, [12]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [13]Medical Oncology, START, San Antonio, TX, USA

415PD **Clinical response and pharmacodynamic assessment of INVAC-1, a DNA plasmid encoding an inactive form of human telomerase reverse transcriptase (hTERT), on immune responses, immune tolerability, tumor burden and circulating tumor DNA (ctDNA) in patients with advanced solid tumors**

J. Medioni[1], M. Brizard[2], L.O. Teixeira[3], L. Doucet[4], Z. Ghrieb[5], A. Angelergues[4], S. Oudard[6], S. Culine[7], O. Adotevi[8], C. Laheurte[8], M-A. Dragon-Durey[9], P. Laurent-Puig[10], J-J. Kiladjian[3], V. Doppler[11], B. Souttou[11], S. Wain-Hobson[11], R. Defrance[11], T. Huet[11], P. Langlade-Demoyen[11]

[1]Medical Oncology Department, Hôpital Européen Georges Pompidou, Paris, France, [2]Service d'Oncologie Medicale, Hôpital Européen Georges Pompidou, Paris, France, [3]Centre d'Investigations Cliniques, Hôpital St. Louis, Paris, France, [4]Oncologie Médicale, Hôpital St. Louis, Paris, France, [5]Centre d'Investigations Cliniques, Hôpital St. Louis, Paris, France, [6]Immunothérapie et traitement Antiangiogénique en Pathologie Cancérologique, Hopital European George Pompidou, Paris, France, [7]Medical Oncology, Hôpital St. Louis, Paris, France, [8]Immunomolecular Therapy of Cancer, UMR1098, Besançon, France, [9]Laboratoire d'Immunobiologie, Hôpital Européen Georges Pompidou, Paris, France, [10]UMR-S 1147, Université Paris-Descartes, Paris, France, [11]Clinical Development, Invectys, Paris, France

416PD **Final results from a phase i clinical trial evaluating the safety, immunogenicity, and anti-tumor activity of SNS-301 in men with biochemically relapsed prostate cancer**

L.T. Nordquist[1], H. Ghanbari[2], J.J. Elist[3], J.C. Oliver[4], W. Gannon[5], A. Shahlaee[2], S. Fuller[2], N. Shore[6]

[1]Medical Oncology, Urology Cancer Center and GU Research Network, Omaha, NE, USA, [2]Clinical Development, Sensei Biotherapeutics, Gaithersberg, MD, USA, [3]Private Medical Practice, Dr. James J. Elist, Beverley Hills, CA, USA, [4]Oncology Development, Accelovance, Raleigh, MA, USA, [5]Oncology Development, Capital City Technical Consulting, Washington, DC, USA, [6]GU Oncology, Carolina Urologic Research Center, Myrtle Beach, SC, USA

417PD **Combination therapy optimization in gastrointestinal cancers using multi-omic molecular profiling**

M.C. Monge Bonilla[1], E. Blais[2], W. Chen[3], M. Pishvain[4], E. Petricoin[5], J.L. Marshall[4]

[1]Oncology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA, [2]Computational Biology Dept., Perthera, McLean, VA, USA, [3]Bioinformatics, Caris Life Sciences, Irving, TX, USA, [4]Lombardi Cancer Center, Georgetown University Hospital, Washington, DC, USA, [5]Scientific Department, Perthera, McLean, VA, USA

418PD NCI-MATCH Arms N & P: Phase II study of PI3K beta inhibitor GSK2636771 in patients (pts) with cancers (ca) with PTEN mutation/deletion (mut/del) or PTEN protein loss

F. Janku[1], O. Jegede[2], S.L. Puhalla[3], P. Konstantinopoulos[4], F. Meric-Bernstam[1], E.P. Mitchell[5], J.A. Zwiebel[6], L.M. McShane[6], S. Li[2], L.V. Rubinstein[6], L.A. Doyle[6], D. Patton[7], B.A. Conley[6], P.J. O'Dwyer[8], L.N. Harris[9], C. Arteaga[10], P.M. Williams[11], S.R. Hamilton[12], A.P. Chen[13], K.T. Flaherty[14]

[1]Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA, [2]ECOG-ACRIN Biostatistics Center, Dana Farber Cancer Institute, Boston, MA, USA, [3]Medical Oncology, The University of Pittsburgh, Pittsburgh, PA, USA, [4]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [5]Medical Oncology, Kimmel Cancer Center-Thomas Jefferson University, Philadelphia, PA, USA, [6]CTEP, National Cancer Institute, Bethesda, MD, USA, [7]Informatics, National Cancer Institute, Bethesda, MD, USA, [8]Medical Oncology, ECOG-ACRIN, Philadelphia, PA, USA, [9]Cancer Diagnosis Program, National Cancer Institute, Bethesda, MD, USA, [10]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA, [11]Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD, USA, [12]Pathology, MD Anderson Cancer Center, Houston, TX, USA, [13]Division of Cancer Treatment and Diagnosis, Center for Cancer Research-National Cancer Institute, Bethesda, MD, USA, [14]Medical Oncology, Massachusetts General Hospital, Boston, MA, USA

419P Double blind concordance study of colo-rectal cancer treatment recommendations between artificial intelligence advisory programme watson for oncology (WFO) & multidisciplinary tumor board (MDT)

S. Sampige Prasannakumar[1], M. Sepulveda[2], C. Rohit Kumar[1], A. Rauthan[3], P. Patil[4], Y. Ramya[1]

[1]Surgical Oncology, Manipal Comprehensive Cancer Centre Manipal Hospital, Bangalore, India, [2]Clinical Research, IBM Health, Florida, NY, USA, [3]Medical Oncology, Manipal Comprehensive Cancer Center Manipal Hospital, Bangalore, India, [4]Medical Oncology, Manipal Comprehensive Cancer Center Manipal Hospital, Bangalore, India

Background: In this era of personalized medicine there is outburst of information and plethora of new treatment strategy. Data Tsunami overwhelms human cognitive capacity. Artificial intelligence is being used for information-intensive decision making. We present here an experience with this technology in cancer treatment decision support.

Methods: WFO was used to obtain treatment recommendations of cases that were previously evaluated by a MDT at a major cancer center in India between 2014 and 2016. A comparison was made between the oncology advisor's recommended treatment and that of the tumor board. Treatment concordance was defined as a tumor board recommendation falling into the oncology advisor's categories of "recommended" or "for consideration" treatments. All non-concordant cases (n = 33) were re-presented to the tumor board in a blinded fashion in 2016 to address time of evaluation differences between the tumor board and the oncology advisor. Results are presented as the proportion of concordant cases.

Results: From 2014-2016 we had 126 colon cancers & 124 rectal cancers. Of colon 62 & 64 were non-metastatic & metastatic respectively, whereas in rectal cancer it was 93 & 31 respectively. Mean age of the patient was 55 years. The overall concordance at first analysis was 87%. At sub group analysis in colon (85% vs 77%) & rectum (97%vs81%) & Overall (92% vs78%) non-metastatic cases had higher concordance level than metastatic cases (Table1). There were 31 cases which were non-concordant that were re-challenged to MDT. After second review the overall concordance level improved from 87% to 95%.

Conclusions: Artificial intelligence treatment recommendations with Watson for Oncology showed high levels of concordance with a multidisciplinary tumor board. This cognitive computing technology holds much promise in helping oncologists make information intensive, evidence based treatment decisions.These findings are encouraging for the use of this technology. Additional investigations are needed to understand concordance in settings where cancer expertise and treatment options may differ.

Legal entity responsible for the study: Ethics Board Committee, Manipal Hospitals Bangalore.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

420P Phase I/II study of ODM-203, a selective dual FGFR/VEGFR inhibitor, in patients with advanced solid tumours

P. Bono[1], C. Massard[2], K. Peltola[3], A. Azaro[4], A. Italiano[5], R.S. Kristeleit[6], U.N. Lassen[7], H-T. Arkenau[8], P. Hakulinen[9], C. Garratt[9], T. Ikonen[9], M. Mustonen[9], J. Rodon[10]

[1]Comprehensive Cancer Center, Helsinki University Central Hospital, Helsinki, Finland, [2]DITEP, Gustave Roussy Institut de Cancérologie, Villejuif, France, [3]Trial Unit, Helsinki University Central Hospital, Helsinki, Finland, [4]Molecular Therapeutics Research Unit, Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [6]Academic Department of Oncology, UCL Cancer Institute, University College London, London, UK, [7]Department of Oncology, Phase 1 Unit, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [8]SCRI, Sarah Cannon Research Institute SCRI UK, London, UK, [9]Orion Corporation, Orion Pharma, Espoo, Finland, [10]Early Drug Development, Vall d'Hebron University Hospital, Barcelona, Spain

Background: ODM-203 is an orally available small molecule with balanced inhibitory effects on FGFR 1-4 and VEGFR 1-3 subtypes. We present here results of the phase 1/2 KIDES study.

Methods: The KIDES study is an open-label, non-randomized, multicentre phase 1/2 first-in-man study of ODM-203 in patients with advanced solid tumors. In the Part 1 dose escalation (3 + 3), ODM-203 was evaluated in 31 patients between 50-800mg daily with food to identify the maximum tolerated dose (MTD). Part 2 expansion included 53 patients to evaluate a new formulation, the recommended phase 2 dose and the dose schedule. Patients continued ODM-203 treatment until disease progression or dose limiting toxicity.

Results: 84 patients (median 57 years, range 28-80), with the most common tumor types being cholangio, breast, colorectal, endometrium, ovarian and thyroid carcinoma, were included, with most patients in Part 2 having FGFR alterations. Six patients remain on treatment. In the dose-escalation Part 1, 800mg/day was considered the highest dose that could not be tolerated although MTD was not formally identified. This was because of a general adverse event (AE) burden and increased bilirubin in most patients. Bilirubin increase was due to UGT1A1 inhibition by ODM-203 and resolved in all cases upon dose reduction/interruption. In Part 2, the optimal dose was determined to be 400mg/day with food. Most AE's were grade 1-2, the most common ones being increased bilirubin (76%), fatigue and asthenia (68%), diarrhoea (60%), stomatitis (41%), arthralgia (41%) and decreased apetite (41%). Most common grade >3 AE's were bilirubin increase (45%), fatigue (6%) and diarrhoea (6%). There were 6 (9%) partial responses (PR) and additionally 24 (35%) patients achieved target lesion reduction. In total, 30 (44%) patients had disease stabilisation (SD) with median of 21 weeks on the study. The clinical benefit rate (CR + PR + SD) was 36/69 (52%).

Conclusions: Patients treated with ODM-203, especially those with FGFR-aberrant or VEGFR sensitive tumours, had preliminary promising anti-tumour response and on-target effects.

Clinical trial identification: NCT02264418.

Legal entity responsible for the study: Orion Corporation Orion Pharma.

Funding: Orion Corporation Orion Pharma.

Disclosure: P. Bono: Honoraria: Orion Pharma during the conduct of the study; Honoraria from Pfizer, MSD, BMS, Novartis, Oncorena and Ipsen outside the submitted work. K. Peltola: Personal fees: Orion Pharma, BMS, Pfizer, Roche, MSD, Ipsen, outside the submitted work; Stock holder: Faron Pharmaceuticals. P. Hakulinen, C. Garratt, T. Ikonen, M. Mustonen: Employee: Orion Corporation Orion Pharma. All other authors have declared no conflicts of interest.

421P Preliminary results of pamiparib (BGB-290), a PARP1/2 inhibitor, in combination with temozolomide (TMZ) in patients (pts) with locally advanced or metastatic solid tumors

M. Johnson[1], M. Galsky[2], M. Barve[3], S. Goel[4], H. Park[5], B. Du[6], S. Mu[7], V. Ramakrishnan[8], K. Wood[9], V. Wang[10], N. Lakhani[11]

[1]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA, [2]Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Medical Oncology, Mary Crowley Cancer Research, Dallas, TX, USA, [4]Medical Oncology, Montefiore Medical Center, Bronx, NY, USA, [5]Medical Oncology, Washington University, St. Louis, MO, USA, [6]Pharmacovigilance and Drug Safety, Beigene USA, Inc., San Mateo, CA, USA, [7]Clinical Pharmacology, BeiGene USA, Inc., Fort Lee, NJ, USA, [8]CDx and Biomarker Development, BeiGene USA, Inc., San Mateo, CA, USA, [9]Clinical Science, BeiGene USA, Inc., San Mateo, CA, USA, [10]Biostatistics, BeiGene USA, Inc., San Mateo, CA, USA, [11]Developmental Therapeutics, START - Midwest, Grand Rapids, MI, USA

Background: DNA damage caused by TMZ can sensitize tumors to the effects of PARP inhibitors. Pamiparib is a selective PARP1/2 inhibitor with potent PARP trapping that can cross the blood-brain barrier and has shown synergistic cytotoxicity with TMZ in nonclinical experiments. In Phase 1 studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed preliminary antitumor activity; single-agent RP2D was defined as 60 mg PO BID.

Methods: This dose-escalation/expansion study (NCT03150810) is enrolling pts using a modified 3 + 3 design to establish the safety and MTD of pamiparib plus TMZ. During dose escalation, pts receive pamiparib 60 mg PO BID plus escalating doses of TMZ QD on Days 1–7 (Arm A) or continuously (Arm B) for each 28-day cycle. The primary endpoint is safety/tolerability, including estimation of MTD and RP2D. Key secondary endpoints are PK profiles of TMZ and pamiparib and antitumor activity (RECIST v1.1) of combination treatment; biomarker (eg, gBRCA) assessment is exploratory.

Results: As of 16 Feb 2018, 16 pts (Arm A, n = 4, 40 mg TMZ; n = 4, 80 mg TMZ; n = 3, 120 mg TMZ; Arm B, n = 4, 20 mg TMZ; n = 1, 40 mg TMZ) with a median age of 69.5 yr (range 50–85) have enrolled; 8 remain on treatment. Prostate and small cell lung cancers (n = 4 each) were the most common tumors; most pts (n = 14) had received ≥3 prior treatments. Most common pamiparib-related AEs were nausea (n = 6), and nausea and thrombocytopenia (n = 5 each) for TMZ. In Arm A, 2 pts at 120 mg TMZ reported a DLT of grade 4 neutropenia >7 days. Neutropenia and thrombocytopenia (n = 4 each) were the only ≥grade 3 AEs occurring in > 2 pts. No AE led to treatment discontinuation or death. Plasma exposure for pamiparib and TMZ were consistent with single-agent trials. One pt with peritoneal cancer in Arm A had a 99.5% decrease in CA125 by wk 12. In the 7 pts with ≥1 post-baseline tumor assessment, 2 pts in Arm A (kidney, n = 1; SCLC, n = 1) achieved unconfirmed PRs.

Conclusions: In pts with solid tumors, pamiparib 60 mg PO BID combined with pulsed or continuous flat dosed TMZ showed preliminary antitumor activity and was generally well tolerated with the expected toxicity of bone marrow suppression.

Clinical trial identification: NCT03150810.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Aarati Rai, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: BeiGene, Ltd.

Funding: BeiGene, Ltd.

Disclosure: M. Johnson: Consulting/advisory role or research funding: Astellas, Boehringer Ingelheim, Celgene, Genentech/Roche, Otsuka, Array Biopharma, AstraZeneca, BerGenBio, Checkpoint Therapeutics, EMD Serono, Genmab, Janssen, Lilly, Mirati Therapeutics, Novartis, OncoMed, Pfizer, Regeneron, or Stem Cells, Inc. M. Galsky: Consultancy fees: Genentech, Merck, Novartis, Astellas, AstraZeneca, BMS; Stock options: Dual Therapeutics. M. Barve: Research funding: Gradalis. S. Goel: Honoraria or research funding: Bayer, Genentech/Roche, or Oncoloytics; patent with a co-inventor, John Mariadason, Ph.D, entitled "Method Of Determining The Sensitivity Of Cancer Cells To EGFR Inhibitors Including Cetuximab, Panitumumab And Erlotinib.", Patent No. 20090258364. B. Du, S. Mu, V. Ramakrishnan, K. Wood, V. Wang: Employee: BeiGene. N. Lakhani: Research funding: Abbvie, Amge, ArQule, Asana Biosciences, BMS, Cerulean Pharma, Dicerna, Foundation Medicine, Macrogenics, Merck, Pfizer, Regeneron, TaiRx, Inc. All other authors have declared no conflicts of interest.

422P First-in-human study of the monopolar spindle 1 (Mps1) kinase inhibitor BAY 1161909 in combination with paclitaxel in subjects with advanced malignancies

P. Lorusso[1], S.P. Chawla[2], J. Bendell[3], A.F. Shields[4], G. Shapiro[5], P. Rajagopalan[6], C. Cyris[7], I. Bruns[8], J. Mei[8], F. Souza[8], D. Rasco[9], J.P. Eder[1], A.W. Tolcher[10]

[1]Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA, [2]Oncology, Sarcoma Oncology Research Center, Santa Monica, CA, USA, [3]GI Oncology Research, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [4]Department of Medicine, Karmanos Cancer Institute, Detroit, MI, USA, [5]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [6]Clinical Pharmacology, Bayer HealthCare Pharmaceuticals Inc, New York, NY, USA, [7]Clinical Statistics, Bayer HealthCare Pharmaceuticals Inc, New York, NY, USA, [8]Translational Medicine Oncology, Bayer HealthCare Pharmaceuticals Inc, New York, NY, USA, [9]Medical Oncology, START, San Antonio, TX, USA, [10]Clinical Research, South Texas Accelerated Research Therapeutics (START); NEXT OncologyTM, San Antonio, TX, USA

Background: Mps1 is a serine threonine kinase and a core component of the spindle assembly checkpoint. Two potent, selective, and orally active Mps1 inhibitors – BAY 1161909 (BAY; lead compound) and BAY 1217389 – have shown improved efficacy in combination with paclitaxel (Pac) in xenograft models, including Pac-insensitive and acquired resistance models. We report here on the safety, tolerability, and maximum tolerated dose (MTD) of the lead compound BAY in combination with Pac.

Methods: Subjects with advanced malignancies (solid tumors) and refractory to standard therapy were eligible. BAY was administered twice daily (BID) in a 2-days on/5-days off dosing schedule in combination with weekly IV Pac starting at 75 mg/m^2 (Pac-75), and then at 90 mg/m^2 (Pac-90). The dose of BAY was doubled in sequential cohorts until the MTD was reached. Pharmacokinetic analyses were done to determine exposure of BAY and Pac.

Results: A total of 37 patients were enrolled and treated in the Pac-75 cohort and 32 in the Pac-90 cohort, with median age 60 in both groups. Breast, NSCLC, and ovarian adenocarcinomas were the most common cancers. The majority of patients (53.6%) had >3 prior lines of anticancer therapy. BAY exposure generally increased in a dose proportional manner and did not affect Pac exposure. In BAY plus Pac-75 cohorts, 16% of patients had grade (G) 3 BAY-related adverse events (AEs), with no G4/G5 events. In the Pac-90 cohorts, 28% of patients had G3 events, one G4 and no G5 BAY-related events. The most common treatment emergent AEs were fatigue (44.9%), anemia (39.1%), alopecia (37.7%), diarrhea (34.8%) and nausea (33.3%). In 35 evaluable patients from the BAY plus Pac-75 group, there were 5 (14%) PRs, 11 SD,17 PD, and 2 patients not determined. In 28 evaluable patients in the BAY plus Pac-90 group, there were 4 (14%) PRs, 13 SD, and 11 PD. Six of 9 patients with a PR had prior Pac. One dose limiting toxicity (ALT increased) was reported in the BAY 180 mg BID plus Pac-90 dose cohort. The MTD was determined as BAY 90 mg BID plus Pac-90.

Conclusions: BAY in combination with Pac demonstrated good tolerability with manageable AEs and preliminary evidence of efficacy. Study with the follow-up compound BAY 1217389 is ongoing.

Clinical trial identification: NCT02138812.

Legal entity responsible for the study: Bayer AG.

Funding: Bayer AG.

Disclosure: P. Rajagopalan, C. Cyris, I. Bruns, J. Mei, F. Souza: Employment: Bayer. All other authors have declared no conflicts of interest.

423P Phase I study of IDO1 inhibitor navoximod (GDC-0919) as monotherapy and in combination with atezolizumab in Japanese patients with advanced solid tumors

N. Yamamoto[1], Y. Fujiwara[1], S. Kondo[1], S. Iwasa[1], K. Yonemori[1], A. Shimomura[1], S. Kitano[1], T. Shimizu[1], T. Koyama[1], T. Ebata[1], N. Sato[2], K. Nakai[3], M. Inatani[4], K. Tamura[1]

[1]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan, [2]Clinical Study Management Department, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, [3]Clinical Pharmacology Department, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, [4]Clinical Science & Strategy Department, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan

Background: Navoximod is a small molecule inhibitor of indoleamine-2,3-dioxygenase 1 (IDO1) which catalyzes the oxidation of L-tryptophan (Trp) into kynurenine (Kyn). This study aimed to investigate maximum tolerated dose (MTD), safety, pharmacokinetics (PK) and pharmacodynamics of navoximod as monotherapy and in combination with atezolizumab, an anti-PD-L1 antibody, in Japanese patients (pts) with advanced solid tumors.

Methods: Phase 1, open-label, 3 + 3 dose-escalation study. Primary endpoints were safety, tolerability, and PK. Pts received navoximod (400, 600 or 1000 mg orally twice daily [BID], for 21 days/cycle) monotherapy (Stage 1) or navoximod (200, 400, 600 or 1000 mg orally BID, for 21 days/cycle) in combination with atezolizumab (1200 mg IV, every 21 days) (Stage 2).

Results: Twenty pts were enrolled in the 400 mg (n = 3), 600 mg (n = 4) and 1000 mg (n = 3) cohorts of Stage 1, and in the 200 mg (n = 3), 400 mg (n = 3), 600 mg (n = 3) and 1000 mg (n = 1) cohorts of Stage 2. Across all cohorts, no DLT was observed and MTD was not reached in either stages. In Stage 1, treatment related adverse events (TRAEs) of any grade occurring in ≥ 20% of pts were chromaturia (50%) and

maculopapular rash (20%). Grade ≥ 3 TRAEs were reported in 2 pts (20%), including maculopapular rash and lipase increased. In Stage 2, TRAEs ≥ 20% were fatigue (20%), chromaturia (60%), decreased appetite (40%), hyponatremia (20%), AST increased (20%), ALT increased (20%) and lymphopenia (20%). Grade ≥ 3 TRAEs were reported in 3 pts (30%), including hyponatremia, AST increased, ALT increased, lymphopenia and neutropenia. C_{max} and AUC of navoximod as monotherapy were dose-proportional from 400 to 1000 mg and PK profile was similar in combination with atezolizumab. Reduction of Kyn in plasma was observed in accordance with concentration of navoximod. Stable disease (SD) was observed in 5 pts including 2 pts with SD > 4months in Stage 1, and in 8 pts including 4 pts with SD > 4months in Stage 2, respectively.

Conclusions: Navoximod as monotherapy and in combination with atezolizumab was generally well-tolerated in Japanese pts with linear PK and evidence of systemic inhibition of IDO1.

Clinical trial identification: JapicCTI-163330.

Legal entity responsible for the study: Chugai Pharmaceutical Co., Ltd.

Funding: Chugai Pharmaceutical Co., Ltd.

Disclosure: N. Yamamoto: Advisory board: Eisai, Takeda, OncoTherapy Science, Otsuka, Boehringer Ingelheim; Corporate sponsored research: Quintiles, Astellas, Chugai, Esai, Taiho, BMS, Pfizer, Novartis, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, ONO. Y. Fujiwara: Advisory board: Bristol-Myers Squibb; Corporate-sponsored Research: Chugai, Incyte Corporation, MSD, Bristol-Myers Squibb. S. Iwasa: Corporate sponsored research: Bristol-Myers Squibb, Chugai. S. Kitano: Advisory board: Bristol-Myers Squibb, MSD. T. Shimizu: Corporate sponsored research: Bristol-Myers Squibb. N. Sato, K. Nakai, M. Inatani: Employment: Chugai. K. Tamura: Advisory Board: MSD; Corporate sponsored research: Chugai, Bristol-Myers Squibb, MSD. All other authors have declared no conflicts of interest.

425P SPIRE: A phase Ib/ randomised IIa open label clinical trial combining guadecitabine with cisplatin and gemcitabine chemotherapy for solid malignancies including bladder cancer

S.J. Crabb[1], S.J. Danson[2], D. Dunkley[3], M. Kalevras[3], A. Whitehead[3], S. Hill[3], K. Fines[3], C. Robb[3], J. Bennett[1], L. Ksiazek[1], S.L. Brown[2], L. Evans[4], M. Serra[5], K. Jones[6], C. McDowell[7], J.W. Catto[8], R. Huddart[5], G. Griffiths[3]

[1]Southampton Experimental Cancer Medicine Centre, University of Southampton, Southampton, UK, [2]Sheffield Experimental Cancer Medicine Centre, University of Sheffield, Sheffield, UK, [3]Southampton Clinical Trials Unit, University of Southampton, Southampton, UK, [4]Department of Oncology, Weston Park Hospital, Sheffield, UK, [5]Division of Radiotherapy and Imaging, Institute of Cancer Research and Royal Marsden, Sutton, UK, [6]Bob Champion Unit, Institute of Cancer Research and Royal Marsden Hospital, Sutton, UK, [7]Combinations Alliance, Cancer Research UK, London, UK, [8]Academic Urology Unit, The Medical School, University of Sheffield, Sheffield, UK

Background: Cisplatin resistance derives, in part, via tumour suppressor gene promotor methylation. In Vitro this reverses on co-administration of a DNA hypomethylating agent. Guadecitabine is a DNA methyltransferase inhibitor developed for optimised delivery of the active metabolite decitabine. SPIRE is an ECMC Combinations Alliance phase Ib/IIa clinical trial to establish a safe dose and schedule to combine guadecitabine with cisplatin/gemcitabine chemotherapy (GC). We report the phase Ib component.

Methods: Patients (pts) with incurable metastatic solid cancer, received GC (G: 1000 mg/m^2, IV, day (D) 8 + 15; C: 70 mg/m^2, IV, D8), and guadecitabine (SC, D1-5) for up to 6 x 21D cycles. Maximum tolerated dose (MTD) was determined with predefined criteria for dose limiting toxicity (DLT; CTCAE v4.03) in cohorts of 3-6 (rolling 6 design). The recommended phase II dose/schedule (RP2D) was expanded to include 6 bladder cancer pts. Subsequent cohorts incorporated GCSF (filgrastim, 300 µg SC, D15-21) if DLTs occurred due to neutropenia. Primary endpoint: guadecitabine MTD. Secondary endpoints: pharmacodynamic (PD) and pharmacokinetic (PK) parameters. Coordination: CRUK Southampton Clinical Trials Unit. Sponsor: University Hospital Southampton NHS Foundation Trust. Funding: Cancer Research UK (C9317/A19903) and Astex Pharmaceuticals.

Results: DLT occurred in 3 of 4 pts (thromboembolism; G4 neutropenia ≥7 days; febrile neutropenia) in cohort 1 (guadecitabine 20 mg/m^2 D1-5), in 1 of 8 pts (febrile neutropenia) in cohort 2 (guadecitabine 20 mg/m^2 D1-5 + GCSF) and 3 of 5 pts (febrile neutropenia; G3 diarrhoea + hypokalaemia; G4 neutropenia/thrombocytopenia ≥7 days + G3 tooth infection) in cohort 3 (guadecitabine 30 mg/m^2 D1-5 + GCSF). PD endpoints of mean plasma LINE-1 methylation depletion and haemoglobin F re-expression were consistent with guadecitabine target effect and PK parameters consistent with guadecitabine single agent data.

Conclusions: Guadecitabine 20 mg/m^2, day 1-5, with GCSF prophylaxis, is the RP2D in combination with GC. A randomised dose expansion is proceeding as neoadjuvant treatment for bladder cancer.

Clinical trial identification: EudraCT: 2015-004062-29.

Legal entity responsible for the study: University Hospital Southampton NHS Foundation Trust.

Funding: Cancer Research UK, Astex Pharmaceuticals.

Disclosure: S.J. Crabb: Consulting/advisory: Roche, Clovis Oncology, Merck; Research support: Clovis Oncology. J.W. Catto: Advisory boards: AstraZeneca; Speaker fees: Nucleix, Roche. R. Huddart: CoI BMS, MSD, Roche, Janssen (ad boards, meeting sponsorship, involvement in trials/trial funding); Elekta- consortium member. All other authors have declared no conflicts of interest.

426P Zirconium-89 (89Zr)-labeled bispecific T-cell engager (BiTE®) AMG 211 PET imaging to determine AMG 211 biodistribution in patients with gastrointestinal (GI) adenocarcinomas

K.L. Moek[1], S.J.H. Waaijer[1], I.C. Kok[1], F.V. Suurs[1], A. Brouwers[2], C.W. Menke-van der Houven van Oordt[3], T.T. Wind[1], J.A. Gietema[1], C.P. Schroder[1], S.V.K. Mahesh[2], A. Jorritsma-Smit[4], M.N. Lub-De Hooge[4], R.S.N. Fehrmann[1], D.J. de Groot[1], E.G.E. de Vries[1]

[1]Medical Oncology, University Medical Center Groningen, Groningen, Netherlands, [2]Radiology, Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, Groningen, Netherlands, [3]Medical Oncology, VUMC Cancer Center Amsterdam, Amsterdam, Netherlands, [4]Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands

Background: AMG 211 is a ~55 kDa BiTE® antibody construct directed against carcinoembryonic antigen (CEA, CEACAM5) on tumor cells and cluster of differentiation 3 (CD3) on cytotoxic T-cells. Biodistribution of bispecific antibodies in humans is largely unknown. Therefore, we performed a first-in-human feasibility study with ^{89}Zr-AMG 211 as PET tracer to explore AMG 211 biodistribution in normal and tumor tissues.

Methods: Nine patients with advanced GI adenocarcinomas underwent ^{89}Zr-AMG 211 PET imaging before (n = 7), during (n = 1) or before and during (n = 1) AMG 211 treatment. Before AMG 211 treatment, a fixed dose of 37 MBq 200 µg ^{89}Zr-AMG 211 alone (n = 2), or in combination with 1,800 µg (n = 4) or 4,800 µg (n = 2) cold AMG 211 was administered over 3 hours (h) followed by PET scans at 3, 6, and 24 h. ^{89}Zr-AMG 211 uptake was measured as standardized uptake value (SUV). ^{89}Zr-AMG 211 integrity in plasma and urine was analyzed with gel electrophoresis and binding of ^{89}Zr-AMG 211 to immune cells by counting Ficoll separated whole blood fractions.

Results: Before AMG 211 treatment, the optimal imaging dose was 200 µg ^{89}Zr-AMG 211 + 1,800 µg cold AMG 211. At 3 h the highest blood pool SUV_{mean} was 4.0, and tracer serum half-life was 3.3 h. Uptake in CD3-rich lymphoid tissues such as the spleen and bone marrow was SUV_{mean} 3.2 and 1.8, respectively. Uptake in these tissues decreased slower than in other normal tissues. ^{89}Zr-AMG 211 remained intact in plasma and was excreted predominantly via the kidneys in degraded forms. Of 43 visible tumor lesions, 37 were PET quantifiable, with a SUV_{max} of 4.0 (interquartile range 2.7 – 4.4) at 3 h using the optimal imaging dose. The maximum tracer uptake differed between tumor lesions 5-fold within and 9-fold between patients. During AMG 211 treatment (n = 2) more tracer was present in the blood pool, while tumor lesions were not visualized, possibly reflecting target saturation.

Conclusions: In this first-in-human study high specific ^{89}Zr-AMG 211 accumulation was observed in CD3-rich lymphoid tissues. In addition, a clear, inter- and intra-individual heterogeneous tumor uptake was seen.

Legal entity responsible for the study: Elisabeth de Vries.

Funding: Amgen.

Disclosure: F.V. Suurs: Research support: Amgen grant (insitution). J.A. Gietema: Research funding (institution): Roche Abbvie Siemens. E.G.E. de Vries: Research grant (institution): Amgen, Genentech, Roche, Chugai, Synthon, CytomX, Nordic Nanovector, Regeneron, G1 Therapeutics, AstraZeneca, Radius Health. Consulting (institution): Pfizer, Sanofi. All other authors have declared no conflicts of interest.

427P Phase I study of AMG 211/MEDI-565 administered as continuous intravenous infusion (cIV) for relapsed/refractory gastrointestinal (GI) adenocarcinoma

K.L. Moek[1], W.M. Fiedler[2], J.C. von Einem[3], H.M. Verheul[4], T. Seufferlein[5], D.J. de Groot[1], V. Heinemann[3], M. Kebenko[2], C.W. Menke-van der Houven van Oordt[4], T.J. Ettrich[5], E. Rasmussen[6], P. Bogner[7], B. Sable[6], S. Stienen[7], E.G.E. de Vries[1]

[1]Medical Oncology, University Medical Center Groningen, Groningen, Netherlands, [2]Department of Internal Medicine II, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [3]Department of Medical Oncology and Comprehensive Cancer Center, University Hospital Grosshadern, LMU Munich, Munich, Germany, [4]Medical Oncology, Vrije University Medical Center (VUMC), Amsterdam, Netherlands, [5]Department of Internal Medicine I, University of Ulm, Ulm, Germany, [6]Medical Oncology, Amgen Inc, Thousand Oaks, CA, USA, [7]Medical Oncology, Amgen Research (Munich) GmbH, Munich, Germany

Background: AMG 211 is a bispecific CEA-directed CD3 T-cell engager (BiTE$^{(R)}$) that inhibits growth of CEA-expressing cancer cells in various cancer models. It was explored as intermittent 3-hour infusion for 5 subsequent days in a Ph 1 study (Pishvaian et al, 2016). The present study used cIV administration suggesting an improved therapeutic index versus an intermittent infusion by reduction of adverse events attributable to high C_{max} and steady state exposure levels maintained above a threshold required for anti-tumor activity.

Methods: To evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy, patients (pts) with relapsed/refractory GI adenocarcinomas were treated with cIV AMG 211 for 7, 14 or 28 days at 0.2-12.8 mg/day in repeated cycles until confirmed

disease progression, occurrence of a dose-limiting toxicity (DLT) or discontinuation for other reasons. A Bayesian logistic regression model was intended to guide dose escalation after a first DLT.

Results: 44 pts (median age 64.5 (range 57, 70), Karnofsky > 70%) were dosed in up to 7 cycles (median 2) in 8 dose cohorts without observing a DLT. The majority (N = 32) were pts with CRC, 6 had pancreatic cancer, 4 cholangiocarcinoma and one each esophageal and appendix adenocarcinoma. AMG 211 was discontinued due to disease progression in 33 pts (73%), adverse event in 7 pts (16%), pts request and due to other reason in 2 pts (4%) each. Adverse events reported in > 20% of pts were fatigue (54%), nausea, abdominal pain, pyrexia (39% each) and diarrhea (32%). PK steady-state concentrations of AMG 211 were reached within 2 days of dosing and maintained throughout the treatment. In general, exposure, assessed by Cmax, Css, and AUC, was increasing with dose. Initial changes in inflammatory and tumor markers were seen. The study was discontinued after observation of anti-AMG 211 antibodies in all pts treated at high doses of > 3.2 mg and drop in exposure with high titers.

Conclusions: PD markers confirmed BiTE® mechanism of action. However, despite an acceptable safety profile immunogenicity leading to insufficient exposure for objective responses precluded the definition of a therapeutic window for AMG 211.

Clinical trial identification: NCT02291614.

Legal entity responsible for the study: Amgen.

Funding: Amgen.

Disclosure: W.M. Fiedler: Participation in advisary boards: Amgen, Pfizer, Novartis, Jazz Pharmaceuticals, Ariad/Incyte; Royalties: Amgen; Research funding: Amgen, Pfizer; Support for meeting attendance: Teva, Amgen, GSO Global, Jazz Pharmaceuticals, Daiichi Sanko Oncology; Support in medical writing: Amgen, Pfizer, Abbvie. H.M. Verheul: Research funding: Amgen, Vitromics, Immunovo, Novartis, Roche; Consulting fees: Boehringer Ingelheim, Pfizer, Roche; Other: Glycostsem advisory board. V. Heinemann: Research grant: Merck KgaA, Pfizer, Amgen, Roche, Boehringer Ingelheim, Celgene, Shire, Bayer, Celgene; Consulting fees: Merck KgaA, Roche AG, Amgen, Sanofi, Lilly, Sirtex, Boehringer Ingelheim, Baxalta, Taiho, Merrimack, Servier; Speakers bureau: Merck KgaA, Roche AG, Amgen, Sanofi, Sirtex, Baxalta, Servier; Travel expenses: Merck KgaA, Roche AG, Amgen, Sanofi, Sirtex, Baxalta, Servier. T.J. Ettrich: Research grant: Baxalta/Shire; Consulting fees: Merck-Serono, Sanofi, Sirtex, Medical, Novartis, Bayer, Bristol-Myers Squibb, Pfizer. E. Rasmussen: Stock: Amgen; Employment: Amgen. P. Bogner: Stocks: LTI-participation according to end-year review (compliant). Employment: Amgen. S. Stienen: Stock options or bond holdings in a for-profit corporation or self-directed pension plan. Employment: Amgen, include ownership of Amgen stock above if applicable. E.G.E. de Vries: Research grant: Amgen, Genentech, Roche, Chugai, Synthon, CytomX, Nordic Nanovector, Regeneron, G1 Therapeutics, AstraZeneca, Radius Health; all payments to the institution. Consulting fees: Pfizer, Sanofi; all payments to the institution. All other authors have declared no conflicts of interest.

428P Interim results from a phase I trial of SL-801: A novel XPO-1 inhibitor, in patients with advanced solid tumors

T.M. Bauer[1], M. Barve[2], E.G. Chiorean[3], P. Lorusso[4], K. Courtney[5], D. Qi[6], A. Olguin[7], J. Bullington[6], M. Sardone[8], V. Dunn[8], S. Shemesh[8], J. Chen[7], C. Brooks[7], J. Wang[9]

[1]Oncology, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [2]Oncology, Mary Crowley Cancer Research, Dallas, TX, USA, [3]Oncology, University of Washington, Seattle, WA, USA, [4]Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA, [5]Medical Oncology, UT Southwestern Medical Center, Dallas, TX, USA, [6]Clinical, Stemline Therapeutics, New York, NY, USA, [7]R&D, Stemline Therapeutics, New York, NY, USA, [8]Clinical Operations, Stemline Therapeutics, New York, NY, USA, [9]Drug Development Unit, Sarah Cannon Research Institute at Florida Cancer Specialists, Sarasota, FL, USA

Background: SL-801 is a novel, oral, small molecule reversible inhibitor of Exportin-1 (XPO-1), a critical nuclear export protein overexpressed in many cancers. SL-801 has demonstrated potent in vitro and in vivo anti-tumor activity against a broad range of hematologic and solid cancers. SL-801's reversible inhibition of XPO-1 may translate to selective activity and potential safety benefits. Interim results from the dose-escalation study are reported.

Methods: STML-801-0115 is a first-in-human, multicenter Phase 1 3x3 dose escalation study in patients with localized unresectable, or metastatic solid tumors resistant to or relapsed following standard therapy. Objectives are to evaluate safety, tolerability, identify maximum tolerated dose (MTD) or optimal dose/regimen, and assess pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity. SL-801 is orally administered on days 1-4 and 8-11 of a 21-day cycle. Starting dose was 5 mg; Currently enrolling 60 mg (escalation ongoing).

Results: As of 4/27/18, 35 patients received SL-801 (median age 64 years [range: 39-76, 18 females, range: 1-11 prior therapies; 69% ≥3rd line). No dose limiting toxicity (DLT) has been identified, and a MTD has not been reached. Median follow-up was 1.4 months (range: 0.2-10.8). Dose-dependent increases in C_{max} and AUC have been observed. The most frequent treatment-related grade 1-2 adverse events (TRAEs) were nausea (46%), vomiting (34%), fatigue (29%), decreased appetite (20%), and diarrhea (17%). Grade 3 TRAEs included nausea (n = 3; 40, 45, 50 mg), vomiting (n = 1; 45 mg), diarrhea (n = 2; 10, 50 mg), acute renal injury (n = 1; 30 mg), and neutropenia (n = 1; 10 mg). No grade 4 or 5 TRAEs reported. Eight patients (23%) had stable disease (SD) and remained on study for 3-15+ cycles. Six patients, with mucinous adenocarcinoma, GE junction, colon, neuroendocrine, basal cell, and breast cancer, had SD for ≥2.5 months; notably, the basal cell carcinoma patient had a SD response >9 months. Radiographic tumor shrinkage >10% noted in 3 patients.

Conclusions: SL-801 appears to be well tolerated in advanced solid tumor patients, and to date 23% of heavily pre-treated patients have achieved SD as best response. Enrollment and dose escalation continue.

Clinical trial identification: NCT02667873.

Legal entity responsible for the study: Stemline Therapeutics.

Funding: Stemline Therapeutics.

Disclosure: D. Qi: Consultant: Stemline Therapeutics. A. Olguin, J. Bullington, M. Sardone, V. Dunn, S. Shemesh, J. Chen, C. Brooks: Employment and stock ownership: Stemline Therapeutics. All other authors have declared no conflicts of interest.

429P NEO2734: A novel potent oral dual BET and P300/CBP inhibitor

F. Giles[1], M. Witcher[2], B. Brown[3]

[1]Developmental Therapeutics, DTC, Chicago, IL, USA, [2]Oncology, McGill University, Montreal, QC, Canada, [3]Oncology, NEOMED Therapeutics 1 Inc, Montreal, QC, Canada

Background: The Bromodomain (BRD) and Extra-Terminal domain (BET) family of proteins are key regulators of epigenetic control. Modulation of the BET family is a developmental therapeutics priority. Cyclic AMP response element binding protein (CREB)-binding protein (CBP) and E1A interacting protein of 300 kDa (EP300 or P300) are highly homologous BRD-containing transcriptional co-activators and are validated oncology targets. We have developed a series of potent dual inhibititors of BET-CBP/P300 with NEO2734 and NEO1132 as lead clinical candidates.

Methods: NEO2734 was profiled against the BET inhibitor iBET762 in cellular assays and in multiple human cancer xenograft models including castrate resistant prostate cancer (CRPC) (Vcap) and colon cancer (MC38).

Results: NEO2734 antiproliferative activity against a variety of solid tumor cell lines (Table). In a MDA-MB-231 Triple negative breast cancer cell line NEO2734 was more efficient at killing the cancer cells (85%) than a range of non-dual BET inhibitors which killed up to 50% of the cancer cells. NEO2734 has major activity at 10mg/kg (p.o.) in both CRPC and a colon cancer xenograft model whereas iBET762 has minimal activity at 30mg/kg (p.o.) both dosed once daily for 18 days. In the CRPC (Vcap) xenograft, mice were treated by oral gavage with NEO2734 (10mg/kg, and 15mg/kg) and the reference compound iBET762 (30mg/kg) for 18 days. In this model, NEO2734 led to potent tumor regression in a dose dependent manner. Much weaker activity was observed for iBET-762 at either 30 mg/kg. The antitumor activity correlated well with the reduction of PSA. The colon cancer xenograft was carried out in Syngeneic mice and the activity was compared with iBET762, anti-CTLA4 and anti-PDL1. NEO2734 was active at 10mg/kg (p.o.), as seen with the anti-PDL1 and superior to the anti-CTLA4 and iBET762.

Table: 429P

Cell line	Tissue Type	IC50 (μM) (72h)		
		NEO2734	iBET762	Cisplatin
T24	Bladder	0.59	7.2	1.4
Molt-4	Blood	0.56	2.4	0.49
KHYG-1		0.18	1.1	0.46
Raji		0.32	1.8	0.91
BT474	Breast	1.7	> 10	49
SK-BR-3		0.76	> 10	1.5
	Colorectum			
DLD-1		0.67	> 10	2.1
SW1116		0.86	> 10	5.9
Hep3B	Liver	0.89	> 10	3.6
SNU-354		0.47	> 10	7.6
	Ovary			
SW626		0.79	> 10	2.3
SW756		0.83	> 10	1.2
	Pancreas			
PL45		1.2	> 10	2.2
SW1990		2.8	> 10	1.8
22Rv1	Prostate	0.61	> 10	2.4
LNCaP clone FGC		0.24	0.99	8.7
VCAP		0.17	0.79	33
SK-MEL-28	Skin	3.9	> 10	7.5
SK-MEL-5		0.96	> 10	4.1

Conclusions: NEO2734, a novel oral potent dual inhibitor of BET and CBP/P300, has significant pre-clinical activity in a spectrum of human solid tumors. Clinical studies are in preparation.

Legal entity responsible for the study: Neomed Therapeutics 1 Ltd.

Funding: Neomed Therapeutics 1 Ltd.

Disclosure: F. Giles: Consultant: Neomed Therapeutics 1. B. Brown: Employee: Neomed Institute. All other authors have declared no conflicts of interest.

430P Phase I study: Safety and tolerability of varlitinib (VAR) in combination with oxaliplatin and capecitabine (COX) or oxaliplatin and 5-FU (FOL) in advanced solid tumours

A. Seet[1], S.P. Choo[2], D.W.M. Tai[3], Y.C.J. Lam[1], W.T. Teng[4], C. Lim[5], T.K.H. Lim[6], I.B. Tan[3], E. Petricoin[7], M. Ng[8]

[1]Medical Oncology, National Cancer Centre Singapore, Singapore, [2]Medical Oncology, National Cancer Center, Singapore, [3]Division of Medical Oncology, National Cancer Centre Singapore, [4]CTE, National Cancer Centre Singapore, [5]Biostatistics, CTE, National Cancer Centre Singapore, Singapore, [6]Department of Pathology, Singapore General Hospital, Singapore, [7]Applied Proteomics and Molecular Medicine, Institute of Biomedical Innovation, George Mason University, Manassas, VA, USA, [8]Division of Medical Oncology, National Cancer Centre (NCC), Singapore

Background: Varlitinib (VAR, ASLAN001) is a potent pan-HER oral tyrosine kinase inhibitor, with efficacy in EGFR mutant and HER2 over-expressing tumours. We evaluated the safety, tolerability and maximum tolerated dose (MTD) of VAR with CAPOX (COX) and mFolfox6 (FOL), in pts with advanced solid tumours.

Methods: Eligible pts had advanced solid tumours, ECOG performance status (PS) 0-1 and adequate organ function. Colorectal cancer (CRC) with RAS/RAF mutations were excluded. COX (Capecitabine 850mg/m^2 BID D1-D14 with oxaliplatin (OX) 130mg/m2 IV D1, Q21 days) or mFolfox6 (5-FU 400mg/m^2 IV bolus D1 and 2400mg/m^2 over 46 hrs with OX 85mg/m^2 IV D1, Leucovorin 400mg/m^2 IV D1, Q14 days) was given with VAR 200-400mg BID. Maximum 6 cycles COX or 9 cycles FOL, followed by VAR alone. Dose-limiting toxicity (DLT) period was 2 cycles.

Results: 30 pts were enrolled, 9 COX and 21 FOL arm. 15 (52%) CRC (all prior OX), 6 (21%) cholangiocarcinoma (CC), 3 (10%) gallbladder cancer and 6 (20%) others. Sex M/F 13/17, median age (range), PS, lines of prior chemo was 62yrs (36-71), 1(0-1) and 3.5(0-7) respectively. 28 pts were evaluable for MTD. MTD of VAR was 300mg/BID when given with FOL or COX.

Table: 430P

Dose	Pt enrolled/ evaluable	DLT
COX + VAR 400mg/BID	3/2	G3 Fatigue x2
COX + VAR 300mg/BID	6/6	G3 Fatigue
FOL + VAR 400mg/BID	4/4	G4 Transaminitis, G3 Raised Bilirubin
FOL + VAR 300mg/BID	11/9	G4 Encephalopathy, G3 Rash
FOL + VAR 200mg/BID	6/6	G3 Encephalopathy

Grade 3/4 AEs (occurring $\geq$ 5%): neutropenia 5 (17%), fatigue 3(10%), transaminitis 2(7%), diarrhoea 2(7%), febrile neutropenia 2(7%), transient metabolic encephalopathy 2(7%). Of 28 pts evaluable for response, 3 (11%) had PR and 16 (57%) SD. Disease control rate (PR+SD) for $\geq$ 12wks was 13 (46%). 5 (18%) had long PFS (223-645 days), comprising a gallbladder and CRC (both HER2-overexpressing, prior platinum), CC, bladder and CRC (prior OX and cetuximab). PK analysis did not show VAR accumulation. Plasma cell free DNA and HER pathway inhibition results will be presented later.

Conclusions: MTD for VAR with COX and FOL was 300mg/BID. Durable efficacy was seen in biliary cancers and CRC. ASLAN pharmaceuticals and the Singapore National Medical Research Council supported this study.

Clinical trial identification: NCT02435927.

Legal entity responsible for the study: National Cancer Centre, Singapore.

Funding: Aslan Pharmaceuticals.

Disclosure: M. Ng: Member: Aslan Pharmaceuticals advisory board; Speaker and research funding: Industry associated funding. All other authors have declared no conflicts of interest.

431P Phase Ib study of safety and tolerability of selinexor in Asian patients with advanced solid cancers

V.Y.M. Heong[1], M.L. Goh[2], W.P. Yong[1], R.A. Soo[2], C.E. Chee[1], S. Raghav[1], B-C. Goh[1], S.C. Lee[1], J. Lim[1], A. Wong[1], D.S.P. Tan[3]

[1]Haematology-Oncology, National University Cancer Institute Singapore (NCIS), Singapore, [2]Haematology-Oncology, National University Hospital, Singapore, [3]Hematology-Oncology, National University Hospital (NUH), National University Cancer Institute, Singapore (NCIS), National University Hospital (NUH), Singapore, Singapore

Background: Selinexor (SEL) is a potent Exportin 1 inhibitor that forces nuclear retention and activation of multiple tumour suppressor proteins resulting in tumour cell death. The safety, tolerability and pharmacokinetics were previously evaluated in the Asian population with preliminary evidence suggesting improved outcomes in tumors driven by the PI3K/AKT and Raf1/MEK/ERK pathway, thymic, NPC and refractory lymphoma.

Methods: SEL was administered orally to patients with advance solid tumour malignancy with PI3K/AKT/RAS mutations, thymic carcinoma, NPC or double expressor/transformed B cell lymphoma or cutaneous T-cell lymphoma in a phase Ib dose expansion study. Patients (pts) were treated using the established RP2D for Asian population of 60mg twice a week for 2 weeks in a 21-day cycle. Response was evaluated every two cycles (RECIST v1.1).

Results: 47 pts (17 M/ 16 F) received 60mg oral SEL. 28, 1 and 4 pts with solid tumours with PI3K/AKT/RAS mutation, NPC and refractory lymphoma respectively were enrolled. 1 lung, 14 colorectal (CRC), 5 gynecological (1 cervix; 4 ovarian), 6 pancreatic and 2 breast respectively had mutations in the PI3K/AKT/RAS pathway. Median PFS for patients with solid malignancy with mutations in the PI3K/AKT/RAS pathway and refractory lymphoma was 40d and 81d respectively, with 1 lymphoma pt still ongoing after 441 days. Median PFS for pts with KRAS mutant CRC and pancreatic cancer was 42 and 31 days respectively. Dose reductions occurred in 7 (14.9%) pts and dose interruptions occurred in 29.8% of pts.

Conclusions: The RP2D dose of SEL is tolerable and safe in the Asian population. This dose will be used in the phase 2 study for further efficacy analysis.

Legal entity responsible for the study: The National Medical Research Council, Singapore.

Funding: The National Medical Research Council, Singapore.

Disclosure: All authors have declared no conflicts of interest.

432P Population pharmacokinetic analyses for talazoparib (TALA) in cancer patients

Y. Yu[1], C. Durairaj[1], H. Shi[2], D.D. Wang[1]

[1]Oncology, Pfizer, Inc., San Diego, CA, USA, [2]Oncology, Pfizer, Inc., Groton, CT, USA

Background: This analysis described the population pharmacokinetics (popPK) of TALA in cancer patients to identify significant covariates, evaluate the PK comparability of 4 x 0.25 mg capsules and 1 x 1 mg capsule as a 1 mg dose, and provide individual PK predictions for PK/pharmacodynamic analysis.

Methods: The data used for the analysis included 6207 PK observations from 490 patients treated with TALA in 4 studies (PRP-001, PRP-002, ABRAZO, and EMBRACA); the detailed PK data will be disclosed in the poster. TALA concentration-time data were analyzed by using a nonlinear mixed-effects modeling approach with NONMEM. Inclusion of covariates was conducted by visual inspection of ETAs vs covariates of interest followed by statistical test (stepwise covariate modeling).

Results: A 2-compartment model with 1st-order absorption best described the PK of TALA. The estimated population-typical value for apparent oral clearance (CL/F) was 6.37 L/h, apparent volume of central compartment (V_2/F) 162 L, and absorption rate constant (k_a) 1.22 1/hour. While food and formulation were significant covariates on k_a, they had no impact on bioavailability (F). Coadministration with strong P-gp inhibitors increased the relative bioavailability by 44.7%. Baseline creatinine clearance was significant for CL/F with a 14.4% and 37.1% decrease in CL/F for patients with mild and moderate renal impairment, respectively. Asian (23.7% higher CL/F), age (on CL/F), and baseline body weight (BWT) (on V_2/F) are significant covariates but not considered clinically relevant. Other covariates tested (sex, liver enzymes, acid-reducing agents) were not significant on relevant PK parameters.

Conclusions: The population PK model adequately described the observed PK data of TALA. Results suggest that no dose adjustment is necessary based on a patient's age, BWT, race, or sex or for patients with mild renal or hepatic impairment or for patients taking acid-reducing agents. TALA can be taken without regard of food. The PK of 1 x 1 mg capsule and 4 x 0.25 mg capsules as 1 mg dose was comparable. The dose of TALA should be reduced to 0.75 mg for patients taking strong P-gp inhibitors or for patients with moderate renal impairment.

Clinical trial identification: NCT01945775, NCT02034916, NCT01286987, NCT01399840.

Editorial acknowledgement: Editorial and medical writing support funded by Pfizer Inc. were provided by Edwin Thrower, PhD, Mary Kacillas and Paula Stuckart of Ashfield Healthcare Communications, Middletown, Connecticut.

Legal entity responsible for the study: Pfizer, Inc.
Funding: Pfizer, Inc.
Disclosure: Y. Yu, C. Durairaj, H. Shi, D.D. Wang: Employee: Pfizer, Inc.

433P An open-label, phase I, dose escalating study evaluating safety, tolerability and pharmacokinetics of oral administration of irinotecan in adult patients with solid tumors

J.A. Palshof[1], I. Kümler[1], P.G. Sørensen[1], B.V. Jensen[2], D.L. Nielsen[2],
[1]Department of Oncology, Herlev Hospital, Herlev, Denmark, [2]Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark

Background: Oral drug formulations have several advantages compared to intravenous formulation. Apart from patient convenience and favorable pharmaco-economics they offer the possibility of frequent drug administration at home. In this study, we present a new oral irinotecan formulation designed as an enteric coated immediate release tablet which in pre-clinical studies has shown good exposure with low variability.

Methods: A phase I, dose escalating study to assess safety, tolerability, pharmacokinetics and efficacy of an oral irinotecan formulation and to establish the maximum tolerated dose (MTD). Each treatment cycle was once-daily irinotecan for 14 days followed by one week rest.

Results: 25 patients were included across four cohorts; 3 patients were included in cohort 1 (20 mg/m^2), 7 patients were included in cohort 2 (30 mg/m^2), 3 patients were included in cohort 3 (25 mg/m^2) and 12 patients were included in cohort 4 (21 mg/m^2). Median age was 67 years, 52% were performance status (PS) 0 while 48% were PS 1. Median number of prior therapies was 3 (range1 to 6). MTD was established at 21 mg/m^2. No responses were observed. Nine patients (36%) had stable disease (SD), lasting median 19 weeks (range 7-45 weeks). Among these 5 patients had previously received irinotecan.No grade 3/4 hematologic toxicities were reported. Totally 6 patients experienced grade 1/2 anemia, 3 patients had grade 1/2 leucopenia and 1 patient had grade 1 trombocytopenia. Most common non-hematological grade 1 and 2 adverse events were nausea, fatigue, diarrhea, vomiting and cholinergic syndrome. Grade 3 toxicities included diarrhea, fatigue, nausea and vomiting, no grade 4 events were reported. PK data showed consistent daily exposures during treatment at days 1 and 14 and no drug accumulation. SN-38 interpatient variability was in the same range as after infusion.

Conclusions: Oral irinotecan was generally well tolerated; side effects were manageable and similar in type to those observed with intravenous irinotecan. Hematological toxicities were few and only grade 1/2. In this heavily pre-treated patient population oral irinotecan demonstrated activity even among patients previously treated with irinotecan.

Clinical trial identification: EudraCT: 2014-005584-32; NCT03295084.

Legal entity responsible for the study: Herlev and Gentofte Hospital, Department of Oncology, Herlev, Denmark.

Funding: Oncoral Pharma ApS, Ballerup, Denmark.

Disclosure: J.A. Palshof, I. Kümler, P.G. Sørensen, B.V. Jensen, D.L. Nielsen: Oncoral Pharma ApS provided study medication.

434P Biomarker-driven access to crizotinib in ALK, MET or ROS1 positive (+) malignancies in adults and children: The French national AcSé program

G. Vassal[1], N. Cozic[2], R. Houot[3], L. Brugières[4], T. Aparicio[5], J-Y. Blay[6], M. Perol[6], P. Brice[7], E. Meriaux[8], B. Geoerger[4], M.R. El Bejjani[9], S. Moalla[9], I. Bièche[10], S. Lantuejoul[11], C. Mahier Ait Oukhatar[12], N. Hoog Labouret[13], D. Moro-Sibilot[14]
[1]Clinical Research Department, Gustave Roussy Cancer Campus, Villejuif, France, [2]Oncostat, Gustave Roussy Cancer Campus, Villejuif, France, [3]Hematology, Hôpital Pontchaillou, Rennes, France, [4]Department of Pediatric and Adolescent Oncology, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France, [5]Gastroenterology and Digestive Oncology, Hôpital Saint Louis, Paris, France, [6]Medical Oncology, Centre Léon Bérard, Lyon, France, [7]Hematology and Oncology, Hôpital St. Louis, Paris, France, [8]Medical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [9]Radiology, Gustave Roussy Cancer Campus, Villejuif, France, [10]Pharmacogenomics Unit, Institut Curie, Paris, France, [11]Department of Biopathology, Centre Léon Bérard, Lyon, France, [12]Research and Development, UNICANCER, Paris, France, [13]Biology, Transfert and Innovation Department, Institut National du Cancer, Boulogne Billancourt, France, [14]Thoracic Pneumology, Hôpital Michallon, Grenoble, France

Background: Crizotinib (czb) was registered for ALK+ NSCLC in 2013 and recently for ROS1+ stage IV NSCLC. Czb targets (ALK, MET, ROS1) are also altered (translocation [tlc], amplification [amp], mutation [mut]) in a wide range of malignancies (malg.) in adults and children. To generate high evidenced-based knowledge and to prevent off-label use, the French National Cancer Institute (INCa) launched the AcSé Program: equal access to tumor molecular diagnosis including an exploratory phase II trial.

Methods: Biomarker testing was proposed to patients (pts) $\geq$ 1 year old (yo) with an advanced disease among more than 15 malg. known to harbor a czb target alteration. If not eligible for any other trial, pts may enter one of the 22 cohorts defined by the type of tumor and target. Tumor response was evaluated every 2 months (mo) using RECIST v1.1. The primary endpoint is the objective response rate (ORR) at 2 mo [complete + partial response]. A two-stage Simon design is applied to each cohort.

Results: From 08/2013 to 03/2018, 13179 pts from 186 centers have entered the biomarker program. Tumor alterations found in pts were: ALK tlc, mut, amp in 14/2070, 8/313, 10/1858; MET amp ($\geq$6 copies/diploid genome) in 395/7932 [251/4171 NSCLC, 60/1232 glioblastomas, 28/939 colon, 35/570 esogastric, 7/640 ovarian cancers]; MET mut in 102/2836; ROS1 tlc in 82/4755 [NSCLC, cholangiocarcinoma, inflammatory myofibroblastic tumor (IMT)]. Overall, 237 pts (median age, 57 [1–92]) received czb (adult 250 mg bid; child 280 mg/m^2 bid).

Table: 434P

Positive cohorts	Pts analyzed	CR/PR at 2 mo	ORR % [IC95%]
ALCL ALK tlc	24	12	54 [34-75]
NSCLC MET amp	25 37 28*	7 20 5**	28 [10 - 46] 54 [38 - 70]
ROS1 tlc MET mut			18 [4 -32]
Esogastric MET amp	9	3	33 [7-70]
IMT ALK tlc / ROS1 tlc	8	3	38 [9-76]

*including 4 pts wIth MET mut on other exon than exon 14
**pts with MET mut exon 14 195 grade $\geq$3 adverse events (AEs) or SAE were reported in 83/237 pts. Grade $\geq$3 AEs were: ALT increased (6%), neutropenia (5%) and lymphopenia (5%).

Conclusions: Czb displayed a wide antitumor activity in several MET, ALK and ROS1+ malg. Equal and safe access across France to molecular testing and targeted therapies outside their approved indication is feasible.

Clinical trial identification: NCT02034981.

Legal entity responsible for the study: UNICANCER.

Funding: ARC Foundation Inca Pfizer.

Disclosure: G. Vassal: Travel, accomodations, expenses: BMS. J-Y. Blay: Advisory Board: Roche, Lilly, Ignyta, Deciphera, Novartis, Bayer, BMS; Corporate-sponsored research: Roche, Lilly, Ignyta, Deciphera, Novartis, Bayer, Novartis, GSK, AstraZeneca, MSD; Other substantive relationships: Surveillance committee of Innate Pharma. M. Perol: Advisory board: Pfizer. P. Brice: Advisory board: Takeda France; Corporate-sponsored research: Takeda Millenium, BMS, MSD. D. Moro-Sibilot: Speaker or advisory board: Eli Lilly, MSD, Roche, Novartis, BMS, Astra Zeneca, Takeda, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

435P Preliminary results of PROCLAIM-CX-072: The first-in-human, dose-finding trial of PD-L1 probody therapeutic CX-072 as monotherapy in patients (pts) with advanced solid tumors

V. Boni[1], J. Garcia-Corbacho[2], P.A. Ott[3], D.C. Cho[4], K.A. Autio[5], N. Uboha[6], A.I. Spira[7], R. Humphrey[8], M. Will[8], A. Naing[9], F. Thistlethwaite[10], E.G.E. de Vries[11], H-T. Arkenau[12]
[1]Medical Oncology, START Madrid-CIOCC HM Hospital Sanchinarro, Madrid, Spain, [2]Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain, [3]Center for Immuno-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [4]Department of Medicine, New York University Langone Medical Center, New York, NY, USA, [5]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [6]Carbone Cancer Center, University of Wisconsin, Madison, WI, USA, [7]Virginia Cancer Specialists, Fairfax, VA, USA, [8]Medical Oncology, CytomX Therapeutics, South San Francisco, CA, USA, [9]Oncology, MD Anderson Cancer Center, Houston, TX, USA, [10]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [11]Medical Oncology, University Medical Center Groningen, Groningen, Netherlands, [12]Sarah Cannon Research Institute SCRI UK, London, UK

Background: Antibodies (Abs) against programmed cell death ligand-1 (PD-L1) have improved survival in many types of cancer when used as monotherapy. However, anti–PD-L1 agents can be associated with high-grade immune-related adverse events (irAEs), particularly when used in combination with other anticancer agents. CX-072 is an anti–PD-L1 Probody™ therapeutic (Pb-Tx) designed to be preferentially activated by proteases in the tumor microenvironment and not in healthy tissue. Preclinically, Pb-Tx exhibited anticancer activity of the parent Ab with reduced toxicities in models of autoimmunity.

Methods: In parts A and A2 of the ongoing phase 1/2 Probody Clinical Assessment In Man (PROCLAIM)-CX-072 study (NCT03013491), CX-072 monotherapy is evaluated in a dose-escalation cohort of pts with advanced, heavily pretreated solid tumors. Part A2 required PD-L1-positive tumors and paired biopsies. Eligible pts were PD-1, PD-L1, and CTLA-4 inhibitor naive, with immunotherapy (IMT) unavailable as a standard of care. CX-072 is given every 14 days in cohorts of intravenous doses ranging from 0.03-30 mg/kg.

Results: As of April 20, 2018, part A/A2 had enrolled 37 pts. Pts had a median (range) of 3 (1-13) prior anticancer treatments. 14 (37.8%) pts are still on treatment at time of data cut. Median (range) time on treatment was 2.1 months (1-10). One DLT was observed (grade 3 febrile neutropenia; 3 mg/kg); MTD was not reached. Grade 3-4 treatment-related events were observed in 4 (10.8%) pts. irAEs with reversible grade 3 events occurred in 3 patients: thrombocytopenia, aminotransferase increases, and dyspnea. Two subjects discontinued CX-072 due to AEs. Across all dose levels, best response based on investigators' assessment in 23 evaluable pts included 2 partial response (thymoma, 3 mg/kg; TNBC, 10 mg/kg), 10 stable disease, and 11 progressive disease.

Conclusions: Preliminary data suggest that CX-072 demonstrates the characteristics of an antibody prodrug with antitumor activity and an acceptable safety profile in heavily pretreated pts with IMT-naive solid tumors. These data warrant further exploration of CX-072 as monotherapy and in combination with other anti-cancer agents.

Clinical trial identification: NCT03013491.

Editorial acknowledgement: Editorial support was provided by Andrew Occiano (ApotheCom, San Francisco, CA).

Legal entity responsible for the study: CytomX Therapeutics, Inc.

Funding: CytomX Therapeutics, Inc.

Disclosure: P.A. Ott: Research grant: BMS, Merck, Celldex, MedImmune, CytomX, ArmoBiosciences, Neon Therapeutics; Consulting: BMS, Merck, Celldex, CytomX, Roche/Genentech, Pfizer, Novartis, Neon Therapeutics; Nonremunerative positions of influence: NCCN melanoma guidelines board member. D.C. Cho: Consulting: BMS, Pfizer, Exelixis, Genentech, Prometheus. K.A. Autio: Research funding: CytomX, Pfizer, Lilly, GSK, Merck, ARMO Biosciences. N. Uboha: Consulting: EMD Serono, Lilly, FlatIron, GLG. A.I. Spira: Research grant: AbbVie; Consulting: AbbVie. R. Humphrey, M. Will: Employee: CytomX. A. Naing: Research funding: NCI, EMD Serono, MedImmune, Healios Onc. Nutrition, Atterocor, Amplimmune, ARMO Biosciences, Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Baxter (spouse). F. Thistlethwaite: Research grant: Novartis; Consulting: Pfizer, BMS, Octimet, Achilles Therapeutics, Evelo Biosciences; Honorarium: Novartis; Speakers' bureau: BMS. E.G.E. de Vries: Research grant (institution): Amgen, Genentech, Roche, Chugai, Synthon, CytomX, Nordic Nanovector, Regeneron, G1 Therapeutics, AstraZeneca, Radius Health; Consulting (institution): Pfizer, Sanofi. All other authors have declared no conflicts of interest.

436P Preliminary results of the first-in-human, dose-finding PROCLAIM-CX-072 trial evaluating the PD-L1 probody therapeutic CX-072 in combination with ipilimumab (ipi) in patients (pts) with advanced solid tumors

R. Plummer[1], R.E. Sanborn[2], E.G.E. de Vries[3], P. Lorusso[4], H-T. Arkenau[5], N. Uboha[6], J. Wydmanski[7], M.J. Fidler[8], V. Boni[9], J. Garcia-Corbacho[10], R. Humphrey[11], M. Will[11], K.A. Autio[12], A.B. El-Khoueiry[13], C.W. Menke-van der Houven van Oordt[14], F. Thistlethwaite[15]

[1]Northern Institute for Cancer Research, Newcastle University, Newcastle Upon Tyne, UK, [2]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA, [3]Medical Oncology, Universitair Medisch Centrum Groningen, Groningen, Netherlands, [4]Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA, [5]Sarah Cannon Research Institute SCRI UK, London, UK, [6]Carbone Cancer Center, University of Wisconsin, Madison, WI, USA, [7]Vegamed, NZOZ, Katowice, Poland, [8]Medical Oncology, Rush University Medical Center, Chicago, IL, USA, [9]Medical Oncology, START Madrid-CIOCC HM Hospital Sanchinarro, Madrid, Spain, [10]Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain, [11]Medical Oncology, CytomX Therapeutics, South San Francisco, CA, USA, [12]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [13]Medical Oncology, USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [14]Medical Oncology, VUMC Cancer Centre Amsterdam, Amsterdam, Netherlands, [15]Medical Oncology, The Christie NHS Foundation Trust and University of Manchester, Manchester, UK

Background: Combination treatment with PD-1 + CTLA-4 checkpoint inhibitors shows improvement in breadth, depth, and durability of response, coupled with a disproportionate increase in immune-related adverse events (irAE). CX-072, a Probody™ therapeutic (Pb-Tx) directed against PD-L1, is designed to be preferentially activated by tumor-associated proteases and not in healthy tissue. Preclinically, anti–PD-1 Pb-Tx + anti–CTLA-4 showed comparable efficacy with improved safety compared to the non–Pb-Tx combination control. This dose-escalation cohort examines safety and tolerability of CX-072 (anti-PD-L1 Pb-Tx) + the CTLA-4 inhibitor ipi in pts with advanced solid tumors.

Methods: In this ongoing phase 1/2 study (NCT03013491), PD-1, PD-L1, and CTLA-4 inhibitor-naive pts receive combination CX-072 + ipi (part B1). Planned doses of CX-072 (0.3, 1, 3, or 10 mg/kg) are administered in combination with ipi (3, 6, or 10 mg/kg) every 21 days for 4 cycles, followed by CX-072 monotherapy every 14 days.

Results: As of April 20, 2018, part B1 enrolled 16 pts. Median age (range) and number of prior anticancer treatments was 60 years (28-70) and 3 (1-12), respectively. 6 pts were still on treatment at time of data cut. Median number (range) of CX-072 (0.3, 1, 3, or 10 mg/kg) and ipi (3 mg/kg) doses were 3 (1-20) and 3 (1-4), respectively. All cohorts through 10 mg/kg CX-072 (dose selected for monotherapy cohort expansion) are now enrolled without reaching the MTD. 1 DLT (grade 3 dyspnea, 0.3 mg/kg CX-072 + ipi) occurred. Grade 3 treatment-related (TR) irAEs occurred in 2 pts (12.5%; colitis and dyspnea/pneumonitis). No subject discontinued due to TR irAEs. Best response in 10 evaluable pts included 1 complete response (anal SCC, 0.3 mg/kg CX-072 + ipi), 2 partial response (non-seminoma testicular, 1 mg/kg CX-072 + ipi; small bowel, 3 mg/kg CX-072 + ipi), 1 stable disease, and 6 progressive disease.

Conclusions: Despite small pt numbers and limited follow up, early data suggest manageable safety profiles at all doses and antitumor activity with CX-072 + ipi in tumor types not approved for checkpoint inhibitors. The study is ongoing and escalation of ipi to 10 mg/kg is pending.

Clinical trial identification: NCT03013491.

Editorial acknowledgement: Editorial support was provided by Andrew Occiano (ApotheCom, San Francisco, CA).

Legal entity responsible for the study: CytomX Therapeutics, Inc.

Funding: CytomX Therapeutics, Inc.

Disclosure: R.E. Sanborn: Research funding/grant: Merck; Investigator initiated Study: BMS, Medimmune; Institutional research support, honoraria: AstraZeneca; Advisory board: AstraZeneca, Seattle Genetics, Takeda, Genentech, Abbvie, Celldex; Travel, accommodations, investigator meeting: Janssen. E.G.E. de Vries: Research grant: Amgen, Genentech, Roche, Chugai, Synthon, CytomX, Nordic Nanovector, Regeneron, G1 Therapeutics, AstraZeneca, Radius Health (institution); Consulting: Pfizer, Sanofi (institution). P. Lorusso: Data safety monitoring board: Agios, FivePrime, Halozyme; Advisory board: Alexion, Ariad, CytomX, GenMab, Genentech, Glenmark, Ignyta, Menarini, Novartis, Omniox, Takeda, imCORE Alliance, Roche-Genentech. N. Uboha: Consulting: EMD Serono, Lilly, FlatIron, GLG. M.J. Fidler: Consulting: Genentech, AstraZeneca, Takeda, AbbVie; Speakers bureau: Merck, Celgene, Genentech, AbbVie. R. Humphrey, M. Will: Employment: CytomX Therapeutics. K.A. Autio: Research funding: CytomX, Pfizer, Lilly, GSK, Merck, ARMO Biosciences. F. Thistlethwaite: Research grant: Novartis; Consulting: Pfizer, BMS, Octimet, Achilles Therapeutics, Evelo Biosciences; Honorarium: Novartis; Speakers' bureau: BMS. All other authors have declared no conflicts of interest.

437P PT-112: A well-tolerated novel immunogenic cell death (ICD) inducer with activity in advanced solid tumors

D.D. Karp[1], D.R. Camidge[2], J.R. Infante[3], T.D. Ames[4], J.M. Jimeno[5], A.H. Bryce[6]

[1]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Medicine, University of Colorado Cancer Center, Aurora, CO, USA, [3]Department of Drug Development, Sarah Cannon Research Institute, Nashville, TN, USA, [4]Department of Research and Development, Phosplatin Therapeutics LLC, New York, NY, USA, [5]Department of Clinical Development, Phosplatin Therapeutics LLC, New York, NY, USA, [6]Department of Internal Medicine, Mayo Clinic Cancer Center, Phoenix, AZ, USA

Background: PT-112, a novel platinum pyrophosphate agent under development in solid tumors and hematological malignancies, is a potent inducer of damage associated molecular patterns (DAMPs) characteristic of ICD. It also affects G1/S cell cycle transition independent of DNA damage or repair pathways. Here we present a clinical update and analysis of single-agent activity in heavily pre-treated pts.

Methods: We treated 62 pts in an all-comer 3x3 Phase I dose escalation study. PT-112 was given IV for 1hr on days 1,8,15 (28d cycle) at dose levels 12 – 420 mg/m^2.

Results: All dose levels completed were deemed safe, with dose-linear pharmacokinetics, and MTD was not reached. Fatigue was the most common side effect. No significant acute neurotoxicity was reported in 533 infusions. Grade 1-2 peripheral neuropathy was seen in 8/62 pts (13%), and Grade 3 in 2 pts (3%) with cumulative doses of 3.1 and 4.3 g/m^2. Neutropenia (6 pts) and thrombocytopenia (8 pts) were limited with no infections or bleeding. Median prior lines of therapy = 5. Tumor control, metabolic and biomarker responses were observed at doses at / above 125 mg/m^2, with PSA reduction in 4 / 8 prostate pts. A non small cell lung cancer pt previously unresponsive to anti-PD-1 immunotherapy achieved a 6+ month RECIST PR at 250 mg/m^2 and complete PET response in liver / bone sites. A small cell lung pt who rapidly progressed on CTLA4 + PD-1 immunotherapy achieved PR at 360mg/m^2, progression free at 7.5 months. Marked tumor reduction at 360 mg/m^2 is ongoing after 6 mos. in a malignant thymoma pt with bulky thoracic disease. Time to response was 5-8 wks in all 3 pts. PFS at 6 mos. was reached in 8 / 46 evaluable pts at / above 125 mg/m^2 (17.4%). The ORR in 28 evaluable pts at / above 250mg/m^2 was 10.7%. At the provisional RP2D, now under confirmation (360 mg/m^2), 2 of 3 pts experienced durable tumor shrinkage.

Conclusions: PT-112 is a novel ICD inducing agent that is safe and well tolerated. Single-agent activity occurred in heavily pre-treated pts. Neither acute neurotoxicity nor kidney damage occurred. Fatigue was the most common side effect. Beneficial activity was observed at a range of doses, indicative of a broad therapeutic index, lack of cross-resistance with standard agents and feasibility for combinations.

Clinical trial identification: NCT: 2266745 IND: 118577.

Legal entity responsible for the study: Phosplatin Therapeutics LLC.

Funding: Phosplatin Therapeutics LLC.

Disclosure: D.D. Karp: Member of the scientific advisory board: Phosplatin Therapeutics. T.D. Ames, J.M. Jimeno: Employee and part owner: Phosplatin Therapeutics. All other authors have declared no conflicts of interest.

438P Safety and efficacy of the PD-1 inhibitor ABBV-181 in patients with advanced solid tumors: Preliminary phase I results from study M15-891

J. Powderly[1], P.A. Cassier[2], A. Cervantes[3], B. Gao[4], A. Gazzah[5], A. Italiano[6], C-C. Lin[7], J.J. Luke[8], V. Moreno[9], K. Peltola[10], D. Rasco[11], A.I. Spira[12], M.M.E. Tanner[13], D. Tosi[14], D. Afar[15], S. Englert[15], A. Parikh[15], A. Reddy[15], G. Vosganian[15], A.W. Tolcher[16]

[1]Carolina Biooncology Cancer Therapy, Huntersville, NC, USA, [2]Department of Medicine, Centre Léon Bérard, Lyon, France, [3]Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain, [4]Medical Oncology, The Crown Princess Mary Cancer Centre, Westmead, Australia, [5]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [6]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [7]Department of Oncology, National Taiwan University Hospital, Taipei City, Taiwan, [8]Medical Oncology, The University of Chicago Medical Centre, Chicago, IL, USA, [9]Medical Oncology-Start Madrid-FJD, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [10]Trial Unit Helsinki University Central Hospital, Helsinki, Finland, [11]Medical Oncology, START, San Antonio, TX, USA, [12]Virginia Cancer Specialists, Fairfax, VA, USA, [13]Medical Oncology, Tampere University Hospital (Tays), Tampere, Finland, [14]Medical Oncology, Institut du Cancer de Montpellier, Montpellier, France, [15]Oncology, AbbVie Inc., Redwood City, CA, USA, [16]Clinical Research, NEXT OncologyTM, San Antonio, TX, USA

Background: ABBV-181 is a humanized, recombinant, IgG1 monoclonal antibody targeting programmed cell death 1 (PD-1), incorporating an Fc mutation to limit FcgR-mediated effector function. Here we present preliminary ABBV-181 monotherapy data.

Methods: Patients (pts) with previously treated advanced solid tumors received ABBV-181 to progression at 1, 3, or 10 mg/kg IV Q2W (3 + 3 dose finding phase). Following dose finding, multi-histology, non-small cell lung cancer (NSCLC) and head and neck squamous cell cancer (HNSCC) cohorts were opened. Dose limiting toxicities (DLTs) were assessed on days 1-28 of dose finding focused on immune mediated (IM) events, hemolysis, and cytopenia. Response is assessed Q8W per response evaluation criteria in solid tumors (RECIST v.1.1) and immune RECIST.

Results: As of January 15, 2018, 53 pts were treated with ABBV-181: 25 in dose finding, 17, 6, and 5 in multi-histology, HNSCC and NSCLC cohorts, respectively. Median age was 61 (range 27-84) years, 41% male, most frequent diagnoses in dose finding and multi-histology: cholangio, ovarian, breast and cervical carcinoma. Median days on study were 43 (range 1-379), 42 (79%) pts had $\geq$ 1 adverse event (AE), 22 pts (42%) had grade $\geq$ 3 AEs and 8 (15%) pts had IM AEs. The most frequent AEs of any grade were: fatigue (18 pts), constipation and vomiting (9 pts each). No DLTs were reported. ABBV-181 was discontinued in 33 (62%) pts, 27 for progression and 1 each for AEs of diabetic ketoacidosis, progression and small intestinal obstruction. PD-L1 was expressed on 7/21 (33%) available pretreatment samples (Dako 28-8 assay with 1% threshold). By investigator assessment, 4/34 (12%) pts with post baseline assessment responded (all in dose finding, all partial responses). Sustained PD-1 saturation on circulating CD4 T cells was observed at all doses. ABBV-181 pharmacokinetics (PK) were approximately dose-proportional in dose finding.

Conclusions: ABBV-181 monotherapy demonstrates target engagement and encouraging efficacy without unexpected safety signals. PK and pharmacodynamic data from dose finding support flat doses of 250 mg Q2W, 375 mg Q3W or 500 mg Q4W for expansion. Enrollment in the expansion cohorts continues.

Clinical trial identification: NCT03000257.

Legal entity responsible for the study: AbbVie Inc.

Funding: AbbVie Inc.

Disclosure: P.A. Cassier: Honoraria: Novartis, Roche-Genentech, Blueprint Medicines, Amgen; Institution research funding: Novartis, Roche/Genentech, Lilly, Blueprint Medicines, Bayer, AstraZeneca, Celgene, Plexxikon, AbbVie, Bristol-Myers Squibb, Merck Serono, Merck, Sharp and Dohme. K. Peltola: Advisory fees: Orion Pharma, BMS, MSD, Pfizer, Ipsen and Roche; Stock holder: Faron Pharmaceuticals. A.I. Spira: Consultant and institutional research support: AbbVie. M.M.E. Tanner: Finnish advisory board: Roche, Novartis, Pfizer; Speakers bureau: Roche, Novartis, Pfizer, Amgen. D. Afar, S. Englert, A. Parikh, A. Reddy, G. Vosganian: Employee and may own stock: AbbVie. A.W. Tolcher: Consultant: AbbVie. All other authors have declared no conflicts of interest.

439P Prospective validation of prognostic scores to improve patient selection for immuno-oncology trials

C. Massard[1], N.H. Segal[2], D.C. Cho[3], V.A. Papadimitrakopoulou[4], N.A. Rizvi[5], B.C. Cho[6], L. Yu[7], H. Yang[7], H-J. Hsieh[7], J. Zhang[7], W. Zhao[7], G. Gao[7], X. Guo[7], S. Abdullah[8], J. Englert[8], J-C. Soria[8], M. Dar[8], L. Roskos[9], C. Ferte[8], S.J. Antonia[10]

[1]Drug Development Department, Institut Gustave Roussy Cancer Campus, Villejuif, France, [2]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3]Department of Medicine, New York University School of Medicine, New York, NY, USA, [4]Department of Thoracic Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [5]Thoracic Oncology, Memorial Sloan Kettering Cancer Center and Columbia University Medical Center, New York, NY, USA, [6]Medical Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea, [7]Biostatistics, MedImmune, Gaithersburg, MD, USA, [8]Medical Oncology, MedImmune, Gaithersburg, MD, USA, [9]Clinical Pharmacology & DMPK, MedImmune, Gaithersburg, MD, USA, [10]Thoracic Oncology, Moffitt Cancer Center, Tampa, FL, USA

Background: Life expectancy estimation is critical to select patients in clinical trials, notably in the phase I setting. However, most protocols use subjective criteria to meet this goal. Several scores have been developed from retrospective studies, but their utility in the immuno-oncology (IO) context remains unknown. The recent recognition of fast progressors under IO treatment further underscores the need for more objective prediction.

Methods: NSCLC and UBC patients (n = 972) prospectively enrolled in 3 phase I trials investigating durvalumab (anti-PDL1) ± tremelimumab (anti-CTLA4) across 160 centers were analyzed. We assessed the variability in the 8- and 12-week life expectancy rate across centers. Clinicopathological variables were used to train (n = 648) and validate (n = 324) a tool (FastProgIO) predicting 12-week life expectancy using a multivariate regression method. We compared FastProgIO to existing published scores (RMH, GRIM, LIPI). The performance was assessed by time dependent true positive rate (TPR) and false positive rate (FPR).

Results: Substantial variability was observed across sites with 26% and 65% of centers having enrolled > 15% of patients with life expectancy < = 8 and 12 weeks, respectively. FastProgIO includes neutrophils, AST, alkaline phosphatase and hemoglobin as the predictive markers. Overall, the TPR of FastProgIO was superior across a 4 to 12 weeks range to RMH, GRIM and LIPI. At 12 weeks, the TPR for FastProgIO was 73%, (90% CI: 67-80%) versus 69%, 65% and 41% for RMH, GRIM and LIPI, respectively. Furthermore, the FPR of FastProgIO (11%, 90%CI: 9.3-13%) was comparable to LIPI (10%), but better controlled than RMH and GRIM (20%, 17%).

Conclusions: The use of subjective criteria to estimate the 12-week life expectancy of patients enrolled in IO trials is clearly suboptimal and can lead to ethical, scientific, medical, and public health conundrums. In this large cohort of patients, FastProgIO appears superior to RMH, GRIM and LIPI to define life expectancy of patients based on easily available baseline clinical characteristics, and can be used to better select patients for IO clinical trials. An extended validation of this model in other tumor types is ongoing and will be presented.

Clinical trial identification: Study 006: NCT02000947 December 4, 2013 Study 1108: NCT01693562 September 26, 2012 Study 10: NCT02261220 October 10, 2014.

Legal entity responsible for the study: MedImmune.

Funding: MedImmune.

Disclosure: C. Massard: Advisory board member: Amgen, Astellas, AstraZeneca, Bayer, Celgene, Genentech, Ipsen, Janssen, Lilly, Novartis, Pfizer, Roche, Sanofi, and Orion. N.H. Segal: Honoraria: MedImmune; Consulting or advisory role: Bristol-Myers Squibb, Pfizer, AstraZeneca, MedImmune, MacroGenics, Imugene, Roche, Genentech, Kyocera, Amgen, Calithera Biosciences; Research funding: MedImmune, Bristol-Myers Squibb, Pfizer, Roche, Genentech, Merck. D.C. Cho: Consultant or advisory board member: Pfizer, BMS, Genentech. Exelixis, Prometheus. V.A. Papadimitrakopoulou: Grant research support and consultancy or advisory board member role: AstraZeneca. N.A. Rizvi: Honoraria or consultants fees: Roche, AstraZeneca, Novartis, Merck, Pfizer, Lilly, and BMS; Equity ownership: Gritstone Oncology and Armo Biosciences. B.C. Cho: Research grant support: Novartis, AstraZeneca, Yuhan, Ono/BMS, MSD, and Bayer; Consultancy or advisory board member: AstraZeneca, Roche, Boehringer Ingelheim, Yuhan, BMS, MSD, and Novartis; Speaker's bureau: AstraZeneca, BMS, MSD, and Novartis; Honorarium: AstraZeneca, Roche, Boehringer Ingelheim, Yuhan, BMS, MSD, and Novartis. L. Yu H. Yang: Employment: MedImmune; Equity ownership: AstraZeneca. H-J. Hsieh: Employment: Genentech, AstraZeneca, and MedImmune; Equity ownership: Genentech. J. Zhang, W. Zhao, G. Gao, X. Guo, S. Abdullah, J. Englert, M. Dar, L. Roskos: Employment: MedImmune and AstraZeneca; Equity ownership: AstraZeneca. J-C. Soria: Employment: MedImmune and AstraZeneca; Equity ownership: AstraZeneca. C. Ferte: Employment: MedImmune and Astrazeneca; Honoraria: Roche, MSD, Merck, and BMS; Consultancy or advisory role: Roche, MSD, Merck, Amgen, and BMS; Travel expenses: BMS, MSD, Merck, Amgen. S.J. Antonia: Research grant support: Novartis; Consultancy or advisory role: BMS, Novartis, Merck; Honoraria: BMS, Novartis, Merck, CBMG, Boehringer Ingelheim, AstraZeneca, MedImmune, Memgen.

440P Intratumoral administration of pro-inflammatory allogeneic, "off-the-shelf", dendritic cells in combination with anti-PD-1 or anti-CD137 has a synergistic anti-tumor effect

A. Karlsson-Parra, G. Fotaki, D. Yu, M. Essand

Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Background: Activated NK-cells are known to play immune-regulatory "helper" functions, being able to recruit and activate "bystander" DCs and to promote cross-presentation of cell-associated antigens to $CD8^+$ T cells by producing IFN-γ and TNF-α. We have recently shown that intratumoral administration of pro-inflammatory allogeneic mouse DCs (alloDCs) induce NK-cell recruitment and that human GMP-produced human alloDCs (ilixadencel) used in clinical trials (NCT00625755, NCT01974661, NCT02686944, NCT02432846), promote enhanced cytotoxicity and strong IFN-γ production in allogeneic NK-cells in vitro. Furthermore, co-culture of ilixadencel with allogeneic PBMCs leads to a pro-inflammatory environment inducing maturation and strongly enhanced cross-presentation in "bystander" DCs. Here we investigated the anti-tumor effect of intratumorally administered pro-inflammatory mouse alloDCs as monotherapy and in combination with anti-PD-1 or anti-CD137.

Methods: AlloDCs were produced from C57BL/6 mice and activated with a cocktail consisting of polyI:C, R848 and IFN-γ. After cryopreservation and subsequent thawing the cells were injected intratumorally 2 or 3 times starting at day 14 post subcutaneous CT-26 tumor cell inoculation in Balb/C mice. AlloDCs were given as monotherapy or

in combination with anti-PD-1 or anti-CD137. The studies were conducted at Charles River Laboratories, Morrisville, NC, USA.

Results: AlloDCs did not significantly delay tumor progression, likewise did not anti-PD-1. Combined treatment with alloDCs/anti-PD-1 significantly delayed tumor progression, while treatment with intratumoral administrations of polyI:C combined with anti-PD-1 showed no significant delay. Anti-CD137 treatment significantly delayed tumor progression and also induced one complete (10%) tumor response. Notably, the combination of alloDCs with anti-CD137 induced a highly significant anti-tumor synergy, including complete tumor eradication in 3 out of 9 mice (33%).

Conclusions: Intratumoral administration of allogeneic pro-inflammatory DCs induces a synergistic anti-tumor response when combined with systemic anti-PD-1 or anti-CD137 treatment.

Legal entity responsible for the study: Immunicum AB, Gothenburg, Sweden.

Funding: Immunicum AB, Gothenburg, Sweden.

Disclosure: A. Karlsson-Parra: Ownership of stocks in Immunicum AB; Employee: Immunicum. All other authors have declared no conflicts of interest.

441P OT-1096: A first-in-class immunoactivating small molecule that targets the thioredoxin reductase/thioredoxin axis causes strong tumor growth inhibition by downregulating intratumoral tregs in a humanized TNBC-PDX model

O. Orwar, I. Lowstedt, K. Andersson, G. Gannedahl, G. Willman, M. Davidsson, W. Stafford, C. Trkulja

Oblique Therapeutics AB, Gothenburg, Sweden

Background: Triple-negative breast cancer is an aggressive subtype associated with poor prognosis and limited treatment options, and new effective medicines are needed. We have developed a novel class of SecTRAP- forming small molecules that lead to a change-of-function of thioredoxin reductase that is cytotoxic to cancer cells (Staffort et al. Sci Transl Med, 2018). However, the immunomodulatory effects of OT-1096 are unknown. This study examined the efficacy of OT-1096 in humanized CD34+ NSG mice bearing patient-derived TNBC xenografts and compared the efficacy of OT-1096 to pembrolizumab. Additionally, the immunoactivating effects of OT-1096 were analyzed.

Methods: NSG mice, humanized with CD34+ stem cells from 3 different human donors were engrafted with TNBC invasive ductal carcinoma patient-derived xenografts. The mice were treated with OT-1096 (10mg/kg IV) tiwk and was compared to treatment with pembrolizumab (10mg/kg initial dose, thereafter 5mg/kg IP) biwk, single agent and in combination with OT-1096. Tumor volume was measured using calipers for 31 days and xenografts were analyzed with FACS to determine immune cell infiltration at day 41(sacrifice).

Results: OT-1096 showed statistically significant tumor growth inhibition (TGI: 63%) when comparing treatments arms with all three donors combined. OT-1096 also presented improved tumor growth control compared to pembrolizumab. FACs analysis of xenografts showed OT-1096-treated tumors to have a lower fraction of Tregs within the TIL population as compared to controls. OT-1096 treatment was both safe and well tolerated.

Conclusions: OT-1096 shows promising results in a humanized mouse TNBC PDX model with improved tumor growth inhibition compared to pembrolizumab. The results suggest that OT-1096 possesses both redox system modulation and beneficial immunomodulatory potential, and warrants further investigations of OT-1096 in TNBC and other malignancies.

Legal entity responsible for the study: Oblique Therapeutics AB.

Funding: Oblique Therapeutics AB.

Disclosure: O. Orwar: Stock owner, board of directors, CEO: Oblique Therapeutics. I. Lowstedt, G. Willman, M. Davidsson: Full-time employee: Oblique Therapeutics. W. Stafford: Employee and shareholder: Oblique Therapeutics. C. Trkulja: Stock owner, board of directors, full-time employee: Oblique Therapeutics. All other authors have declared no conflicts of interest.

442TiP A phase I first-in-human, dose-escalation and expansion study to evaluate the safety and tolerability of NUC-3373 in patients with locally advanced, unresectable or metastatic solid malignancies

S. Blagden[1], P. Spiliopoulou[2], L. Spiers[1], C. Gnanaranjan[3], C. Qi[4], V.K. Woodcock[1], J. Moschandreas[4], H.E.J. Tyrrell[1], L. Griffiths[6], C. Butcher[5], E. Ghazaly[3], T.R.J. Evans[2]

[1]Department of Oncology, Churchill Hospital University of Oxford, Oxford, UK, [2]Institute of Cancer Sciences, Beatson Institute for Cancer Research, Glasgow, UK, [3]Centre for Haemato-oncology, Barts Cancer Centre, London, UK, [4]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Centre for Statistics in Medicine, Oxford, UK, [5]Oncology Clinical Trials Office, University of Oxford, Oxford, UK

Background: The anti-cancer activity of 5-FU, and its other forms: floxuridine and capecitabine, is largely attributable to its active metabolite, fluorodeoxyuridine-monophosphate (FUDR-MP) that inhibits the enzyme thymidylate synthase (TS) and depletes the dTMP pool essential for cancer cell replication. Although 5-FU based agents remain the cornerstone of treatment for many tumour types, key cellular resistance mechanisms of breakdown, activation and transport limit their effectiveness. NUC-3373 is a phosphoramidate transformation of FUDR-MP designed to bypass these resistance pathways. It efficiently inhibits TS and depletes the dTMP pool within 2-4 hours. NUC-3373 is resistant to dihydropyrimidine dehydrogenase-mediated degradation and does not generate the toxic metabolite dhFU. NUC3373 has an advantageous PK/PD profile compared to 5-FU, with plasma $t_{1/2}$=9.7 h vs 8-14 mins, enabling the study of a more convenient alternate weekly dose-scheduling (Ghazaly et al ESMO, 2017).

Trial design: The primary study objective is to determine the RP2D and schedule of NUC3373 in patients with advanced cancers. Secondary objectives include safety, anti-tumour activity and PK/PD. In Part I, NUC-3373 was administered as an IV infusion on days 1, 8, 15 and 22 of a 28-day cycle. In Part II, NUC-3373 was administered on days 1 and 15 of a 28-day cycle. For PK analyses, blood samples were collected at 12 timepoints up to 48 h post-dose during cycle 1. Plasma and intracellular metabolites were measured by UPLC-MS/MS. Levels of free and bound TS were measured in PBMCs by western blotting. To date, thirty-six patients have been enrolled: Part I n = 29; Part II n = 7. Dose escalation is ongoing to establish the RP2D. Cohorts in Part I received NUC-3373 at 125, 250, 500, 750, 1125 and 1500 mg/m^2 and cohorts in Part II at 1500 and 1875 mg/m^2.

Clinical trial identification: NCT02723240.

Legal entity responsible for the study: Nucana plc.

Funding: Nucana plc.

Disclosure: S. Blagden: Advisor: Ellipses, Director of RNA Guardian Ltd.; Advisory boards: Clovis and Novartis; Research funding Nucana plc (unrelated to NUC-3373). T.R.J. Evans: Institution receives financial support for the costs of conducting this clinical trial and other studies with another of Nucana's compounds. Institution has also been reimbursed for time in a one-off advisory board for Nucana for another of their compounds. All other authors have declared no conflicts of interest.

443TiP First-in-human trial design for W0101: A first-in-class antibody-drug conjugate targeting IGF-1R and identification of the target patient population

C.A. Gomez-Roca[1], E. Garralda-Cabanas[2], F. Cruzalegui[3], F. Ausseil[3], G. Zorza[3], O. Delfour[3], J. Besse[3], B. Akla[4], S. Gautier[5], J. Adam[6], M. Lacroix-Triki[6], A. Passioukov[3], R. Roche[7], M. Pavlyuk[7], C. Massard[8]

[1]Medical Oncology & Clinical Research, Institut Universitaire du Cancer -Toulouse-Oncopole, Toulouse, France, [2]Early Drug Development Unit, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [3]Translational Medicine, Institut de Recherche Pierre Fabre, Toulouse, France, [4]Oncology Innovation Unit, Institut de Recherche Pierre Fabre, St Julien en Genevois, France, [5]Biometry Department, Institut de Recherche Pierre Fabre, Toulouse, France, [6]Pathology Department, Gustave Roussy, Villejuif, France, [7]Oncology Innovation Unit, Institut de Recherche Pierre Fabre, Toulouse, France, [8]DITEP, Gustave Roussy, Villejuif, France

Background: IGF-1R is over-expressed by neoplastic cells in many human cancers, associated with tumorigenesis, metastasis and treatment resistance. W0101 is a First-in-Class Antibody Drug Conjugate (ADC), designed for treatment of patients with tumors overexpressing membrane IGF-1R. Preclinically, internalization and anti-tumor activity of W0101 was shown in models expressing membrane IGF-1R (AACR 2018). To select potential responders to W0101 we developed a prototype immuno-histochemistry assay using a proprietary monoclonal antibody detecting a specific epitope on human IGF-1R, different from that of W0101. Using this test, we evaluated the membrane expression of IGF-1R in samples of squamous non-small-cell lung cancer (sqNSCLC), head-and-neck cancer and ER+ HER2- invasive breast cancer. This assay is currently used for retrospective assessment of patients included in this study. Here we present the design of a phase I/II international, multicentre, open label dose escalation and dose expansion study of intravenous infusion of W0101 in patients with advanced or metastatic solid tumors.

Trial design: This phase I/II consists of 2 parts: an initial dose escalation phase (I) followed by an expansion cohort (s) phase (II). In the dose escalation phase, 2 schedules of administration in 2 successive cohorts of patients will be assessed: Q2W schedule (A1) and a Q3W or Q4W schedule (A2). The first dose and the schedule of administration in cohort A2 will be determined using all safety and pharmacokinetics data generated in cohort A1 and using a PK/PD model. The phase I will allow to determine the Maximum Tolerated Dose and Schedule (MTDS) and to characterize dose-limiting toxicities (DLTs). The dose-toxicity relationships established via a Bayesian Logistic Regression Model will support the dose escalation process and will be used to assess the MTDS and recommended doses for expansion. Following completion of the dose escalation phase, the expansion phase will enroll up to 4 cohorts of patients prospectively tested for overexpression of IGF-1R to assess preliminary efficacy. A Simon design will be used for futility analysis.

Clinical trial identification: NCT03316638.

Legal entity responsible for the study: Pierre Fabre Medicament Represented by Institut de Recherche Pierre Fabre.

Funding: Has not received any funding.

Disclosure: F. Cruzalegui, F. Ausseil, O. Delfour, J. Besse, B. Akla, S. Gautier, A. Passioukov, R. Roche, M. Pavlyuk: Full-time employee: Institut de Recherche Pierre

Fabre. G. Zorza: Pierre-Fabre full-time employee. J. Adam, M. Lacroix-Triki: Funded the immunohistochemistry study performed at Gustave Roussy: Institut de Recherche Pierre Fabre. All other authors have declared no conflicts of interest.

444TiP Phase I/II study investigating safety, tolerability, pharmacokinetics, and preliminary antitumor activity of anti-PD-L1 monoclonal antibody BGB-A333 alone and in combination with anti-PD-1 monoclonal antibody tislelizumab in patients with advanced solid tumors

J. Desai[1], M. Voskoboynik[2], B. Markman[3], J. Hou[4], D. Zeng[5], T. Meniawy[6]

[1]Oncology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia, [2]Oncology, Nucleus Network, Melbourne, Australia, [3]Medical Oncology, Monash Health and Monash University, Melbourne, Australia, [4]Immuno-Oncology, BeiGene USA, Inc., Emeryville, CA, USA, [5]Clinical Science, BeiGene USA, Inc., Emeryville, CA, USA, [6]Linear Clinical Research and Sir Charles Gairdner Hospital, University of Western Australia, Nedlands, Australia

Background: PD-1 and its ligand, PD-L1, play critical roles in immune modulation of tumor progression. Tislelizumab is a humanized IgG4 monoclonal antibody against PD-1. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors at the recommended phase 2 dose (RP2D) of 200 mg administered every 3 weeks (Q3W). BGB-A333 is a humanized IgG1 monoclonal antibody against PD-L1 that increased functional activities of human T cells in in vitro studies, and showed antitumor activity in various cancer xenograft models. BGB-A333 blocks the interaction between PD-L1 and CD80 (B7-1), which in turn releases inhibitory signals to T cells, enhances T-cell expansion, and prevents T-cell anergy induction. Therefore, the combination of anti-PD-1 and anti-PD-L1 can potentially elicit stronger antitumor immunity through blockade of multiple complementary immune-suppressive signals in tumor microenvironments.

Trial design: This open-label study (NCT03379259) consists of two phases, each phase consisting of two parts. Phase 1 will investigate the safety and tolerability of the BGB-A333 alone and in combination with tislelizumab. Phase 1A (BGB-A333 dose escalation) will follow a 3 + 3 design to establish the RP2D of BGB-A333. Phase 1B (combination dose confirmation) explores the safety and tolerability of IV BGB-A333 (dose determined from dose escalation) in combination with IV tislelizumab (200 mg Q3W). Phase 2 will evaluate the antitumor activity of BGB-A333 alone and in combination with tislelizumab. Phase 2A (BGB-A333 dose expansion) has two cohorts: non-small cell lung cancer and urothelial carcinoma. Phase 2B (combination dose expansion) will enroll patients with specific tumor types, which will be chosen based on data from phase 2A and other studies. The primary endpoint of the phase 2 study is overall response rate. A total of 156 patients are estimated to be enrolled; as of 11 April 2018, 9 patients have been enrolled.

Clinical trial identification: NCT03379259.

Editorial acknowledgement: Medical writing and editorial assistance provided by Aarati Rai, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: BeiGene, Ltd.

Funding: BeiGene, Ltd.

Disclosure: J. Desai: Honoraria, consulting/advisory role, or research funding: Amgen, GlaxoSmithKline, Novartis, Bionomics, Lilly, Plexxikon, or Roche. B. Markman: Consulting fees and travel/accomodations expenses: Novartis and BeiGene. J. Hou, D. Zeng: Employee: Beigene. T. Meniawy: Honoraria, travel/accommodations expenses, consulting fees: AstraZeneca, Roche/Genentech and MedImmune; Research funding: Bristol-Myers Squibb, Incyte, BeiGene, AstraZeneca/MedImmune, Regeneron, Bayer, Merck Serono, Roche/Genentech. All other authors have declared no conflicts of interest.

445TiP Comprehensive profiling and molecularly guided therapy (MGT) for carcinomas of unknown primary (CUP): CUPISCO: A phase II, randomised, multicentre study comparing targeted therapy or immunotherapy with standard platinum-based chemotherapy

A. Krämer[1], F. Losa[2], L.M. Gay[3], D.R. Page[4], S. Foser[4], T.I. Mughal[5], J.S. Ross[3], G. Baciarello[6], L.R. Mileshkin[7], S. Osborne[8], H. Moch[9]

[1]Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ) and Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany, [2]Medical Oncology Department, Hospital Sant Joan Despí – Moises Broggi, Barcelona, Spain, [3]Pathology Group, Foundation Medicine, Inc., Cambridge, MA, USA, [4]Personalised Healthcare, F. Hoffmann-La Roche Ltd, Basel, Switzerland, [5]Hematology and Oncology, Tufts University Medical Center, Boston, MA, USA, [6]Department of Medical Oncology, Gustave Roussy, Villejuif, France, [7]Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia, [8]PDMA Operations (Biometrics), F. Hoffmann-La Roche Ltd, Basel, Switzerland, [9]Department of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland

Background: CUPs are heterogeneous tumours of diverse origins that often have poor prognoses and high unmet clinical need. Their heterogeneity makes the conduct of clinical trials difficult. The CUPISCO study aims to compare the overall efficacy and safety of MGT with standard platinum-based chemotherapy for patients (pts) with CUP.

Trial design: Eligible pts have a histological diagnosis of adeno- or poorly differentiated carcinoma without detectable primary tumour according to ESMO diagnostic guidelines (nonspecific CUP subset per ESMO definition only); Eastern Cooperative Oncology Group performance status 0–1; ≥1 measurable lesion; and are naive to systemic therapy. All pts receive hybrid capture-based comprehensive genomic profiling (FoundationOne®, FoundationACT®) to assess tumour genomic alterations, microsatellite instability and tumour mutational burden. Pts who achieve complete response [CR], partial response [PR] or stable disease [SD] after 3 induction chemotherapy cycles of carboplatin/paclitaxel, carboplatin/gemcitabine or cisplatin/gemcitabine are randomised (3:1) to investigator's choice (IC) from 9 MGT regimens (7 targeted therapy regimens, 2 immunotherapy regimens) or 3 further chemotherapy cycles. Randomisation is stratified by gender and response during the induction period (CR + PR vs SD). A key element of the trial design is a 'Molecular Tumour Board (MTB)', comprising the investigator, reference pathologist, reference oncologist and cancer genomics consultant (when needed), who advise investigators on MGT choice based on tumour genomic profiles. Pts with progressive disease during the induction period will be assigned to IC of MGT regimens with advice from the MTB. The primary efficacy endpoint is investigator-assessed progression-free survival (time from randomisation to first occurrence of disease progression per Response Evaluation Criteria in Solid Tumors v1.1, or death from any cause). Enrolment of 790 pts is planned across 23 countries and ~101 sites. Recruitment is ongoing; 5 pts have been screened to date (NCT03498521).

Clinical trial identification: NCT03498521.

Editorial acknowledgement: Support for third-party writing assistance for this abstract, furnished by Blair Jarvis, MSc, of Health Interactions, was provided by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: A. Krämer: Honoraria: Roche and Bayer; Consulting or advisory role: Roche, Bayer and Daiichi; Research funding: Bayer; Patents, royalties, other intellectual property: Bayer; Travel, accommodation and expenses: Roche. L.M. Gay: Employment: Foundation Medicine Inc.; Ownership of stock or other interests: Gilead Sciences and Foundation Medicine, Inc. D.R. Page: Employment: Roche/Genentech; Immediate family member employment: Novartis; Ownership of stock or other interests: Roche; Immediate family member ownership of stock or other interests: Novartis. S. Foser: Employment: Roche/Genentech; Ownership of stock or other interests: Roche. T.I. Mughal: Employment: Foundation Medicine, Inc.; Leadership: Foundation Medicine, Inc.; Stock or other ownership at Foundation Medicine, Inc.; Honoraria: Sanofi; Patents, royalties, other intellectual property for Oxford University Press and Informa. J.S. Ross: Employment: Foundation Medicine, Inc.; Leadership: Foundation Medicine, Inc.; Ownership of stock or other interests: Foundation Medicine Inc.; Honoraria: Pfizer and EMD Serono; Research funding: Foundation Medicine Inc. G. Baciarello: Consulting or advisory role: Janssen and Sanofi; Travel, accommodation and expenses: Janssen, Astellas, AstraZeneca and Sanofi. L.R. Mileshkin: Travel, accommodation and expenses: Roche and BeiGene. S. Osborne: Employed: Roche. H. Moch: Consulting or advisory role: Roche and Definiens; Research funding: Roche. All other authors have declared no conflicts of interest.

446TiP REVEAL: A phase I/II, open-label, multicenter, dose escalation and dose expansion study of NKTR-262 [TLR 7/8 agonist] plus NKTR-214 [CD122-biased agonist] with or without nivolumab (nivo) in patients (pts) with locally advanced or metastatic solid tumor malignancies

A. Diab[1], M. Marcondes[2], M.A. Tagliaferri[3], U. Hoch[4], J. Zhang[3], W. Rubas[5], S. Kivimae[5], J. Zalevsky[6], A.P. Conley[1], E. Borazanci[7], S.P. D'Angelo[8]

[1]Department of Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [2]Oncology Clinical Development, Nektar Therapeutics, San Francisco, CA, USA, [3]Clinical Development, Nektar Therapeutics, San Francisco, CA, USA, [4]Oncology, Nektar Therapeutics, San Francisco, CA, USA, [5]Oncology, Nektar Therapeutics, San Francisco, CA, USA, [6]Biology, Nektar Therapeutics, San Francisco, CA, USA, [7]Oncology, Honor Health/TGen, Scottsdale, AZ, USA, [8]Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background: Cancer treatments that couple pharmacological activation of tumor antigen presentation with activation and expansion of $CD8^+$ T and NK cells in the tumor environment have the potential to induce an effective anti-tumor immune response in pts. NKTR-262 is a small molecule agonist of toll-like receptors (TLRs) 7/8 designed to be retained in the tumor micro-environment to activate antigen-presenting cells (eg, dendritic cells) to create new antigen-specific cytotoxic T cells. As a CD122-biased agonist, NKTR-214 monotherapy increases newly proliferative $CD8^+$ T cells in tumors. NKTR-262 + NKTR-214 is expected to increase expansion of antigen-specific $CD8^+$ T cells. In preclinical studies, a single intratumoral (IT) injection of NKTR-262 + IV NKTR-214 resulted in complete abscopal effects in tumor models (Kivimae, SITC '17). Preliminary clinical data show NKTR-214 + nivo enhances immune-stimulatory responses (Diab, SITC '17). The REVEAL trial will assess safety and anti-tumor activity of NKTR-262 + NKTR-214 with or without nivo for the treatment of selected cancers.

Trial design: Primary objectives of the phase 1 dose escalation are to identify the recommended phase 2 dose of the doublet, NKTR-262 + NKTR-214 and of the triplet, NKTR-262 + NKTR-214 + nivo. Secondary objectives include antitumor activity including ORR, PFS and OS. Pts will receive IT NKTR-262 at escalating doses q3w until

biological response. The study will enroll eligible pts with advanced and/or metastatic melanoma, Merkel cell carcinoma, triple-negative breast cancer, ovarian carcinoma, renal cell carcinoma, colorectal cancer, urothelial carcinoma, or sarcoma. Eligibility includes measurable disease per RECIST 1.1 with at least 2 lesions (1 amenable to IT injection and biopsy collection). ~48 pts will be enrolled in phase 1 and ~345 pts in phase 2. Pts in the NKTR-262 + NKTR-214 cohorts will have progressed on prior approved therapies and pts in the NKTR-262 + NKTR-214 + nivo cohorts will be naïve to immunotherapy treatment. Trial is open and recruiting.

Clinical trial identification: NCT03435640.

Legal entity responsible for the study: Nektar Therapeutics, San Francisco, CA.

Funding: Nektar Therapeutics, San Francisco, CA.

Disclosure: A. Diab: Consulting or advisory role: Nektar, CureVac, Celgene; Travel, accommodations, expenses: Nektar Research funding (to institution): Nektar, Idera, Celgene, Pfizer. M. Marcondes: Employment: Nektar; Stock or Other Ownership: Nektar. M.A. Tagliaferri: Employment: Nektar; Leadership: Nektar; Stock and other ownership interests: Nektar; Consulting or advisory role (immediate family member): Bluebird Bio, Nektar; Patents, royalties, other intellectual property: Nektar; Travel, accommodations, expenses: Bluebird Bio, Nektar. U. Hoch, J. Zhang: Employment: Nektar Stock; Other ownership interests: Nektar. W. Rubas: Employment: Nektar (immediate family member): Pharm-Olam; Stock and other ownership Interests: Nektar. S. Kivimae: Employment: Nektar; Stock and other ownership interests: Nektar; Patents, royalties, other intellectual property: Nektar. E. Borazanci: Consulting or advisory role (an immediate family member): Teva, Biogen, Genzyme, Novartis consulting or advisory role: Fujifilm, Ipsen; Speakers' bureau (an immediate family member): Teva, Genzyme, Biogen, Novartis; Speakers' bureau: Ipsen, Taiho Pharmaceutical Research funding (to institution): Bristol-Myers Squibb, Pharmacyclics, Idera, Daiichi Sankyo, Minneamrita Therapeutics, Ambry Genetics, MabVax, Lilly, Samumed. S.P. D'Angelo: Consulting or advisory role: EMD Serono, Amgen, Nektar, Immune design, GlaxoSmithKline; Travel, accommodations, expenses: Adaptimmune, EMD Serono. All other authors have declared no conflicts of interest.

447TiP The cancer molecular screening and therapeutics program (MoST): A molecular screening platform with multiple, parallel, signal-seeking therapeutic substudies

S. Thavaneswaran[1], L. Sebastian[2], M. Ballinger[1], M. Cowley[3], J. Grady[3], A. Joshua[4], C. Lee[2], K. Sjoquist[2], W. Hague[2], J. Simes[2], D. Thomas[1]

[1]Genomic Cancer Medicine, The Garvan Institute of Medical Research, Darlinghurst, Australia, [2]Clinical Trials Research, The NHMRC Clinical Trials Centre, Camperdown, Australia, [3]Bioinformatics, The Garvan Institute of Medical Research, Darlinghurst, Australia, [4]Medical Oncology, The Kinghorn Cancer Centre, Darlinghurst, Australia

Background: Innovative approaches are needed to translate molecular opportunities into clinical care. MoST tests a novel paradigm for evaluation of biomarker-driven treatments (tx) for patients (pts) with advanced cancer, with a particular focus on rare or neglected cancers.

Trial design: Tx-refractory pts (N = 1000) undergo molecular screening using archival tumour tissue. Results are reviewed by the Molecular Tumor Board (MTB) to identify actionable variants and eligibility for substudies. A master protocol allows expedited addition of ≥ 12 open-label, phase Ib/IIa, single-arm substudies, with 16 pts per module deemed reasonable for signal-seeking purposes. The primary objectives are to identify potential clinical activity for biomarker-driven tx, biomarkers that predict for response, and to evaluate the MoST study design. Three substudies are active: 1) palbociclib - molecular eligibility includes amplification/activating mutations in cyclin D pathway genes, or loss of function mutations in CDKN2A; 2) olaparib+durvalumab (ola+durva) – molecular eligibility is a homologous recombination repair gene defect; 3) durvalumab+tremelimumab (durva+treme) offers a tx in the absence of actionable findings. Further substudies planned include vismodegib and eribulin for tumours with PTCH1 or SMO mutations, and CD31 positivity respectively. Since September 2016, recruitment to screening has exceeded targets. Of the 571 pts enrolled to April 2018, 474 MTB reports have been issued, 57 are in progress, 31 had insufficient tissue and 43 died prior to issue of a MTB report. Median time to MTB report issue was 44 days over latest quarter (n = 89). Rare cancers comprise at least 44%; an actionable mutation to inform therapy reported in > 40%. Palbociclib (n = 16) and durva+treme (n = 4x16, 64 pts) substudies have completed recruitment; ola+durva (n = 3x16 pts) is currently recruiting. The distribution of actionable mutations across cancers, and in particular rare cancers will be informative, as it comprises the essential first steps to gaining access to novel, personalized treatments for pts.

Clinical trial identification: Framework protocol Trial ID ACTRN12616000908437. Registered 08 July 2016. Therapeutic substudy 1 (palbociclib) Trial ID ACTRN12616000931471. Registered 13 July 2016. Therapeutic substudy 2-5 (durvalumab plus tremelimumab) Trial ID ACTRN12616001019493. Registered 02 August 2016. Therapeutic substudy 6-8 (olaparib plus durvalumab) Trial ID ACTRN12617001000392. Registered 11 July 2017.

Legal entity responsible for the study: Human Research Ethics Committee, St Vincent's Hospital; approval reference: HREC/16/SVH/23. Coordinating Centre for Molecular Screening: Garvan Institute of Medical Research, Darlinghurst NSW 2010. Coordinating Centre for Therapeutic Substudies: NHMRC Clinical Trials Centre, Camperdown NSW 2050.

Funding: The NSW Office for Health and Medical Research, granted 2/3/15: H15/13965 Therapeutic substudies to date have been funded by AstraZeneca Australia and Pfizer, which includes drug supply.

Disclosure: All authors have declared no conflicts of interest.

448TiP MEDIOLA: A phase I/II trial of olaparib (PARP inhibitor) in combination with durvalumab (anti-PD-L1 antibody) in pts with advanced solid tumours – new ovarian cancer cohorts

R.T. Penson[1], Y. Drew[2], M.J.A. de Jonge[3], S-H. Hong[4], Y.H. Park[5], A. Wolfer[6], J. Brown[7], M. Ferguson[8], M.E. Gore[9], R.H. Alvarez[10], B. Kaufman[11], C. Gresty[12], H.K. Angell[12], K. Meyer[13], M. Lanasa[13], P. Herbolsheimer[13], S. Domchek[14]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Northern Centre for Cancer Care, Newcastle Upon Tyne, UK, [3]Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, [4]Seoul St Mary's Hospital, Catholic University of Korea, Seoul, Republic of Korea, [5]Samsung Medical Center, Seoul, Republic of Korea, [6]Lausanne University Hospital, Lausanne, Switzerland, [7]Beatson West of Scotland Cancer Centre, Glasgow, UK, [8]NHS Tayside, Dundee, UK, [9]The Royal Marsden Hospital NHS Foundation Trust, London, UK, [10]Cancer Treatment Centers of America, Augusta University, Augusta, GA, USA, [11]Sheba Medical Center, Ramat Gan, Israel, [12]AstraZeneca, Cambridge, UK, [13]AstraZeneca, Gaithersburg, MD, USA, [14]Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Background: Olaparib (Lynparza®) is a poly(ADP-ribose) polymerase (PARP) inhibitor that prevents the repair of single-strand DNA breaks. Durvalumab (Imfinzi®) is a programmed cell death ligand 1 (anti-PD-L1) inhibitor, which functions by promoting antitumour immune responses. Inhibition of vascular endothelial growth factor (VEGF) has been reported to enhance PARP inhibitor activity. Combinations of immune checkpoint inhibitors and bevacizumab have shown promising results in other tumour types. Here, the efficacy and safety of bevacizumab (anti-VEGF-A antibody) is investigated in combination with olaparib + durvalumab in platinum-sensitive relapsed (PSR) non-gBRCAm ovarian cancer (OC) pts (NCT02734004).

Trial design: Initially, 148 pts were enrolled across several tumour types (small-cell lung cancer, gastric cancer, germline BRCA-mutated [gBRCAm] breast cancer, or PSR gBRCAm OC). Pts received olaparib 300 mg po bid for a 4-wk run-in, followed by olaparib 300 mg po bid and durvalumab 1.5 g IV q4w. Primary endpoints were disease control rate (DCR) at 12 wks, safety and tolerability. Secondary endpoints: pharmacokinetics (PK), DCR at 28 wks, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Tumours were assessed at baseline, 4 wks and every 8 wks thereafter. Enrolment was completed for these initial cohorts, and new PSR OC cohorts (Table) have been added, based on the preliminary results. These cohorts have no olaparib run-in, tumour assessments are performed at baseline and every 8 wks thereafter, bevacizumab 10 mg/kg is given q 2 weeks, and pts with 1–2 prior chemotherapy lines are allowed.

Table: 448TiP New MEDIOLA cohorts

OC cohort name	Drugs	Population	Primary endpoint
Expansion (N = 80)	Olaparib+Durvalumab	gBRCAm	ORR
Doublet (N = 30)	Olaparib+Durvalumab	non-gBRCAm	DCR 24 wks
Triplet (N = 30)	Olaparib+Durvalumab+ Bevacizumab	non-gBRCAm	DCR 24 wks

Other endpoints: Safety and tolerability, PK, DCR at 56 wks, ORR, PFS, and OS. Biomarker endpoints: Analysis of tumour-infiltrating lymphocytes and PD-L1 expression.

Clinical trial identification: NCT02734004.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: R.T. Penson: Scientific advisory boards: Amgen Inc., Genentech, Inc., AstraZeneca, Endocyte Inc., Eisai Inc., Vascular Biogenics Ltd, Baxalta Oncology, AbbVie, Clovis Oncology, Tesaro; Research funding: Genentech Inc., ImClone Systems Inc., Endocyte Inc., AstraZeneca, Eisai Inc., Amgen Inc., Vascular Biogenics Ltd; Royalties: BMJ, Blackwell; Publishing Medicine at a Glance, UpToDate Commercial: Advance Medical: Second Medical Opinion. B. Kaufman: Advisory board: AstraZeneca. C. Gresty, H.K. Angell, K. Meyer, M. Lanasa, P. Herbolsheimer: Employee and stockholder: AstraZeneca. S. Domchek: Honoraria: AstraZeneca, Clovis, and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

449TiP MASTER KEY project: A basket/umbrella trial for rare cancers in Japan

S. Noda[1], K. Yonemori[2], N. Shirakawa[3], H.S. Okuma[1], T. Shimizu[4], A. Hirakawa[5], T. Shibata[6], T. Sukigara[1], N. Okita[1], A. Kawai[7], N. Yamamoto[4], K. Nakamura[1], H. Mano[8], T. Nishida[9], Y. Fujiwara[1]

[1]Clinical Research Support Office, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Pediatric Oncology, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan, [5]Department of Biostatistics and Bioinformatics, The University of Tokyo, Tokyo, Japan, [6]Center for Research Administration and Support, National Cancer Center, Tokyo, Japan, [7]Department of Musculoskeletal Oncology and Rehabilitation, National Cancer Center Hospital, Tokyo, Japan, [8]Division of Cellular Signaling, National Cancer Center Research Institute, Tokyo, Japan, [9]Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan

Background: Rare cancers have had a challenge in establishing standard therapies for patients compared to major cancers, due to the lack of basis for clinical studies and investigations. We started a biomarker driven basket/umbrella trial using a "master protocol", called the MASTER KEY Project, which aims to find more efficient ways to evaluate treatments for rare cancers and to build a treatment development infrastructure by collaborating with industries. Similar studies including NCI-MATCH trial are ongoing; however, MASTER KEY Project is the first to be reported for such large scale trials that focuses only on rare cancers.

Trial design: The project consists of two main parts: the prospective registry study part and the multiple clinical trials (sub-study) part. Patients with advanced rare cancers (annual incidence less than 6 cases per 100,000 population)/cancers of unknown primary/rare pathological subtypes of major cancers, who have priorly been evaluated by a molecular diagnostic testing, such as a validated next generation sequencing assay, are enrolled into the registry study. The primary objective of the registry study is to collect consecutive data on biomarker, patient background, and prognosis to build a large-scale database highly reliable for use as historical control data in future clinical trials. In the sub-studies, drugs are provided by various industries, who are collaborators. Sub-studies are placed under a "master protocol", allowing new sub-studies to be added at any time. Each sub-study is ordinarily a single arm study and will enroll 5-20 patients with the appropriate biomarker of interest, regardless of histopathologic tumor type. A biomarker-negative sub-study will also be available so that all patients have a chance to be enrolled in a sub-study. The project opened in May 2017. As of April 2018, more than 200 of a planned 100 patients/year have been enrolled in the project. There are three ongoing sub-studies. Two of them are biomarker related studies, which enroll patients harboring BRAF mutation and mismatch repair deficiency, respectively. In addition, three sub-studies are under planning and they will open by fall of 2018.

Clinical trial identification: UMIN000027552.

Legal entity responsible for the study: National Cancer Center Hospital.

Funding: Eisai Co., Ltd., Daiichi Sankyo Co., Ltd., Astellas Pharma Inc., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Bristol-Myers Squibb Co., Ltd., Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd. and Novartis Pharma Co.,Ltd., Japan Agency for Medical Research and Development.

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology 29 (Supplement 8): viii149, 2018
doi:10.1093/annonc/mdy280

ENDOCRINE TUMOURS

450PD Potential therapeutic targets in recurrent and metastatic parathyroid carcinomas revealed by next-generation sequencing

M. Cui, Y. Hu, Q. Liao, Y. Zhao
Department of General Surgery, PUMCH, Beijing, China

451P Pharmacokinetic drug-drug interaction between mitotane and etoposide in the treatment of adrenocortical carcinoma

A. Jouinot[1], B. Royer[2], S. Moeung[3], E. Chatelut[3], A. Bellesoeur[1], G. Assié[4], A. Thomas-Schoemann[5], J. Bertherat[4], F. Goldwasser[1], B. Blanchet[5]
[1]Medical Oncology, Cochin Hospital, Paris Descartes University, CARPEM, AP-HP, Paris, France, [2]Clinical Pharmacology and Toxicology Department, CHU Besancon, Besancon, France, [3]Institut Claudius-Regaud, Université de Toulouse, INSERM, Centre de Recherches en Cancérologie de Toulouse, Toulouse, France, [4]Endocrinology, Center for Rare Adrenal Diseases, Cochin Hospital, Paris Descartes University, AP-HP, Paris, France, [5]Clinical Pharmacology, Cochin Hospital, Paris Descartes University, AP-HP, Paris, France

Background: Association between mitotane and platinum-etoposide chemotherapy is the front-line treatment in metastatic adrenocortical carcinoma (ACC), although this regimen shows limited efficacy. Drug-drug interaction between mitotane -which is a strong pharmacokinetic inductor of CYP3A4 and BRCP- and etoposide –which is a substrate of CYP3A4 and BRCP- may contribute to chemoresistance in ACC. The aim of this study was to evaluate the pharmacokinetic interaction between mitotane and etoposide.

Methods: From December 2016 to October 2017, this observational study included 5 consecutive ACC patients treated with platinum-etoposide (120 to 150 mg/m^2 J1-J2-J3 at cycle 1) chemotherapy in referral center for rare adrenal diseases and oncology department of Cochin hospital, Paris. Plasma etoposide concentrations were measured using liquid chromatography at 0, 4 and 24h after each etoposide infusion. In the absence of dose-limiting toxicity, a dose escalation of etoposide was proposed from cycle 2.

Results: Patients received a median of 3 [2 to 6] chemotherapy cycles, in association with mitotane (4 patients, median mitotane plasma concentration of 14.2 mg/L) or after mitotane discontinuation (1 patient, plasma concentration 1 mg/L). Etoposide clearance was higher in association with mitotane (4.95 L/h [2.67 to 6.20]) than after discontinuation (2.53 L/h [2.02 to 2.78], Wilcoxon p = 0.014) or in a reference population not treated with mitotane (1.81 L/h)[1]. Etoposide dose escalation was performed in 4 patients treated with mitotane, resulting in 2 minor tumor response at 300mg/m^2 and 1 febrile neutropenia.

Conclusions: Drug-drug interaction between mitotane and etoposide may partly explain the low efficacy of platinum-etoposide chemotherapy in ACC. Given the elimination half-life of mitotane is extremely long (18-159 days), this observation suggests further a potential benefit of increasing etoposide dosage in patients receiving mitotane than stopping mitotane before chemotherapy initiation in ACC patients.

Legal entity responsible for the study: Blanchet Benoit and Jouinot Anne.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology 29 (Supplement 8): viii150–viii204, 2018
doi:10.1093/annonc/mdy281

GASTROINTESTINAL TUMOURS, COLORECTAL

452O DPYD genotype-guided dose individualization of fluoropyrimidine therapy: A prospective safety and cost-analysis on DPYD variants DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A

L.M. Henricks[1], C.A.T.C. Lunenburg[2], F.M. de Man[3], D. Meulendijks[4], G.W.J. Frederix[5], E. Kienhuis[3], G-J.M. Creemers[6], A. Baars[7], V.O. Dezentjé[8], H. Rosing[9], J.H. Beijnen[9], E. van Werkhoven[10], A.B.P. van Kuilenburg[11], R.H.N. van Schaik[12], R.H.J. Mathijssen[3], J.J. Swen[13], H. Gelderblom[2], A. Cats[14], H-J. Guchelaar[13], J.H.M. Schellens[1]

[1]Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [2]Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [4]Dutch Medicines Evaluation Board, CBG-MEB, Utrecht, Netherlands, [5]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands, [6]Department of Medical Oncology, Catharina Hospital, Eindhoven, Netherlands, [7]Department of Internal Medicine, Hospital Gelderse Vallei, Ede, Netherlands, [8]Department of Internal Medicine, Reinier de Graaf Hospital, Delft, Netherlands, [9]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [10]Department of Biometrics, The Netherlands Cancer Institute, Amsterdam, Netherlands, [11]Laboratory Genetic Metabolic Diseases, Department of Clinical Chemistry, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [12]Department of Clinical Chemistry, Erasmus Medical Center, Rotterdam, Netherlands, [13]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, Netherlands, [14]Department of Gastrointestinal Oncology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands

453PD 1st-line mFOLFOXIRI + panitumumab vs FOLFOXIRI treatment of RAS wt mCRC: A randomized phase II VOLFI trial of the AIO (KRK-0109)

M. Geissler[1], T. Klingler[1], J. Riera Knorrenschild[2], A. Tannapfel[3], J. Greeve[4], T. Seufferlein[5], S. Kanzler[6], S. Held[7], V. Heinemann[8], A. Reinacher-Schick[9], U.M. Martens[10]

[1]Internal Medicine, Oncology/Hematology, Klinikum Esslingen, Esslingen, Germany, [2]Oncology, Uniklinikum Giessen und Marburg, Marburg, Germany, [3]Pathology, Ruhr-Universität Bochum, Bochum, Germany, [4]Gastroenterology, St. Vincenz Krankenhaus, Paderborn, Germany, [5]Department of Internal Medicine I, Ulm Medical University, Ulm, Germany, [6]Department of Internal Medicine II, Leopoldina Krankenhaus Schweinfurt, Schweinfurt, Germany, [7]Statistik, Clinassess, Leverkusen, Germany, [8]Department of Medical Oncology and Comprehensive Cancer Center, Ludwig Maximilians University - Grosshadern, Munich, Germany, [9]Oncology, Ruhr University Bochum Medizinische Universitätsklinik, Bochum, Germany, [10]Oncology, SLK-Kliniken Heilbronn GmbH, Heilbronn, Germany

454PD Influence of treatment with prior bevacizumab: A combined analysis of individual patient data from ASPECCT and WJOG6510G trial which compared panitumumab versus cetuximab in patients with wild-type KRAS exon 2 metastatic colorectal cancer

H. Taniguchi[1], T. Yamanaka[2], D. Sakai[3], K. Yamazaki[4], K. Muro[5], M. Peeters[6], T.J. Price[7]

[1]Department of GI Oncology, National Cancer Center Hospital East, Kashiwa-shi, Japan, [2]Department of Biostatistics, Yokohama City University Hospital, Yokohama, Japan, [3]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan, [4]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [5]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan, [6]Oncology, U.Z.A. University Hospital Antwerp, Edegem, Belgium, [7]Medical Oncology, The Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia

455PD NORDIC9: A randomized phase II trial comparing first-line palliative full-dose monotherapy (S-1) with reduced dose-combination therapy (SOx) in older and frail patients with metastatic colorectal cancer (mCRC)

S.B. Winther[1], H. Skuladottir[2], E. Hofsli[3], C-H. Shah[4], M.K. Yilmaz[5], P.J. Österlund[6], Å. Berglund[7], B. Glimelius[7], C. Qvortrup[8], H. Sorbye[9], P. Pfeiffer[10]

[1]Department of Oncology, Department of Clinical Research, SDU, Odense University Hospital, Odense, Denmark, [2]Department of Oncology, Regional Hospital West Jutland, Herning, Denmark, [3]Department of Oncology, Trondheim University Hospital, Trondheim, Norway, [4]Theme Cancer, Karolinska University Hospital, Stockholm, Sweden, [5]Department of Oncology, Aalborg University Hospital, Aalborg, Denmark, [6]Department of Oncology, Tampere University Hospital (Tays), Tampere, Finland, [7]Department of Immunology, Genetics and Pathology, Uppsala University Hospital, Uppsala, Sweden, [8]Department of Oncology, Odense University Hospital, Odense, Denmark, [9]Oncology, Haukeland Universitetssykehus, Bergen, Norway, [10]Academy of Geriatric Cancer Research, AgeCare, Department of Oncology, Odense University Hospital, Odense, Denmark

456PD Serial circulating tumor DNA analysis for detection of residual disease, assessment of adjuvant therapy efficacy and for early recurrence detection in colorectal cancer

T. Reinert[1], T.V. Henriksen[1], M.H. Rasmussen[1], H. Sethi[2], R. Salari[2], S. Shchegrova[2], R. Swenerton[2], H-T. Wu[2], S. Sharma[2], E. Christensen[1], P. Natarajan[2], S. Dashner[2], T. Tin[2], A. Olson[2], H. Pawar[2], B. Zimmermann[2], L.H. Iversen[3], M.R. Madsen[4], J. Lin[2], C.L. Andersen[1]

[1]Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark, [2]RND, Natera, San Carlos, CA, USA, [3]Department of Surgery, Aarhus University Hospital, Aarhus, Denmark, [4]Department of Surgery, Herning Regional Hospital, Herning, Denmark

457PD Kinase fusions in colorectal cancers: A unique biologic subset

R. Madison[1], F. Pietrantonio[2], L. Juckett[1], C. Cremolini[3], J. Chung[1], L.A. Albacker[4], V.A. Miller[1], S.J. Klempner[5], M.B. Resnick[6], E. Yakirevich[6], S.-H.I. Ou[7], M. Fakih[8], A.B. Schrock[1], J.S. Ross[1], S.M. Ali[1]

[1]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA, [2]Oncology and Hemato-Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Polo Oncologico, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy, [4]Cancer Genomics, Foundation Medicine, Inc., Cambridge, MA, USA, [5]Medical Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA, [6]Pathology, Rhode Island Hospital & Alpert Medical School of Brown University, Providence, RI, USA, [7]Medicine, Chao Family Comprehensive Cancer Center, Irvine, CA, USA, [8]Medical Oncology & Therapeutics Research, City of Hope, Duarte, CA, USA

458PD Causal modeling of CALGB/SWOG 80405 (Alliance) identifies primary (1°) side-related angiogenic drivers of metastatic colorectal cancer (mCRC)

R.K. Das[1], L. Furchtgott[1], F-S. Ou[2], D. Swanson[3], B. Hayete[1], B. Harms[1], D. Cunha[1], J. Latourelle[1], D. Wuest[1], I. Khalil[1], C. Washburn[1], K. Rich[1], C.D. Blanke[4], J. Meyerhardt[5], D. Niedzwiecki[6], A. Nixon[7], E.M. O'Reilly[8], F. Innocenti[9], H-J. Lenz[10], A. Venook[11]

[1]Precision Medicine, GNS Healthcare, Inc, Cambridge, MA, USA, [2]Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN, USA, [3]Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway, [4]Medical Oncology, Oregon Health Science University, Portland, OR, USA, [5]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [6]Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC, USA, [7]Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA, [8]Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [9]Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, US, USA, [10]Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [11]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA

459PD **Long-term results of postoperative chemoradiation therapy with capecitabine and oxaliplatin versus capecitabine alone for locally advanced rectal cancer: A randomized, multicenter, phase III trial**

N. Li[1], J. Jin[2], Y. Li[1], Y. Zhu[3], W. Wang[4], J. Wang[5], Y. Feng[3], L. Liu[3], S. Wang[1], Y. Song[1], Y. Liu[1], Y. Tang[6], W. Liu[1], H. Ren[1], H. Fang[1]

[1]Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, [2]Radiation Oncology, National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China, [3]Radiation Oncology, Cancer Hospital, Zhejiang Province, Hangzhou, China, [4]Radiation Oncology, Guizhou Cancer Hospital, Guiyang, China, [5]Radiation Oncology, Hebei Provincial Cancer Hospital, Shijiazhuang, China, [6]Radiation Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS), Beijing, China

460PD **The value of chemotherapy in stage II colon cancer: Much less than we thought**

L. Wu[1], J. Fu[2], W. Fu[3], J. Du[4], L. Wang[1]

[1]Gastroenterology, Second Affiliated Hospital of Zhejiang University University School of Medicine, Hangzhou, China, [2]Oncology, Zhejiang University Jinhua Hospital, Jinhua, China, [3]Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [4]Department of Colorectal Surgery, Zhejiang University Jinhua Hospital, Jinhua, China

461PD **Folfox and intra-arterial DEBIRI as front-line treatment in patients with non resectable colorectal cancer liver metastases (FFCD 1201 phase II trial)**

S. Pernot[1], P. Artru[2], D. Tougeron[3], C. Montérymard[4], D. Smith[5], C. De La Fouchardière[6], J-L. Raoul[7], L. Dahan[8], R. Guimbaud[9], P. Michel[10], J-L. Jouve[11], O. Pellerin[12], J. Taieb[13]

[1]Department of Gastroenterology and Digestive Oncology, Hospital European Georges Pompidou, Paris, France, [2]Institut of Cancerology, Hospital Jean Mermoz, Lyon, France, [3]Department of Hepato Gastroenterology, CHU Poitiers, Poitiers, France, [4]Biostatistic, FFCD-, Dijon, France, [5]Department of Oncology, CHU Bordeaux Hospital St. André, Bordeaux, France, [6]Department of Medical Cancerology, Centre Léon Berard, Lyon, France, [7]Medical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [8]Department of Gastroenterology and Oncology, CHU La Timone Adults, Marseille, France, [9]Nuclear Medicine, Institut Claudius Regaud, Toulouse, France, [10]Department of Hepatogastroenterology, Normandie Univ, UNIROUEN, Inserm 1245, IRON Group, Rouen University Hospital, Rouen, France, [11]Department of Hepato Gastroenterology, CHU François Mitterrand, Dijon, France, [12]Department of Interventional Radiology, Hospital European Georges Pompidou, Paris, France, [13]Department of Gastroenterology and Digestive Oncology, Hospital European Georges Pompidou - Sorbonne Paris Cité, Paris Descartes University, Paris, France

462PD Postoperative carcinoembryonic antigen (CEA) association with survival and oxaliplatin benefit in stage II colon cancer (CC): Post hoc analysis of the MOSAIC trial

E. Auclin[1], T. Andre[2], J. Taieb[3], M. Banzi[4], J-L. van Laethem[5], J. Tabernero[6], T. Hickish[7], A. de Gramont[8], D. Vernerey[9]

[1]Oncology, Hopital Européen George Pompidou, Paris, France, [2]Service d'Oncologie Médicale, Sorbonne Université et Hôpital Saint-Antoine, Paris, France, [3]Department of Gastroenterology and Digestive Oncology, Hopital European George Pompidou, Paris, France, [4]Oncology, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy, [5]Oncology, Erasme University Hospital-(Universite Libre de Bruxelles), Brussels, Belgium, [6]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [7]Oncology, Royal Bournemouth Hospital and University, Bournemouth, UK, [8]Medical Oncology, Institut Hospitalier Franco-Britannique, Levallois Perret, France, [9]Statistics, CHU Besançon, Hôpital Jean Minjoz, Besançon, France

463P Real-world dosing of regorafenib (REG) in metastatic colorectal cancer (mCRC): Final results from the prospective, observational CORRELATE study

J.M. O'Connor[1], M. Ducreux[2], L.N. Petersen[3], L. Öhler[4], F. Bergamo[5], J-P. Metges[6], J.W. de Groot[7], J-Y. Wang[8], B. García Paredes[9], E. Dochy[10], S. Fiala-Buskies[11], A. Cervantes[12], A. Falcone[13]on behalf of the CORRELATE investigators

[1]Department of Clinical Oncology, Institute Alexander Fleming, Buenos Aires, Argentina, [2]Gastrointestinal Oncology Unit, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France, [3]Department of Oncology, Rigshospitalet, Copenhagen, Denmark, [4]Internal Medicine I, Department of Oncology, St. Josef Krankenhaus, Vienna, Austria, [5]Medical Oncology Unit 1, Department of Clinical and Experimental Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy, [6]Service d'Oncologie et de Radiothérapie, CHU de Brest – Hôpital Morvan, Brest, France, [7]Department of Medical Oncology, Isala, Zwolle, Netherlands, [8]Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung City, Taiwan, [9]Medical Oncology, Hospital Clínico San Carlos, Madrid, Spain, [10]Global Medical Affairs Oncology, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, [11]Development, Integrated Analysis, Bayer AG, Wuppertal, Germany, [12]Department of Medical Oncology, University Hospital of Valencia, Valencia, Spain, [13]Department of Medical Oncology, University of Pisa, Pisa, Italy

Background: REG 160 mg/day 3 weeks on/1 week off is approved for the treatment of patients with treatment-refractory mCRC. This final analysis of the prospective, observational CORRELATE study describes REG real-world dosing in mCRC.

Methods: CORRELATE (NCT02042144) was conducted in 13 countries across Europe, Latin American, and Asia and enrolled patients with mCRC for whom the decision to treat with REG was made by the treating physician. The primary aim was to assess safety.

Results: Of 1037 patients, 57% started treatment at 160 mg, 30% at 120 mg, and 13% at $\leq$ 80 mg. The mean and median percent of the approved dose was 75%. At baseline, median age was 65 years, most patients were ECOG performance status (PS) 0–1 (87%), and 56% had KRAS mutations; age and ECOG PS was similar between dose groups (160 vs 120 mg; Table). Dose reductions were more frequent in the 160 versus 120 mg group, while the proportion of patients having an interruption/delay or treatment modification was similar. Treatment modifications were most commonly due to treatment-emergent adverse events (TEAEs) (66%). Overall, most discontinuations (49%) were due to radiologic disease progression, whereas 19% were due to REG-related TEAEs. Overall, TEAEs of any grade occurred in 95% of patients, and were deemed REG related in 80%. Grade $\geq$3 TEAEs occurred in 62% of patients, and were attributed to REG in 36%. The most common REG-related grade $\geq$3 TEAEs were fatigue (9%), hand–foot skin reaction (7%), and hypertension (6%). Grade 5 TEAEs occurred in 17% of patients and were considered REG related in 1%. Median overall survival (OS) was 7.6 months (95% CI 7.1–8.2) and the estimated 1-year OS was 34%.

Table: 463P

%	Starting dose 160 mg (N = 591)	Starting dose 120 mg (N = 315)	Total (N = 1037)
Median age*	64 (24–85)	65 (33–89)	65 (24–93)
Sex, male/female	58/42	66/34	61/39
ECOG PS 0–1/2–4	89/4	85/9	87/6
Metastatic site at study entry, liver/lung	73/57	69/57	72/57
Median treatment duration†	2.6 (0.03–29.5)	2.4 (0.03–20.6)	2.5 (0.03–29.5)
Treatment modification	65	63	65
Dose reduction	47	34	40
Treatment interruption/delay	50	47	48
Treatment modification due to AEs	76	58	66

*years (range);
†months (range)

Conclusions: In this real-world, observational study, the starting dose of REG for nearly half of patients was less than 160 mg/day. Common TEAEs were generally consistent with the known safety profile of REG in mCRC.

Clinical trial identification: NCT02042144.

Editorial acknowledgement: Editorial assistance in the preparation of this abstract was provided by Katrin Gudmundsdottir of SuccinctChoice Medical Communications (London, UK), with financial support from Bayer.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: J.M. O'Connor: Advisory board attendance: Merck Serono, Bayer, Servier; Speaker's bureau: Merck Serono, Bayer, Servier. M. Ducreux: Grants/research support:

Roche, Merck Serono; Advisory board attendance: Roche, Merck Serono, Celgene, Bayer, Servier, Amgen, Ipsen; Honoraria: Bayer, Roche, Merck Serono, Servier, Amgen, Novartis, Ipsen and Lilly; Travel, accommodations, expenses: Roche, Ipsen, Merck Serono, Merck Sharp & Dohme, Lilly, Amgen. J-P. Metges: Honoraria from Lilly, Sanofi, Novartis, Merck Serono. J.W. de Groot: Advisory board attendance, Bayer, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Servier, Roche. J-Y. Wang: Grants/research support: Roche; Advisory board attendance: Bayer; Speaker's bureau: Bayer, Merck Serono, Pfizer, Roche. B. García Paredes: Advisory board: Sanofi. E. Dochy: Full-time employment: Bayer. S. Fiala-Buskies: Full-time employee, Stock ownership: Bayer. A. Cervantes: Grants, Research support: Roche, Merck Serono, Servier; Advisory board: Bayer, Roche and Merck Serono; Honoraria: Bayer, Amgen, Roche, Lilly, Merck Serono, Servier, Novartis, Takeda, BeiGene, Astellas Pharma. A. Falcone: Grants, Research support: Amgen, Roche, Merck Serono, Servier, Bayer Merck Sharp & Dohme; Advisory board: Amgen, Roche, Merck Serono, Servier, Bayer Bristol-Myers Squibb; Honoraria: Amgen, Roche, Merck Serono, Servier, Bayer. All other authors have declared no conflicts of interest.

464P Safety and efficacy of trifluridine/tipiracil (FTD/TPI) in metastatic colorectal cancer (mCRC) patients according to previous treatment with regorafenib in the international phase IIIb PRECONNECT study

J. Taieb[1], A. Falcone[2], S. Lonardi[3], T.J. Price[4], J-B. Bachet[5], L. Wyrwicz[6], F. Ciardiello[7], M. Becquart[8], N. Mounedji[8], E. Van Cutsem[9]

[1]Department of Gastroenterology and Digestive Oncology, Hopital European George Pompidou, Paris, France, [2]Department of Medical Oncology, University of Pisa, Pisa, Italy, [3]Dip. Oncologia Clinica e Sperimentale, Istituto Oncologico Veneto IRCCS, Padua, Italy, [4]Haematology and Oncology Clinical Cancer Research, Queen Elizabeth Hospital, Woodville, Australia, [5]Service d'Hepato-Gastro-Entérologie, Groupe Hospitalier Pitié Salpetriere, Paris, France, [6]Department Of Digestive System Oncology, Centrum Onkologii-Instytut im. M. Sklodowskiej Curie, Warszawa, Poland, [7]Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [8]Global Medical Affairs Oncology, Servier, Suresnes, France, [9]Digestive Oncology, University Hospitals Gasthuisberg/Leuven and KULeuven, Leuven, Belgium

Background: The oral chemotherapy trifluridine/tipiracil (FTD/TPI or TAS-102) is approved for treatment of previously treated mCRC patients (pts) beyond the second line, in the same setting as regorafenib. Optimal treatment sequencing between the two at this stage is not established. Here, a descriptive post hoc sub-group analysis assessed safety and efficacy of FTD/TPI in mCRC pts according to previous treatment with regorafenib in a preliminary analysis of the phase 3b PRECONNECT study (NCT03306394).

Methods: PRECONNECT is enrolling pts with histologically confirmed mCRC previously treated with available therapies, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0/1. Pts receive oral FTD/TPI (35 mg/m^2 bid) on days 1–5 and 8–12 of each 28-day cycle. Of the 462 patients who received at least one dose at cutoff (1 Nov 2017), 166 (36%) were pretreated with regorafenib.

Results: Patient subgroups pretreated (n = 166) and non-pretreated (n = 296) with regorafenib were broadly similar, with a slight imbalance for RAS mutant status (61% vs 47%), left-sided tumour (58% vs 65%) and treatment line (12% vs 36% receiving FTD/TPI third line), respectively. There was no difference in rate of emergent or drug-related any grade adverse events (AEs), or drug-related grade ≥3 AEs in pts treated with FTD/TPI between the regorafenib pretreated and regorafenib non-pretreated subgroups (98% vs 96%; 77% vs 79%; and 54% vs 51%, respectively). The most common drug-related grade ≥3 AEs were neutropenia (43% vs 40%) and anemia (8% vs 7%). Median FTD/TPI treatment duration were 2.7 and 3.1 months, with a median PFS of 2.7 (95% CI 2.2-3.3) and 3.3 months (95% CI 2.8-3.7), disease control rate was 38% (95% CI 30–46) and 43% (95% CI 37-49) and median time to ECOG-PS ≥2 was 8.5 and 8.7 months in the regorafenib pretreated and regorafenib non-pretreated, respectively.

Conclusions: FTD/TPI may be used either before or after regorafenib with similar efficacy results making treatment safety profile and patient quality of life major points to determine treatment option in third-line for mCRC patients.

Clinical trial identification: EudraCT: 2016-002311-18.

Legal entity responsible for the study: Laboratoires Servier.

Funding: Laboratoires Servier.

Disclosure: J. Taieb: Honoraria speaker or advisory role: Servier, Roche, Lilly, Celgene, Shire, Amgen, Sanofi, Merck, Lilly, Sirtex. A. Falcone: Compensation for participation Advisory Boards, Research Grants to institution: Amgen, Bayer, Merck, MSD, Roche, Lilly, Servier, Bristol. S. Lonardi: Consulting or advisory role: Amgen, Bayer, Merck, Lilly; Speakers' bureau: Lilly; Roche, BMS; Research funding: Amgen. T.J. Price: Advisory board: Amgen (paid self), Merck, Roche, Takeda (paid self). J-B. Bachet: Honoraria: Amgen, Bayer, Celgene, Merck Serono, Roche, Shire, Servier. L. Wyrwicz: Funding or fees: Halozyme, Eisai, Merck. F. Ciardiello: Advisory board role: Servier, Merck, Roche, Amgen, Bayer, Symphogen. M. Becquart, N. Mounedji: Employee: Servier. E. Van Cutsem: Grants: Amgen, Bayer, BMS, Boehringer, Celgene, Ipsen, Lilly, Merck, MSD, Novartis, Roche, Servier; Honoraria: Bayer, BMS, Celgene, Lilly, Novartis, Servier.

465P Treatment pattern and outcomes of trifluridine/tipiracil therapy for metastatic colorectal cancer in the real-world data from the JFMC50 study

T. Kawakami[1], K. Yamazaki[2], E. Oki[3], M. Shimokawa[4], N. Takahashi[5], M. Yokota[6], S. Tokunaga[7], T. Esaki[8], M. Gamoh[9], A. Maeda[10], Y. Tsuji[11], A. Sakai[12], K. Hatanaka[13], Y. Shimada[14], M. Shiozawa[15], Y. Komatsu[16], H. Okuda[17], M. Ohue[18], Y. Maehara[19]

[1]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [2]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Shizuoka, Japan, [3]Department of Surgery and Science, Graduate School of Medical Sciences Kyushu University, Fukuoka, Fukuoka, Japan, [4]Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Japan, [5]Department of Gastroenterology, Saitama Cancer Centre, Saitama, Japan, [6]General Surgery, Kurashiki Central Hospital, Kurashiki, Japan, [7]Medical Oncology, Osaka City General Hospital, Osaka, Japan, [8]Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan, [9]Department of Medical Oncology, Osaki Citizen Hospital, Osaki, Miyagi, Japan, [10]Surgery, Ogaki Municipal Hospital, Ogaki, Japan, [11]Medical Oncology, Tonan Hospital, Sapporo, Japan, [12]Gastroenterology, Hyogo Cancer Center, Akashi, Japan, [13]Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan, [14]Clinical Oncology, Kochi Health Sciences Center, Kochi, Japan, [15]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, [16]Cancer Chemotherapy, Hokakido University Cancer Center, Sapporo, Japan, [17]Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan, [18]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan, [19]Kyushu Central Hospital of the Mutural Aid Association of Public School Teachers, Fukuoka, Japan

Background: Randomized phase 3 trials, RECOURSE and TERRA, established trifluridine/tipiracil (FTD/TPI) as a salvage-line therapy for patients with metastatic colorectal cancer (mCRC). This retrospective, large cohort study, JFMC50, aims to assess the treatment pattern and outcomes of FTD/TPI for mCRC in routine clinical practice.

Methods: We collected data of patients with mCRC who received FTD/TPI during July 2014-September 2016 in Japanese institutions. However, we examined patients who fulfilled the eligibility criteria, through their backgrounds, treatment course, clinical outcomes, including the OS, time to treatment failure (TTF), disease control rate (DCR), and safety. The main eligibility criteria were the ECOG performance status (PS) 0-2 and the starting dose of FTD/TPI close to the standard dose.

Results: From 127 Japanese institutions, we collected data of 2030 patients and assessed 1770 patients. Patients' backgrounds were the median age [67 (23-92) years], males (60.1%), ECOG PS 0/1/2 (33.7%/56.7%/9.5%), right-sided tumor (25.4%), and prior regorafenib treatment (23.3%). The median OS and TTF were 8.1 and 2.7 months, respectively; the DCR was 21.0%. Major grade 3 or 4 adverse events were leukopenia, neutropenia, and anemia (25.9%, 39.3%, and 17.7%, respectively). At the data cutoff date, 1756 patients discontinued FTD/TPI therapy. The median OS because of treatment termination due to disease progression was 11.6 months in the progression after progressive disease (PD) by RECIST (n = 122), 9.2 months in PD by RECIST (n = 930), 7.8 months in the elevation of tumor marker (n = 109), and 4.9 months in clinical PD (n = 206).

Conclusions: Both efficacy and safety of FTD/TPI in the clinical practice were compatible with clinical trials. The continuous use of FTD/TPI after PD by RECIST could contribute to longer survival; however, further investigation is warranted.

Clinical trial identification: UMIN000027585.

Editorial acknowledgement: The authors would like to thank Enago for the English language review.

Legal entity responsible for the study: Japanese Foundation for Multidisciplinary Treatment of Cancer.

Funding: Taiho Pharmaceutical Co., Ltd.

Disclosure: T. Kawakami: Honoraria: Takeda, Chugai Pharma, Merck Serono, Lilly Japan, Taiho Pharmaceutical. K. Yamazaki: Speaker's bureau: Chugai, Takeda, Taiho, Yakult, Merck Serono, Lili, Sanofi, Bayer. E. Oki: Speakers' bureau: Taiho Pharmaceutical, Chugai. M. Shimokawa: Statistical consulting fee: Sysmex. T. Esaki: Speakers' bureau from Taiho, Bristol, Eli Lilly, Eisai, Daiichi-Sankyo, Merck Serono, Chugai, Ono, Takeda; Research funding: Daiichi-Sankyo, Merck Serono, Taiho, MSD, Novartis, Dainippon Sumitomo, Ono; Honoraria: Eli Lilly, Kyowa Kirin. Y. Tsuji: Honoraria: Merck Serono, Eli Lilly Japan, Chugai, Taiho, Ono, Daiichi Sankyo, Yakult Honsha, Eisai and Medicon outside the submitted work. Y. Shimada, Y. Komatsu: Research funding, Honoraria: Taiho Pharmaceutical. M. Ohue: Speakers' bureau: Taiho Pharmaceutical; Research funding: Taiho Pharmaceutical, Chugai. Y. Maehara: Speakers' bureau, Research funding: Taiho Pharmaceutical. All other authors have declared no conflicts of interest.

466P Phase II trial to evaluate efficacy and tolerance of regorafenib monotherapy in patients (pts) over 70 with previously treated metastatic colorectal adenocarcinoma (mCRC) FFCD 1404 - REGOLD

T. Aparicio[1], A. Darut Jouve[2], F. Khemissa[3], C. Montérymard[4], P. Artru[5], L. Cany[6], O. Romano[7], B. Valenza[8], C. Le Foll[9], C. Delbaldo[10], C. Falandry[11], M. Duluc[12], Y. Rinaldi[13], J.L. Legoux[14], M. Ben Abdelghani[15], E. Assenat[16], M. Dhooge[17], D. Smith[18], G. Des Guetz[19], C. Lepage[20]

[1]Gastroenterology, CHU Saint Louis, Paris, France, [2]Oncology, Institut of Cancerology of Burgundy, Dijon, France, [3]Department of Hepatology Gastro Enterology, CH Perpignan, Hospital Saint Jean, Perpignan, France, [4]Biostatistic, FFCD-, Dijon, France, [5]Oncology, Hospital Jean Mermoz, Lyon, France, [6]Department of Radiotherapy and Oncology, Polyclinique Francheville, Perigueux, France, [7]Oncology, Centre Galilee, Lille, France, [8]Oncology, CHI of Fréjus – Saint-Raphaël, Fréjus, France, [9]Centre de Traitement du Cancer - Site de Marne la Vallée, Grand Hôpital de l'Est Francilien, Jossigny, France, [10]Oncology, Hôpital des Diaconesses - Croix Saint Simon, Paris, France, [11]Oncology, CH Lyon Sud, Pierre Bénite, France, [12]Department of Hepato Gastroenterology and Medical Oncology, CHU La Timone Adults, Marseille, France, [13]Department of Hepato Gastroenterology, Hospital European Marseille, Marseille, France, [14]Hepato-Gastroenterolgy and Digestive Oncology, C.H.R. Orleans - La Source, Orleans, France, [15]Department of Oncology, Centre Paul Strauss Centre de Lutte contre le Cancer, Strasbourg, France, [16]Digestive Oncology, CHU Saint Eloi, Montpellier, France, [17]Department of Hepato Gastroenterology, Hospital Cochin, Paris, France, [18]Digestive Oncology, CHU of Bordeaux, Bordeaux, France, [19]Department of Oncology, CHU Dupuytren, Limoges, France, [20]Department of Hepato Gastroenterology and Digestive Oncology, University hospital Dijon ; EPICAD INSERM LNC-UMR 1231, University of Burgundy and Franche Comté, Dijon, France

Background: Regorafenib (REG) significantly increases overall survival (OS) in previously treated mCRC pts. However, no prospective trial specific to elderly population including geriatric parameter evaluation has evaluated the safety and efficacy of REG in its registered indication.

Methods: Multicenter one-arm phase II that enrolled pts $\geq$70 years, ECOG performance status $\leq$1, with mCRC after failure of fluoropyrimidine-based chemotherapy, anti-VEGF and anti-EGFR treatment. Primary endpoint was tumor control rate 2 months after initiation of REG administered at 160mg/day (3weeks on/1 week off).

Results: 43 pts were enrolled from January 2016 to April 2017, median age 77 (range 70 – 91), ECOG 0: 37.2%, ECOG 1: 60.5%, altered activities of daily living (ADL) in 37.5%. Median time from diagnosis of metastases to enrolment: 27.7 months, median number of previous lines: 3. At the time of analysis, the median follow-up was 13.3 months and 62.8% pts had died. One patient never started treatment. The median duration of REG treatment was 45.0 days [5 to 440]. 8 patients were not evaluable for the primary endpoint. Tumor control rate at 2 months in the 35 evaluable pts was 31.4% [18.7% – 46.6%]. Among the 11 pts with tumor control, 9 (81.8%) were $<$ 80 yrs. In the 42 treated pts, median progression free survival (PFS) and OS were 2.2 [1.9-3.3] and 7.5 [5.5-14.6] months, respectively. Modification of the initial dose was performed in 54.3% of the 116 cycles delivered. A grade 3-4 adverse event was observed in 37 (88.1%) pts notably: asthenia (45.2%), hand foot syndrome (21.4%), arterial hypertension (21.4%), and diarrhea (7.1%). Treatment was stopped for toxicity without progression in 12 (28.6%) pts. Among them, 10 (83.3%) pts were ECOG 1, 6 (50%) were over 80 years and 6 (50%) had abnormal baseline ADL. No toxic death was observed.

Conclusions: Treatment with REG in heavily pretreated elderly pts gives a tumor control at 2 months in around 30% of pts. The median PFS and OS are comparable to those observed in the pivotal study. With caution due to small number, drop-out rate for treatment toxicity seems higher in pts with ECOG 1, age over 80 yrs and abnormal ADL.

Clinical trial identification: EudraCT: 2015-002086-29.

Legal entity responsible for the study: Fédération Francophone de Cancérologie Digestive.

Funding: Bayer.

Disclosure: T. Aparicio: Consulting or advisory role: Pierre Fabre, Ipsen, Halio DX, Bristol-Myers Squibb; Travel, accommodations, expenses: Ipsen, Novartis, Ipsen, Roche, Hospira; Honoraria: Pfizer, Roche, Sanofi, Léo Pharma, Amgen, Bristol-Myers Squibb, Servier; Research funding: Bayer. A. Darut Jouve: Travel, accommodations, expenses: Novartis, Bayer. F. Khemissa: Travel, accommodations, expenses: Ipsen, Roche, Sanofi, Bayer; Honoraria: Sanofi, Roche, Bayer; Speakers' bureau: Sanofi, Roche. P. Artru: Consulting or advisory role: Roche, Merck; Travel, accommodations, expenses: Roche, Merck, Bayer; Honoraria: Roche, Amgen, Bayer, Servier, Lilly, Merck; Speakers' bureau: Roche, Merck, Servier. L. Cany: Travel, accommodations, expenses: Novartis. O. Romano: Consulting or advisory role: Roche, Sanofi, Pierre Fabre; Travel, accommodations, expenses: Novartis; Honoraria: Roche, Sanofi, Pierre Fabre; Research funding: Sanofi. C. Falandry: Consulting or advisory role: Pfizer, AstraZeneca, Novartis, Teva, Pierre Fabre, Roche; travel, accommodations, expenses: AstraZeneca, Roche, Pfizer; Honoraria: Pfizer, AstraZeneca, Novartis. M. Duluc: ravel, accommodations, expenses: Ipsen. J.L. Legoux: Consulting or advisory role: Lilly, Novartis; Travel, accommodations, expenses: Merck Serono, Lilly, Ipsen, Novartis; Honoraria: Novartis Research funding: Sanofi/Regeneron. M. Ben Abdelghani: Consulting or advisory role: Amgen, Sanofi, Merck Serono, Bayer, Ipsen, Novartis/Pfizer Travel, accommodations, expenses: Roche, Amgen, Novartis/Pfizer, Ipsen, Bayer, Sandoz, Sanofi. E. Assenat: Consulting or advisory role: Ipsen, Sanofi; Travel, accommodations, expenses: Bayer, Ipsen; Honoraria: Bayer, Sirtex Medical. M. Dhooge: Travel, accommodations, expenses: Norgine SAS. C. Lepage: Consulting or advisory role: Advanced Accelerator Applications; Travel, accommodations, expenses: Amgen, Novartis, Ipsen, Bayer; Honoraria: Novartis. All other authors have declared no conflicts of interest.

467P Prospective evaluation of regorafenib dose escalation strategy with low starting dose in patients with colorectal cancer

T. Masuishi[1], T. Suzuki[2], Y. Sukawa[2], C.K. Imamura[3], H. Satake[4], Y. Kumekawa[5], S. Funakoshi[6], M. Kotaka[7], Y. Horie[8], S. Kawai[9], H. Okuda[10], T. Terazawa[11], C. Kondoh[12], K. Kato[13], K. Yoshimura[14], H. Ishikawa[15], Y. Hamamoto[16], N. Boku[17], T. Kanai[2], H. Takaishi[16]

[1]Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [3]Department of Clinical Pharmacokinetics and Pharmacodynamics, Keio University School of Medicine, Tokyo, Japan, [4]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan, [5]Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan, [6]Department of Internal Medicine, Division of Medical Oncology, Tokyo Saiseikai Central Hospital, Tokyo, Japan, [7]Surgery, Sano Hospital-Gastrointestinal Cancer Centre, Kobe, Hyogo, Japan, [8]Department of Clinical Oncology, St Marianna University School of Medicine, Kawasaki City, Japan, [9]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [10]Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan, [11]Cancer Chemotherapy Center, Osaka Medical College, Takatsuki, Osaka, Japan, [12]Department of Medical Oncology, Toranomon Hospital, Tokyo, Japan, [13]Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [14]Innovative Clinical Research Center, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan, [15]Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Kyoto, Japan, [16]Cancer Center, Keio University School of Medicine, Tokyo, Japan, [17]Gastrointesitnal Medical Onclogy, National Cancer Center Hospital, Tokyo, Japan

Background: Regorafenib is the first small-molecule multikinase inhibitor with survival benefit as a salvage line therapy for metastatic colorectal cancer (mCRC). However, severe toxicities often occur early and require dose reduction and/or interruption. To improve dose intensity and treatment outcome, we investigated regorafenib dose escalation strategy with low starting dose. The association between systemic exposure and tolerability was also analyzed.

Methods: In this phase II, single arm, multicenter study, we enrolled patients with refractory mCRC. Regorafenib was initiated at 120 mg/day. In patients who experienced neither hand-foot skin reaction nor grade $\geq$2 adverse reactions without dose reduction or interruption until day 15 in the first cycle, the dose of regorafenib was escalated to standard dose of 160 mg/day at day 15. The primary endpoint was disease control rate (DCR). With power of 80% and two-sided alpha of 5%, 67 patients were required to reject 30% of DCR expecting 45% of DCR. Serum concentrations of regorafenib and its active metabolites (M-2, N-oxide metabolite; M-5, N-oxide/N-desmethyl metabolite) at days 8, 15 and 22 in the first cycle were assessed.

Results: From September 2016 to December 2017, 68 patients were enrolled. The DCR was 32.4% (95% CI, 21.5-44.8) with no patients achieving complete or partial response. The dose of regorafenib was escalated to 160 mg at day 15 in only six patients of 39 patients without dose reduction or interruption until day 15. In 55 patients without dose reduction or interruption due to adverse reactions until day8, the serum concentrations of regorafenib at day 8 in the six patients whose dose was escalated to 160 mg were significantly lower than those in the other 49 patients (median, 3978 nM; range, 2487-13614 nM vs. 6951 nM; 2822-17621 nM; $P = 0.028$). The serum concentrations of sum of regorafenib and active metabolites (M-2 and M-5) at day 8 showed similar tendency (6582 nM; 2913-21388 nM vs. 11730 nM; 4596-33211 nM; $P = 0.064$).

Conclusions: This dose escalation strategy with low starting dose for regorafenib did not improve DCR. Lower systemic exposure was associated with better tolerability.

Legal entity responsible for the study: Hiromasa Takaishi.

Funding: Keio University.

Disclosure: T. Masuishi: Honoraria: Bayer. H. Satake: Honoraria: Bayer, Chugai Pharma, Eli Lilly Japan, Merck Serono, Takeda, Taiho Pharmaceutical, Yakult Honsha. N. Boku: Investigator initiated trial funded by Bayer. All other authors have declared no conflicts of interest.

468P Regorafenib for metastatic colorectal carcinoma: A registry-based analysis

K. Kopeckova[1], R. Chloupkova[2], B. Melichar[3], Z. Linke[1], L.B. Petruzelka[4], J. Finek[5], O. Fiala[5], J. Tomasek[6], I. Kiss[7], J. Prausova[1], T. Buchler[8]

[1]Oncology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic, [2]Institute of Biostatistics and Analyses, Masaryk University Brno, Brno, Czech Republic, [3]Oncology, Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic, [4]Oncology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic, [5]Oncology, University Hospital Plzen, Plzen, Czech Republic, [6]Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic, [7]Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, South Moravian, Czech Republic, [8]Oncology, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic

Background: Regorafenib is a multikinase inhibitor approved for the therapy of patients with metastatic colorectal carcinoma (mCRC) previously treated with a fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy, and (in wild-type RAS

tumours) anti-EGFR therapy. The aim of the present study was to analyse the outcomes of treatment with regorafenib in real-world clinical practice based on data from a national registry.

Methods: The CORECT registry (http://corect.registry.cz) is a non-interventional database of patients with colorectal cancer treated with targeted agents. The analysis included 451 evaluable patients treated with regorafenib for mCRC.

Results: The median age at diagnosis was 61.1 years. The primary tumor was in the left colon or rectum in 343 patients (76.1%), right colon in 81 patients (18.0%), data on location were not available for 27 patients (6.0%). KRAS mutation was detected in 202 patients (44.8%) and NRAS mutation in 40 patients (8.9%). The median duration of treatment was 2.7 months (range 0.0-23.4 months). Partial response was seen in 12 patients (3.2%). Progression of the disease was reported in 170 patients (44.7%) and disease stabilisation for at least 6 weeks in 110 patients (28.9%). Progression-free and overall survival data are shown in the table. Improved outcomes were observed in patients with longer interval from diagnosis of mCRC and in those without liver metastases. Age, tumor sidedness, and RAS status were not associated with outcome of regorafenib therapy. The main cause of treatment discontinuation was disease progression (71.3%) followed by general deterioration in the absence of radiological progression in 93 patients (24.5%), and adverse events related to regorafenib in (4.2%).

Table: 468P Progression-free survival and overall survival of patients treated with regorafenib

	Median (95% CI)	3-month survival (95% CI)	6-month survival (95% CI)
Progression-free survival	3.5 months (3.2–3.7)	57.6% (52.5–62.4)	25.2% (20.9–29.9)
Overall survival	9.3 months (7.9–10.7)	88.8% (85.2–91.5)	68.7% (63.6–73.3)

Conclusions: Overall survival of patients treated with regorafenib in real-world clinical practice exceeded that achieved in randomised trials.

Legal entity responsible for the study: Katerina Kopeckova and Tomas Buchler.

Funding: The Institute of Biostatistics and Analysis, Faculty of Medicine, Masaryk University, Brno received financial support for the CORECT registry from Bayer, Amgen, Merck and Roche. Supported by Grant AZV 15-26535A from the Czech Health Research Council.

Disclosure: K. Kopeckova: Research support: Bayer. B. Melichar: Consulting fees: Roche, Novartis, Astellas, Bristol-Myers Squibb, MSD, Merck, Pfizer, Janssen; Travel: Roche, Novartis, Astellas, Bristol-Myers Squibb; Provision of writing assistance: Roche, Bristol-Myers Squibb Payment for lectures: Roche, Novartis, Astellas, Bristol-Myers Squibb, MSD, Merck, Pfizer, Janssen. J. Finek: Lecture honoraria, travel grants: Roche, Merck, Pfizer, Novartis, Amgen. O. Fiala, T. Buchler: Research funding, travel grants, honoraria: Roche, Merck, Bayer, Servier, BMS, MSD, Sanofi, Amgen. J. Tomasek: Grants, consulting fees, travel: Bayer. I. Kiss: Speakers' honoraria: Roche, Merck, Amgen. All other authors have declared no conflicts of interest.

469P The combination of TAS-102 and bevacizumab as the third line chemotherapy for metastatic colorectal cancer (TAS-CC3 Study)

H. Kamiyama[1], Y. Yoshida[2], H. Yoshida[3], C. Kosugi[4], K. Ishibashi[5], K. Ihara[6], M. Takahashi[1], H. Kuramochi[7], A. Fukazawa[8], H. Sonoda[9], K. Yoshimatsu[10], A. Matsuda[11], S. Yamaguchi[6], H. Ishida[5], S. Hasegawa[2], T. Yamada[3], K. Sakamoto[1], K. Koda[4]

[1]Coloproctological Surgery, Juntendo University School of Medicine, Tokyo, Japan, [2]Gastroenterological Surgery, Fukuoka University School of Medicine, Fukuoka, Japan, [3]Gastroenterological Surgery, Nippon Medical School, Tokyo, Japan, [4]Surgery, Teikyo University Chiba Medical Center, Ichihara, Chiba, Japan, [5]Digestive Tract and General Surgery, Saitama Medical University, Saitama, Japan, [6]Surgical Oncology, Dokkyo Medical University, Tochigi, Japan, [7]Department of Chemotherapy, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Japan, [8]Surgery, Iwata City Hospital, Shizuoka, Japan, [9]Gastroenterological Surgery, Shiga Medical University, Shiga, Japan, [10]Surgery, Tokyo Women's Medical University, Tokyo, Japan, [11]Surgery, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Chiba, Japan

Background: TAS-102 improved overall survival of refractory colorectal cancer patients with median progression free survival (PFS) of 2.0 months (RECOURSE trial). Subsequently, the combination of TAS-102 and Bevacizumab has been shown to extend median PFS with 3.7 months (C-TASK FORCE). However, this study included patients with 2nd line and 3rd line chemotherapy. Our study was planned exclusively for patients receiving this combination as the 3rd line chemotherapy to investigate clinical impact of this combination beyond cytotoxic doublet.

Methods: This phase II study was conducted in investigator-initiated, open-label, single-arm, multicentered manner in Japan. Eligible patients were 20-80 years old, and had to have an Eastern Cooperative Oncology Group performance status of 0 or 1; had confirmed unresectable metastatic colorectal cancer (mCRC) with histologically diagnosed adenocarcinoma; were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin in the 1st and the 2nd line chemotherapy; and had no previous treatment with regorafenib. TAS-102 (35 mg/ m^2) was given orally twice daily on days 1–5 and 8–12 in a 4-weeks cycle, and bevacizumab (5 mg/ kg) was administered by intravenous infusion for 30 minutes in every 2 weeks. The primary endpoint was progression free survival (PFS), and the secondary endpoints were time to treatment failure (TTF), response rate (RR), overall survival (OS), and safety.

Results: Between June 1, 2016, and August 31, 2017, 32 patients with mCRC were enrolled in this study. The median PFS was 4.5 months. Partial response was observed in 2 patients. The most common adverse events above grade 3 were neutropenia (15 patients) followed by thrombocytopenia (4 patients). Treatment-related serious adverse events were reported in one patient. There were no non-hematologic adverse events above grade 3. No treatment-related deaths occurred.

Conclusions: This is the first study which involves the combination of TAS-102 and Bevacizumab as the 3rd line chemotherapy in the setting beyond cytotoxic doublet, and showed to improve PFS for the patients with mCRC. This combination has a potential to be one of therapeutic options of the 3rd line chemotherapy for mCRC.

Clinical trial identification: University Hospital Medical Information Network UMIN#000022438.

Legal entity responsible for the study: TAS-CC3 Study Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

470P Safety run-in evaluation of the phase I trial of trifluridine/tipiracil (FTD/TPI) in combination with oxaliplatin and a monoclonal antibody (bevacizumab or nivolumab) in patients (pts) with metastatic colorectal cancer (mCRC)

A. Calvo Ferrandiz[1], L. Dahan[2], A. Hollebecque[3], G. Prager[4], T. Andre[5], G. Argiles Martinez[6], R. Bordonaro[7], A. Stein[8], G. Tortora[9], C. Leger[10], N. Amellal[11], J. Tabernero[12]

[1]Medical Oncology Dept, Hospital General Universitario Gregorio Marañon, Madrid, Spain, [2]Service d'HGE et d'Oncologie, CHU La Timone Enfants, Marseille, France, [3]Drug Development Department (DITEP: Département d'Innovations Thérapeutiques et Essais Précoces), Institut Gustave Roussy, Villejuif, France, [4]Comprehensive Cancer Center Vienna, Medical University Vienna, Vienna, Austria, [5]Service d'Oncologie Médicale, Sorbonne Université et Hôpital Saint-Antoine, Paris, France, [6]Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [7]S.C. di Oncologia Medica ARNAS, Azienda Ospedaliera Garibaldi, Catania, Italy, [8]Onkologie, Hämatologie, KMT mit Sektion Pneumologie, UKE Universitätsklinikum Hamburg-Eppendorf KMTZ, Hamburg, Germany, [9]U.O.C. di Oncologia/Policlinico G.B. Rossi, AOUI and University of Verona, Verona, Italy, [10]Oncology Medical Division, Servier France, Suresnes, France, [11]Oncology Medical Division, Servier, Suresnes, France, [12]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

Background: The addition of the monoclonal antibody bevacizumab to chemotherapy has shown survival benefits in pts with mCRC. Another potential strategy is to combine chemotherapy with immunotherapies to enhance antitumor effect of the immune system. In vivo studies have shown an increase in anti-tumor activity when combining FTD/TPI with oxaliplatin or bevacizumab; and an increase in tumor immunogenicity after treatment with FTD/TPI and oxaliplatin, leading to a better tumor response to anti-PD-1 exposure.

Methods: Further to the dose-escalation part (24 pts), the recommended dose (RD) was defined as FTD/TPI 35 mg/m^2 bid, days 1–5 q14, together with oxaliplatin 85 mg/m^2 (day 1). Safety data were collected during expansion part from 12 evaluable pts treated with the doublet at the RD with either nivolumab 3 mg/kg (n = 6) or bevacizumab 5 mg/kg (n = 6) administered at day 1. Pts were monitored for safety for the first 2 months of treatment before allowing further enrollment. Eligibility criteria included measurable disease, performance status (PS) 0-1, normal organ function, and progression after >1 prior anti-tumor therapy (excluding oxaliplatin).

Results: Baseline characteristics were median age of 67 years (range 52 to 75 years); PS 0/1 (3/9 pts), male/female (8/4 pts); and colon/rectum (5/7 pts). Drugrelated adverse events (AEs) reported in $\geq$ 2 pts were neutropenia, diarrhoea, asthenia, and nausea; mainly (93%) grade 1-2. The most common grade 3 or 4 drugrelated event was neutropenia. Grade 1 neurotoxicity attributed to oxaliplatin was observed in 2 pts. No immune-related AE due to nivolumab were reported. Best overall response included 2 partial responses after 2 months of treatment (1 pt in bevacizumab cohort, 1 MSI-H pt in nivolumab cohort). Pharmacokinetics parameters for FTD/TPI were aligned with historical data.

Conclusions: The safety data showed that the two triplets were well tolerated. Expansion enrollment is continuing in both cohorts to confirm preliminary evidence of activity in a larger number of patients.

Clinical trial identification: NCT02848443.

Legal entity responsible for the study: Institut de Recherches Internationales Servier (I.R.I.S.).

Funding: Institut de Recherches Internationales Servier (I.R.I.S.).

Disclosure: A. Hollebecque: Lilly, Amgen; Travel expenses: Servier, Amgen. G. Prager: Advisory boards, Speakers fee: Servier, Roche, BMS, Taiho. T. Andre: Consulting, advisory fees, travel expenses: Roche/Genentech, Amgen, Bristol-Myers Squibb, Honoraria: Roche/Genentech, Sanofi, Baxter, Bayer, Bristol-Myers Squibb, Amgen, MSD Oncology, Servier, XBiotech, Novartis. R. Bordonaro: Honoraria, consulting or

advisory role: Proacta, Sanofi; Speakers' bureau: Novartis, Roche, Sanofi; Travel, accommodations, expenses: Novartis, Roche, Bayer, Astellas. A. Stein: Consulting or advisory role: Amgen, Bristol-Myers Squibb, Merck KGaA, Roche; Speakers' bureau: Amgen, Bayer, Celgene, Lilly, Merck KGaA, Roche, Sanofi; Servier research funding: Merck KGaA (Inst), Roche (Inst), Sanofi (Inst); Travel, accommodations, expenses: Roche. G. Tortora: Consulting or advisory role: Celgene; Merck Serono; Travel, accommodations, expenses: Merck Serono; Roche. C. Leger, N. Amellal: Employee: Servier. J. Tabernero: Advisory boards: Bayer, Boehringer Ingelheim, Genentech/Roche, Lilly, MSD, Merck Serono, Merrimack, Novartis, Peptomyc, Roche, Sanofi, Symphogen, Taiho. All other authors have declared no conflicts of interest.

471P A phase I study to determine the maximum tolerated dose of trifluridine/tipiracil and oxaliplatin in patients with refractory metastatic colorectal cancer: LUPIN study

M. Suenaga[1], T. Wakatsuki[1], M. Ogura[1], T. Ichimura[1], E. Shinozaki[1], I. Nakayama[1], H. Osumi[1], Y. Ota[1], K. Chin[1], T. Mashima[2], H. Seimiya[2], D. Takahari[1], K. Yamaguchi[1]

[1]Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan, [2]Molecular Biotherapy, Cancer Chemotherapy Center of JFCR, Tokyo, Japan

Background: The effectiveness of reintroduction of oxaliplatin for metastatic colorectal cancer (mCRC) refractory to both oxaliplatin and irinotecan was previously reported in a single arm, open-label phase II study (RE-OPEN, Suenaga, 2015). We conducted a phase I study to determine the maximum tolerated dose (MTD) and the safety of oxaliplatin plus trifluridine/tipiracil (FTD/TPI, also known as TAS-102) in patients with refractory mCRC (UMIN000015764).

Methods: Three dosages of intravenous oxaliplatin (50, 65 and 85 mg/m^2) on days 1 and 15 and a fixed dose of FTD/TPI 35 mg/m^2 bid on days 1–5, 15–19 every 4 weeks were investigated in patients with refractory mCRC by using a 3 + 3 design. Eligible patients had received prior oxaliplatin-based treatment that achieved a response or stable disease followed by confirmed disease progression at least 6 months before entering the study.

Results: 12 patients were enrolled in the study. Characteristics of patients were as follows: median age, 62 (range, 47–68) years; male/female, 6/6; ECOG PS 0, 75%; number of prior regimens ≥3, 33.3%; and median oxaliplatin-free interval, 24.3 (range, 6.2–71.4) months. 3 of 6 patients of the oxaliplatin 85mg/m^2 cohort had dose-limiting toxicities (DLTs): treatment delay on 2nd cycle ≥8 days due to grade ≥2 neutropenia or grade 2 AST/ALT increased. No DLTs were observed in the other cohorts. The median number of treatment cycles was 3 (range, 1–9): 9 patients continued the treatment until disease progression; and 3 patients discontinued due to toxicity or patient's refusal. In safety, grade ≥3 adverse events were neutropenia (n = 3), thrombocytopenia (n = 1), anorexia (n = 1) and nausea (n = 1). There was no evidence of allergic reaction to oxaliplatin and severe peripheral sensory neuropathy.

Conclusions: According to the results of this phase I study, a combination of trifluridine/tipiracil 35 mg/m^2 bid on days 1–5, 15–19 and oxaliplatin 85 mg/m^2 on days 1 and 15 every 4 weeks could be a candidate for recommended dose of the trifluridine/tipiracil+oxaliplatin regimen in patients with refractory mCRC.

Clinical trial identification: UMIN000015764 (release date, 1/12/2014).

Legal entity responsible for the study: Cancer Institute Hospital of the Japanese Foundation for Cancer Research.

Funding: Japanese Foundation for Cancer Research.

Disclosure: All authors have declared no conflicts of interest.

472P Sidedness of the primary tumor on the effect of TAS-102 for refractory metastatic colorectal cancer

S. Ueda[1], Y. Tsuboguchi[2], Y. Nakatani[2], A. Tsuya[3], S-I. Nishina[4], K. Akiyoshi[2], S. Okazaki[5], S. Tokunaga[2], H. Daga[2]

[1]Medical Oncology, Osaka City General Hospital, Nara, Japan, [2]Medical Oncology, Osaka City General Hospital, Osaka, Japan, [3]Clinical Oncology, Osaka City General Hospital, Osaka, Japan, [4]Medical Oncology, Ako Central Hospital, Ako-city, Japan, [5]Medical Oncology, Kyoto Medical Center, Kyoto, Fushimi-ku, Japan

Background: TAS-102 study was shown to have clinical activity in a large population of Japanese and Western patientswith heavily pretreated metastatic colorectal cancer, including those whose disease was refractory to fluorouracil.But we know few date of TAS-102 in daily medical practice. So we assessed efficacy and safety of TAS-102 for refractory metastatic colorectal cancer.

Methods: We retrospectively reviewed the data of 86 patientswho received TAS-102 treatment in our institution between June2014 and October2017.TAS-102 (with each dose consisting of 35 mg per square meter) was administered twice daily, 5 days on and 2 days off for 2 weeks, followed by 2 weeksrest period. The regimen was repeated every 4 weeks.

Results: The median age was 69 years (range, 27–87). Performance status of 1 and 2 were 39 and 47 patients. RAS wild and mutant were 39 and 47 patients. Primary tumor site of right and left were 25 and 61 patients. All patients had received prior chemotherapy regimens containing a fluoropyrimidine, oxaliplatin, and irinotecan. 41 patients received 4 or more prior chemotherapy. Response rate and disease control rate of all were 1% and 24%. Right and left-sided of response rate were 4% and 0%. Right and left-sided of disease control rate were 32% and 19%. Median PFS was 62 days, right and left-sided were 55 and 64 days. Median OS was 216 days, right and left-sided were 262 and 200 days. OS was longer than previously reported. 40 patientsreceived subsequent chemotherapy. Adverse events were mild with 18% of Grade 4 neutropenia and 4% of Grade 3 febrile neutropenia.

Conclusions: TAS-102 was active and tolerable for heavily treated refractory metastatic colorectal cancer. There were no significant difference of PFS and OS in primary tumor site.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

473P Influence of the proton pump inhibitor esomeprazole on the bioavailability of regorafenib

F.M. de Man[1], K.G.A.M. Hussaarts[1], M. de With[1], E. Oomen-De Hoop[1], H.K. van Halteren[2], N.C.H.P. van der Burg-De Graauw[3], F.A.L.M. Eskens[1], T. van Gelder[4], R.W.F. van Leeuwen[4], R.H.J. Mathijssen[1]

[1]Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [2]Internal Medicine, Admiraal de Ruijter Hospital, Vlissingen, Netherlands, [3]Internal Medicine, Bravis Hospital, Roosendaal, Netherlands, [4]Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands

Background: The multikinase inhibitor regorafenib (REG) is currently registered for the treatment of colorectal cancer (CRC), gastrointestinal stromal tumors (GIST), and hepatocellular carcinoma. REG exhibits a pH-dependent solubility, and therefore acid reducing drugs such as proton pump inhibitors (PPIs, e.g. esomeprazole) might reduce REG absorption by increasing the stomach pH as was shown for many other kinase inhibitors (van Leeuwen, Lancet Oncol, 2014). We performed a randomized, 3-phase, cross-over trial to compare the exposure of REG alone to REG with esomeprazole (concomitantly or 3 hours prior to REG intake) in CRC and GIST patients.

Methods: Patients were randomized into 2 sequence groups consisting of 3 phases: REG intake alone, REG with concomitant esomeprazole (for 5 days), and REG 3 hours preceded by esomeprazole (for 5 days). Pharmacokinetic (PK) blood sampling was performed at the 21th, 49th and 77th day of the trial. All patients were treated with REG 120 mg at steady-state. Primary endpoint was the relative difference (RD) in geometric means for REG $AUC_{0\text{-}24h}$. A linear mixed model was used to analyze log-transformed area under the curve (AUC). For multiple testing a Bonferroni correction was applied.

Results: A total of 14 patients were evaluable for the primary endpoint. Exposure ($AUC_{0\text{-}24h}$) to REG alone was: 55.9 μg*h/mL (CV: 40.3%). For REG with concomitant esomeprazole or with esomeprazole 3 hours prior $AUC_{0\text{-}24h}$ was: 53.7 μg*h/mL (CV: 33.5%) and 53.6 μg*h/mL (CV: 42.6%) respectively. No significant differences were identified when REG alone was compared to REG with concomitant esomeprazole (RD: -3.9%, 95% CI: -20.5-16.1%, p = 1.0) or REG with esomeprazole 3 hours prior (RD: -4.1%, 95% CI: -22.8-19.2%, p = 1.0). Furthermore, no significant differences were observed in other PK parameters of REG and its active metabolites M-2 and M-5 (i.e. C_{max}, T_{max}). Most common adverse events ≥ grade 2 were hypertension (71%), fatigue (43%) and hand foot skin reaction (36%).

Conclusions: The use of esomeprazole concomitantly or 3 hours prior to REG intake did not alter REG pharmacokinetics. Our results indicate that PPIs like esomeprazole can be combined with REG without the appearance of a significant drug interaction.

Clinical trial identification: NCT02800330, 01-05-2016.

Legal entity responsible for the study: Erasmus University Medical Center.

Funding: Bayer.

Disclosure: R.H.J. Mathijssen: Research support: Astellas, Bayer, Boehringer Ingelheim, Cristal Therapeutics, Novartis, Pamgene, Pfizer, Roche Sanofi; Consultation fees: Novartis, Servier, Travel support: Astellas, Pfizer. All other authors have declared no conflicts of interest.

474P A novel biomarker combination and its association with resistance to chemotherapy combinations with bevacizumab: First results of the PERMAD trial

T. Seufferlein[1], L. Lausser[2], A. Stein[3], G. Prager[4], S. Kasper[5], M. Niedermeier[6], L. Müller[7], S. Kubicka[8], A-O. König[9], P. Büchner-Steudel[10], K. Wille[11], L. Perkhofer[12], A. Hann[1], A.W. Berger[1], D. Arnold[13], H. Kestler[14], T.J. Ettrich[1]

[1]Department of Internal Medicine I, Ulm University, Ulm, Germany, [2]Institute of Medical Systems Biology, Ulm University, Ulm, Germany, [3]University Cancer Center Hamburg (UCCH), University Medical Center HH-Eppendorf, Hamburg, Germany, [4]Comprehensive Cancer Center Vienna, Medical University Vienna, Vienna, Austria, [5]Medical Oncology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany, [6]Private Practice, Memmingen, Germany, [7]Onkologie UnterEms, Leer, Germany, [8]Cancer Center Reutlingen, Klinikum am Steinenberg Reutlingen, Reutlingen, Germany, [9]Gastroenterology, GI-Oncology, Universitätsmedizin Göttingen, Göttingen, Germany, [10]Internal Medicine I, Martin-Luther-University Halle-Wittenberg, Halle, Germany, [11]Hämatology, Oncology, University Hospital Ruhr-University-Bochum, Minden, Germany, [12]Internal Medicine I, Ulm Medical University, Ulm, Germany, [13]Med. Abteilung, Asklepios Klinik Altona, Hamburg, Germany, [14]Institute for Medical Systems Biology, Ulm University, Ulm, Germany

Background: Antiangiogenic agents are frequently used in the systemic treatment of metastatic colorectal cancer (mCRC). Since these strategies target not the tumor but the tumor associated endothelium establishing positive or negative predictive biomarkers is challenging. Recent research indicated a potentially predictive value of cytokines and angiogenic factors (CAF) for early detection of progression during treatment with chemotherapy and bevacizumab. The PERMAD trial is a two-phase trial with the primary objective to evaluate of the impact of a personalized, marker-driven treatment approach with early detection of progression and modification of treatment. The aim of the first phase is to establish a combination of CAFs that allows early detection/prediction of disease progression (PD) under a treatment with FOLFOX plus bevacizumab (Bev). The second phase is a randomized part with marker-driven switch of anti-angiogenic agent and maintenance of the chemotherapy backbone until definite radiological PD compared to a conventional treatment approach of changing chemotherapy and antiangiogenic agent at time of radiologic PD. Here we report the results from the first phase examining samples of 50 patients.

Methods: During the run-in phase 102 CAFs were established in blood samples taken prior to treatment and q2w thereafter until PD. Using machine learning we aimed at establishing a combination of 5 out of the 102 CAFs that fulfilled these criteria: cytokines should be affected by PD, but not by treatment itself and should indicate PD at least 2 months prior to the time of PD as determined by MD-CT which was performed every 2 months.

Results: Using our machine learning approach we could establish a combination of markers from 30 patients that is associated with $>$ 80% accuracy with PD 2 months prior to radiological PD under a treatment with FOLFOX plus Bev. This combination will be corroborated in another 20 patients (data presented at the meeting) and used for the second, randomized part of the trial.

Conclusions: Using advanced bioinformatics we have identified a biomarker combination that is associated with subsequent PD with a high accuracy under a treatment with FOLFOX plus Bev.

Clinical trial identification: NCT02331927.

Legal entity responsible for the study: Ulm University Hospital.

Funding: Sanofi-Aventis.

Disclosure: T. Seufferlein: Research funding: Celgene, Sanofi; Consulting or advisory role: Celgene, Lilly Pharma, Boehringer Ingelheim, Merck Serono, Amgen. A. Stein: Consulting or advisory role: Merck KGaA, Bristol-Myers Squibb, Amgen, Roche, MSD; Speakers' bureau: Roche, Sanofi, Bayer, Lilly, Celgene, Amgen, Merck KGaA, Servier, Bristol-Myers Squibb; Travel, accommodations, expenses: Roche, Bristol-Myers Squibb; Research funding: Roche, Sanofi, Merck KGaA, Bristol-Myers Squibb. A.W. Berger: Consulting or advisory role: Sanofi; Travel, accommodations, expenses: Taiho Pharmaceutical. D. Arnold: Consulting or advisory role: Roche, Bayer, Merck Serono, Servier, Biocompatibles, Terumo, Helsinn Therapeutics; Travel, accommodations, expenses: Roche/Genentech, Bayer, Merck Serono; Honoraria: Bayer, Merck Serono, Roche/Genentech, Servier, Terumo; Research funding: Roche/Genentech, Sanofi. T.J. Ettrich: Research grants: Baxalta/Shire; Consulting fees, other remuneration (payment): Merck-Serono, Sanofi, Sirtex, Medical, Novartis, Bayer, Bristol-Myers Squibb, Pfizer. All other authors have declared no conflicts of interest.

475P Updated analysis and exploratory analysis of primary tumor location in the TRICOLORE trial: A randomized phase III trial of S-1 and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment for metastatic colorectal cancer

M. Nakamura[1], A. Takashima[2], T. Denda[3], M. Gamoh[4], I. Iwanaga[5], Y. Komatsu[6], M. Takahashi[7], H. Ohori[8], T. Sekikawa[9], M. Tsuda[10], Y. Kobayashi[11], Y. Miyamoto[12], M. Kotake[13], C. Ishioka[7], K. Shimada[14], A. Sato[15], S. Yuki[16], S. Morita[17], S. Takahashi[7], T. Yamaguchi[18]

[1]Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan, [2]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [3]Division of Gastroenterology, Chiba Cancer Center Hospital, Chiba, Japan, [4]Department of Medical Oncology, Osaki Citizen Hospital, Osaki, Japan, [5]Department of Medical Oncology, Kitami Red Cross Hospital, Kitami, Japan, [6]Cancer Center, Hokkaido University Hospital, Sapporo, Hokkaido, Japan, [7]Department of Medical Oncology, Tohoku University Hospital, Sendai, Japan, [8]Medical Oncology, Ishinomaki Red Cross Hospital, Ishinomaki, Japan, [9]Division of Medical Oncology, Showa University Northern Yokohama Hospital, Kanagawa, Japan, [10]Department of Gastroenterological Oncology, Hyogo Cancer Center, Hyogo, Japan, [11]Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan, [12]Department of Gastroenterlogical Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan, [13]Department of Surgery, Kouseiren Takaoka Hospital, Toyama, Japan, [14]Department of Internal Medicine, Division of medical Oncology, Showa University Kouto-Toyosu Hospital, Tokyo, Japan, [15]Department of Medical Oncology, Hirosaki University Graduate School of Medicine, Aomori, Japan, [16]Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [17]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [18]Department of Surgery/ Hereditary Tumor Research Project, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

Background: The TRICOLORE trial previously demonstrated that S-1 and irinotecan (IRI) plus bevacizumab (Bmab) was non-inferior to mFOLFOX6 or CapeOX plus Bmab in terms of progression-free survival (PFS) as first-line treatment for metastatic colorectal cancer (mCRC), irrespective of RAS status (Komatsu Y, et al. ESMO 2017, and Yamada Y, et al. Ann Oncol. 2018). We now report the final overall survival (OS) after a median follow-up of more than 3 years. The results of this trial were subjected to an exploratory analysis to determine if primary tumor location (TL) influenced the response to S-1 and IRI plus Bmab.

Methods: This trial was a randomized, open-label, phase 3 trial. Chemotherapy-naïve patients with mCRC were randomly assigned to receive either mFOLFOX6 or CapeOX plus Bmab (arm A) or S-1 and IRI plus Bmab (arm B, given as a 3-week regimen [7.5 mg/kg Bmab, 150 mg/m^2 IRI on day 1, and 40 − 60 mg S-1 twice daily for 2 weeks, followed by a 1-week rest] or a 4-week regimen [5 mg/kg Bmab, 100 mg/m^2, IRI on days 1 and 15, and 40 − 60 mg S-1 twice daily for 2 weeks, followed by a 2-week rest). Patients' data were finally updated in September 2017.

Results: At this final analysis, the median overall survival (mOS) was 32.6 months with arm A and 34.3 months with arm B (median follow-up, 48.7 months). The hazard ratio (HR) for OS was 0.89 (95% CI: 0.72 − 1.10). Median progression-free survival (mPFS) in arm A/B were 10.8/14.0 months (HR 0.86, 95% CI: 0.71–1.04, $p < 0.0001$ for non-inferiority). In right-sided TL, mOS and mPFS in arm A/B were 25.6/28.1 months (HR 0.82, 95% CI 0.56-1.21) and 9.6 /11.4 months (HR 0.85, 95% CI 0.60-1.22), respectively. In left-sided TL, mOS and mPFS in arm A/B were 35.5/36.8 months (HR 0.89, 95% CI 0.68-1.15) and 11.3/15.0 months (HR 0.82, 95% CI 0.66-1.03), respectively.

Conclusions: Our updated analysis reconfirmed that S-1 and IRI plus Bmab is non-inferior to mFOLFOX6 or CapeOX plus Bmab in terms of PFS. S-1 and IRI plus Bmab is now recommended as a 1st-line treatment for mCRC irrespective of primary TL and RAS status.

Clinical trial identification: UMIN000007834.

Legal entity responsible for the study: Tokyo Cooperative Oncology Group (TCOG).

Funding: Taiho Pharmaceutical Co. Ltd.

Disclosure: A. Takashima: Corporate-sponsored research: Taiho, Takeda. T. Denda: Corporate-sponsored research: Sanofi, Boehringer Ingelheim, MSD. M. Gamoh: Corporate-sponsored research: Chugai, Taiho, Daiichi Sankyo, Yakult. Y. Komatsu: Other substantive relationships: Taiho Pharmaceutica, Lilly, MSD, Ono Pharmaceutical, Novartis, Chugai Pharma, Yakult, Merck Serono, Pfizer, Bayer. M. Takahashi: Corporate-sponsored research: Ono Yakuhin, MSD; Other substantive relationships: Ono Yakuhin, Chugaim Merck-Serono, Daiichi-Sankyo, Nihon-kayaku, Yakult, Taiho, Eli Lilly, Kyowa-Kirin. C. Ishioka: Corporate-sponsored research: Mochida, Kyowa-Kirin, Eizai, Chugai, Tsumura, Novartis, Merck-Serono, Daiichi-Sankyo, Takeda, Nihon-Kayaku, Yakult, Taiho, Ono, Astellas, Asahikasei-Parma, Kissei, Bristol other substantive relationships: Mochida, Chugai, Novartis, Merck-Serono, Daiichi-Sankyo, Takeda, Nihon-Kayaku, Yakult, Taiho, Ono, Asahikasei-Parma, Eli Lilly, Bayer. A. Sato: Membership on an advisory board or board of directors: Taiho Pharmaceutical Co., Ltd., Chugai Pharma Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd.; Corporate-sponsored research: Taiho Pharmaceutical Co., Ltd., Chugai Pharma Co., Ltd. S. Yuki: Honoraria: Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Bayer Yakuhin, Ltd., Taiho Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Sanofi Co. Ltd. S. Morita: Corporate-sponsored research: Taiho; Honorarium: Taiho. T. Yamaguchi: Honorarium: Taiho. All other authors have declared no conflicts of interest.

476P Aflibercept in combination with irinotecan, fluorouracil and leucovorin (FOLFIRI) as first-line chemotherapy in metastatic colorectal cancer (mCRC) patients: A phase II multicentric study

A. Lapeyre-Prost[1], S. Pernot[2], J. Sigrand[3], F. Mary[4], K. Le Malicot[5], T. Aparicio[6], L. Dahan[7], F-X. Caroli-Bosc[8], T. Lecomte[9], S. Racine Doat[10], L. Marthey[11], J. Desrame[12], C. Lepage[13], J. Taieb[14]

[1]Gastroenterology Department, Hopital European George Pompidou, Paris, France, [2]Department of Gastroenterology and Digestive Oncology, Hopital European George Pompidou, Paris, France, [3]Digestive Oncology, CHU La Timone, Marseille, France, [4]Gastroenterology Department, Hôpital Avicenne, Bobigny, France, [5]EPICAD INSERM LNC-UMR 1231, FFCD - Burgundy University, Dijon, France, [6]Gastroenterology Department, Saint Louis Hospital AP-HP, Paris, France, [7]Department of Gastroenterology and Oncology, CHU La Timone Adults, Marseille, France, [8]Gastroenterology Department, CHU Angers, Angers, France, [9]Hepato-Gastroenterology Department, CHU de Tours, Hôpital Trousseau, Chambray-lès-Tours, France, [10]Hepato-Gastroenterology Department, Groupe Hospitalier Pitié Salpetriere, Paris, France, [11]Hepato-Gastroenterology Department, Antoine Béclère Hospital, Clamart, France, [12]Gastroenterology Department, Hôpital Privé Jean Mermoz, Lyon, France, [13]HepatoGastroenterology and Digestive Oncology Department, University Hospital Dijon, University of Burgundy and Franche Comté, FFCD, EPICAD INSERM LNC-UMR 1231, Dijon, France, [14]Department of Gastroenterology and Digestive Oncology, Hospital European Georges Pompidou - Sorbonne Paris Cité, Paris Descartes University, Paris, France

Background: FOLFIRI (5FU/leucovorin/irinotecan) + aflibercept significantly improves median overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) in patients (pts) with previously treated metastatic colorectal cancer (mCRC). The aim of this study was to investigate efficacy and tolerability of adding aflibercept to FOLFIRI in the first line setting.

Methods: Pts with untreated documented mCRC received aflibercept plus FOLFIRI every 14 days until progression or unacceptable toxicity in an open, phase II single arm, multicenter trial. The primary endpoint was the 6-months PFS rate. Secondary endpoints were overall PFS, OS and tolerability. A two- steps Simon design was used with H_0: 55% and H_1= 75%, respectively (one-sided $\alpha = 5\%$, 1-β=90%). Data were analyzed in intention to treat population. The study was stopped at the first stage.

Results: 41 patients were included and 40 analyzed (1 consent withdrawal) in 9 French centers between 10/2014 and 02/2017. Median age was 65 y (46-81), 42% were men, 53% had two or more metastatic sites. Eighteen patients (54.5%, IC [38.940; 69.509]) were alive and non-progressive at 6 months. Treatment with FOLFIRI plus aflibercept was therefore considered ineffective, inclusions were stopped. Median follow-up was 20.5 months (95% CI (15,11 ; 27,86)). ORR was 54% and disease control rate was 80%. Median duration of treatment was 5.2 months, median PFS and OS were 8,3 and 21.9 months respectively. Grade 3-4 adverse events were mainly gastrointestinal (18 pts, 45% : mucositis (15%), diarrhea (12,5%), abdominal pain (10%)) and vascular (13 pts, 32,5% : hypertension (17,5%) and venous thromboembolism (15%)). Severe hematological toxicities occurred in 7,5% of pts. 87.5% of patients had at least one dose modification during treatment. 37 pts received a second line therapy.

Conclusions: First line FOLFIRI+ aflibercept for mCRC pts is feasible but with significant toxicities leading to dose reduction in the majority of patients. Median PFS and OS were close to those reported with classical doublet and targeted agents in this setting.

Clinical trial identification: EudraCT: 2013-004081-33.

Legal entity responsible for the study: Fédération Francophone de Cancérologie Digestive.

Funding: Sanofi.

Disclosure: S. Pernot: Honoraria: Amgen, Sanofi; Travel, accomodations, expenses: Amgen, Merck, Servier, Bayer T. Aparicio: Conference: Pfizer, Roche, Sanofi, Léo Pharma, Amgen, BMS, Servier, Shire, Ipsen; Board: Pierre Fabre Ipsen, HalioDX, BMS; Travels: Ipsen, Novartis, Roche, Hospira; Research: Novartis. L. Dahan: Honoraria: Sanofi, Amgen. T. Lecomte: Consultant, expert: Sanofi; Courses, trainings: Lilly, Merck, Amgen; Invitations to national or international congresses: Amgen C. Lepage: Clinical research: Ipsen, Novartis Oncology; Courses: Advanced Accelerator Applications; Invitations to national or international congresses: Amgen, Ipsen, Novartis Oncology, Bayer. J. Taieb: Consultancy: Roche, Merck KGaA, Amgen, Celgene, Lilly, Baxalta, Servier, Sirtex Medical; Speaker's bureau: Servier, Amgen, Baxalta, Roche/Genentech, Sanofi, Merck, Lilly. All other authors have declared no conflicts of interest.

477P Folfiri-aflibercept vs folfiri-bevacizumab as second line treatment of RAS mutated metastatic colorectal cancer in real practice

A. Ottaiano[1], M. Capozzi[2], C. De Divitiis[2], A. Cassata[2], A. De Stefano[2], S. Tafuto[2], A. Avallone[2], G. Nasti[1]

[1]SSD Innovative Therapies for Abdominal Metastases - Abdominal Oncology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy, [2]Abdominal Oncology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy

Background: To date the treatment of RAS mutated (-M) metastatic colorectal cancer (mCRC) patients (pts) relies on the administration of oxaliplatin-based chemotherapy and bevacizumab as first line. Intensive debate is open about second-line treatments.

Methods: This is a real practice study; consecutive RAS-M unresectable mCRC were treated at the oncologist discretion at progression to FOLFOX/BEVA (fluorouracil, folinic acid, oxaliplatin, bevacizumab) with FOLFIRI/BEVA (fluorouracil, folinic acid, irinotecan, bevacizumab) (arm A) or FOLFIRI/AFLI (FOLFIRI, aflibercept) (arm B). We have analyzed differences in outcome and response between the two therapy sequences.

Results: Seventy-four patients were treated from January 2014 to January 2018; 31 treated with arm A, 43 with arm B. Among clinical factors there was a predominance of more extended disease (>two metastatic sites) in arm B (25/31 [51.2%] vs 40/43 [32.3 %] arm A; $p = 0.0414$). Fifty-nine pts were evaluable for response through RECIST: arm A, 5 PR, 15 SD, 8 PD; arm B, 5 PR, 16 SD, 10 PD. Second-line chemotherapy doses were reduced in 32.3% of pts in arm A and 38.1% in arm B. There were no grade 4 toxic events (NCI-CTC v4.0). The mean distance from first-line discontinuation to second-line start was 0.8 months in arm A and 2.4 months in arm B. Duration of first-line chemotherapy was significantly shorter in pts treated in arm B (12 pts < 6 months arm B vs 1 pt in arm A; $p = 0.0278$). Analysis of overall survival (OS) was done excluding these 13 pts to avoid prognostic interferences. Median OS were 22.7 in arm A vs 25.5 months in arm B (+ 2.8 months; $P = 0.6855$, HR: 1.12; 95% CI: 0.62 to 2.03). No maintenance treatment was done in arm B while in arm A BEVA with or without fluorouracil and folinic acid was done; censoring the analysis of OS at the end of the induction phase of both arms favored arm B ($P = 0.0425$; HR: 0.42; 95% CI: 0.15 to 1.15).

Conclusions: In our real practice, oncologists tend to administer FOLFIRI/AFLI in more extended RAS-M mCRC and to delay start of therapy. FOLFIRI/BEVA and FOLFIRI/AFLI are equally effective second-lines albeit FOLFIRI/AFLI, during the induction phase (6 months), is associated with a lower risk of death.

Legal entity responsible for the study: Istituto Nazionale Tumori di Napoli, IRCCS "G. Pascale".

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

478P In the pathway to response: Is aflibercept an optimal treatment for RASwt mCRC patients after progression to 1st line containing anti-EGFR?

E. Mata Velasco[1], E. González-Flores[2], I. Juez Martel[3], V. Alonso[4], P. Iranzo Gomez[5], N. Martinez Lago[6], C. Lopez[7], J.M. Cabrera Romero[8], M.J. Safont Aguilera[9], A. Ruiz Casado[10], M. Salgado Fernandez[11], B. González Astorga[12], P. Escudero[5], F. Rivera Herrero[13], C. Pericay Pijaume[14], R. Vera[1]

[1]Medical Oncology, Complejo Hospitalario de Navarra, Pamplona, Spain, [2]Medical Oncology, Hospital Universitario Virgen de las Nieves, Granada, Spain, [3]Medical Oncology, Hospital Universitario de Fuenlabrada, Madrid, Spain, [4]Medical Oncology Service, Hospital Miguel Servet, Zaragoza, Spain, [5]Medical Oncology, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain, [6]Medical Oncology, Hospital Universitario A Coruna, A Coruna, Spain, [7]Medical Oncology, Marques de Valdecilla University Hospital, Santander, Spain, [8]Medical Oncology, Hospital de Sabadell Corporacis Parc Tauli, Sabadell, Spain, [9]Medical Oncology, Hospital General Universitario Valencia, Valencia, Spain, [10]Medical Oncology, Hospital Puerta de Hierro, Majadahonda, Spain, [11]Medical Oncology, Complejo Hospitalario de Ourense, Ourense, Spain, [12]Medical Oncology, Hospital Universitario San Cecilio, Granada, Spain, [13]Medical Oncology, Hospital Universitario Marques de Valdecilla, Santander, Spain, [14]Medical Oncology, Hospital de Sabadell Corporacis Parc Tauli, Sabadell, Spain

Background: VELOUR trial compared FOLFIRI+/-aflibercept in 1226 mCRC patients after progression to oxaliplatin-based treatment, regardless of biological previous therapies. mOS (13.50 vs 12.06 months) and mPFS (6.90 vs 4.67 months) were increased, which led to aflibercept approval. We do not have yet enough information on aflibercept after anti-EGFR treatment. Our goal was to analyze efficacy and safety data of aflibercept in this specific context.

Methods: Retrospective analysis of clinical, therapeutic, and survival data collected from 120 consecutive RASwt mCRC patients treated from 2012 to 2017 with FOLFIRI-aflibercept after progression to standard chemotherapy + anti-EGFR in 12 Spanish hospitals.

Results: Median age was 60, 62.5% male, 37.5% female. 24% were right-sided tumours and 76% left-sided, with primary tumour resection in 41%. 100% RASwt, 5% BRAFmt. All patients received prior anti-EGFR therapy and 96% had ECOG 0/1. Median of FOLFIRI-Aflibercept cycles was 12, with 33% ORR. mPFS was 6.9 months (95% CI 6.0-7.7). BRAF, ECOG, primary tumour resection and n° of metastatic sites had statistical significance in univariate analysis; and primary tumour resection was also significant in multivariate analysis. mOS was 14.5 months (95% CI 9.7-19.3), with statistical significance in univariate for primary tumour resection, ECOG, and n° of metastatic sites. ECOG and n° of metastatic sites reached significance in multivariate analysis. As for toxicity, only 18.3% needed aflibercept dose reduction. 2nd line treatment was discontinued in 71.8% (mostly due to progression: 51.7%, 6.7% toxicity,1.7% surgery). 37% reached G3-4 toxicity (16.6% hematologic, 7.5% HTN, 5.9% asthenia, 2.5% perforation) 59% received a 3rd line therapy: 23% TAS-102, 18% regorafenib, 9% capecitabine.

Conclusions: RASwt mCRC patients reached similar results to those reported in VELOUR trial. The efficacy of subsequent aflibercept-containing 2nd line was maintained regardless of prior anti-EGFR. The efficacy of subsequent aflibercept-containing 2nd line was maintained regardless of prior anti-EGFR. Our results suggest that FOLFIRI-aflibercept, after 1st line with anti-EGFR, is a good treatment strategy for RASwt mCRC.

Legal entity responsible for the study: Ruth Vera García.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

479P A phase II study of bevacizumab and irinotecan plus alternate-day S-1 as a second-line therapy for colorectal cancer: The AIRS study

M. Honda[1], C. Matsuda[2], C. Tanaka[3], K. Kondo[4], T. Takahashi[5], C. Kosugi[6], Y. Tokunaga[7], H. Takemoto[8], H.M. Kim[9], J. Sakamoto[10], K. Oba[11], H. Mishima[12]

[1]Minimally Invasive Surgical and Medical Oncology, Fukushima Medical University, Fukushima, Japan, [2]Gastroenterological Surgery, Osaka University, Osaka, Japan, [3]Surgery, Gifu Prefectural General Medical Center, Gifu, Japan, [4]Surgery, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan, [5]Surgical Oncology, Gifu University Graduate School of Medicine, Gifu, Japan, [6]Department of Surgery, Teikyo University Chiba Medical Center, Ichihara, Chiba, Japan, [7]Surgery, Kyoto Japan Post Hospital, Kyoto, Japan, [8]Surgery, Kinki Central Hospital, Osaka, Japan, [9]Surgery, Rinku General Medical Center, Izumisano, Japan, [10]Surgery, Tokai Central Hospital, Kakamigahara, Japan, [11]Biostatistics, The University of Tokyo School of Public Health, Tokyo, Japan, [12]Surgery, Aichi Medical University, Nagakute, Japan

Background: The aim of this single-arm phase II clinical trial was to evaluate whether the alternate-day administration of S-1 plus irinotecan would reduce the incidence of severe diarrhea in comparison to consecutive-day S-1 administration (standard IRIS regimen) in second-line treatment in patients with metastatic colorectal cancer.

Methods: Patients with metastatic colorectal cancer after failure with first-line treatment of oxaliplatin and fluoropyrimidine were enrolled. Irinotecan (150 mg/m2) and bevacizumab (5mg/kg) were given intravenously on day 1. Oral S-1 was administered on alternate-days at a dose of 40-60mg twice a day. Cycles were repeated every two weeks. The primary endpoint was the incidence of grade $\geq$3 diarrhea. Our hypothesis set the 21% as a threshold incidence and 10% as an expected incidence from previous studies with one-sided alpha = 0.05. The secondary endpoints included the relative dose intensity, progression free survival, overall survival and other adverse events.

Results: A total of 51 patients were enrolled. The incidence of grade $\geq$3 diarrhea was 15.7% (8/51). Other common grade $\geq$3 adverse events were neutropenia, anemia, thrombocytopenia and fatigue were 13.7% (7/51), 5.9% (3/51), 2.0% (1/51) and 5.9% (3/51), respectively. The relative dose intensities of irinotecan, bevacizumab, and S-1 were 80.0%, 86.8%, and 77.7%, respectively. The median progression free survival and overall survival were 8.4 months (5.8 - 9.8) and 17.1 months (11.8 - 22.3).

Conclusions: The alternate day S-1 administration doesn't have significant effectiveness to reduce diarrhea in patients who received second line treatment for metastatic colorectal cancer.

Clinical trial identification: UMIN000008947.

Legal entity responsible for the study: Epidemiological and Clinical Research Information Network (ECRIN).

Funding: Taiho Pharmaceutical Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

480P The safety and efficacy of FOLFOXIRI plus molecular target therapy as a first-line treatment for metastatic colorectal cancer: A multicentre retrospective study

T. Ogata[1], H. Satake[2], M. Ogata[1], Y. Hatachi[1], M. Hamada[3], H. Yasui[1]

[1]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [2]Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan, [3]Department of Surgery, Kansai Medical University Hospital, Hirakata, Japan

Background: The TRIBE study showed that FOLFOXIRI plus bevacizumab therapy is an effective treatment for metastatic colorectal cancer (mCRC). This study aimed to determine the safety and effectiveness of FOLFOXIRI therapy as a first-line treatment.

Methods: We retrospectively collected data of patients with mCRC treated with FOLFOXIRI from March 2014 to December 2017 in two centres.

Results: Fifty-five patients were enrolled in this study (median age, 60 years; males 25, females 30). The tumour location was classified as right and left in 15 and 40 patients, respectively. Twenty-nine and twenty-six patients had RAS wild-type disease and mutation-type disease, respectively. Anti-VEGF and anti-EGFR antibodies were used in 38 and 17 patients, respectively. The most common grade 3 or 4 adverse event was neutropenia (51%). Skin toxicities and hypomagnesaemia showed a statistically higher frequency among patients with anti-EGFR antibodies ($P < 0.001$ and $P = 0.039$, respectively). The overall response rate (ORR) was 67% (complete response [CR], 7 patients; partial response [PR], 30 patients; not evaluated [NE], 1 patient), and the disease control rate was 96% (stable disease, 16 patients). The median progression free survival (mPFS) was 11.0 (0.43 − 45.3) months and the median overall survival (mOS) was 41.9 (1.00 − 45.3) months. In FOLFOXIRI plus anti-VEGF antibodies, the ORR was 55% (CR, 5 patients; PR 16 patients), and in FOLFOXIRI plus anti-EGFR antibodies, the ORR was 94% (CR, 2 patients; PR, 14 patients; NE, 1 patient) ($P = 0.271$). With a median follow up of 18.4 months, mPFS and mOS were not significantly different in patients with anti-EGFR antibodies or anti-VEGF antibodies (hazard ratio [HR], 3.12 [0.883 − 11.0]; $P = 0.143$ and $P = 0.063$, respectively). Twelve patients had progressive disease (PD) during the induction phase. In these patients, mOS was significantly poorer (13.2 months versus 41.9 months; HR, 23.3 [6.77 − 80.1]; $P < 0.001$).

Conclusions: FOLFOXIRI plus molecular target therapy showed impressive results for patients with mCRC. The response rate was significantly higher in patients with anti-EGFR antibodies, although skin toxicities and hypomagnesaemia tend to occur in these patients.

Legal entity responsible for the study: Kobe City Medical Center General Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

481P Phase II study of cetuximab rechallenge in patients with ras wild-type metastatic colorectal cancer: E-rechallenge trial

H. Osawa[1], E. Shinozaki[2], M. Nakamura[3], Y. Ohhara[4], Y. Shindo[5], M. Shiozawa[6], H. Uetake[7], H. Matsumoto[8], N. Ureshino[9], H. Satake[10], T. Kobayashi[11], T. Suto[12], S. Kitano[13], Y. Ohashi[14], K. Uemura[15], K. Yamaguchi[16]

[1]Department of Oncology and Hematology, Edogawa Hospital, Tokyo, Japan, [2]Gastrointestinal Oncology, Cancer Institute Hospital of JFCR, Tokyo, Japan, [3]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan, [4]Department of Gastroenterology, Sapporo Medical Center, Sapporo, Japan, [5]Gastroenterological Surgery, Nakadori General Hospital, Akita, Japan, [6]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, [7]Specialized Surgeries, Tokyo Medical and Dental University, Tokyo, Japan, [8]Department of Surgery, Cancer and Infectious Diseases Center, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan, [9]Medical Oncology, Saga-Ken Medical Center Koseikan, Saga, Japan, [10]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan, [11]Department of Medical Oncology, Kyorin University Faculty of Medicine, Mitaka, Japan, [12]Department of Gastroenterological Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan, [13]Graduate School of Engineering, Osaka University, Osaka, Japan, [14]Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo, Japan, [15]Division of Biostatistics and Bioinformatics, Interfacluty Initiative in Information Studies, The University of Tokyo, Tokyo, Japan, [16]Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan

Background: Several previous reports indicated that cetuximab (Cmab) rechallenge may be efficacious in patients for whom Cmab was previously effective. On the other hand, some reports did not support this. Considering the plasticity of sensitive clone, we assumed that an anti-EGFR antibody-free interval (aEFI) and efficacy may be correlated. This current study investigates the efficacy and safety of Cmab rechallenge as a salvage chemotherapy.

Methods: The E-Rechallenge tiral is a multicenter phase II study in mCRC patients who have become refractory to fluoropyrimidines, L-OHP, CPT-11, Cmab and bevacizumab, and in whom previous treatment with Cmab was effective in any earlier line (achieving CR, PR, or SD that persisted for $\geq$6 months). The other main eligibility criteria are; RAS wild-type, measurable disease, aEFI $\geq$16 weeks between the last dose of Cmab during previous treatment and the start of Cmab rechallenge. Protocol treatment is the combination of weekly Cmab with biweekly CPT-11. The primary endpoint is response rate (RR). Secondary endpoints are progression free survival (PFS), overall survival (OS), association between the aEFI and efficacy, and safety. Using a single-stage binominal design, 45 patients were required; a RR of $\geq$ 20% was considered promising, and a RR of $\leq$ 5% unacceptable (one-sided $\alpha = 2.5\%$, $\beta = 10\%$). Additional research of ctDNA was conducted optionally.

Results: Between Dec 2014 and Oct 2017, 33 patients were enrolled. Patients' characteristics were as follows; mean age 64.4, male/female 84.8%/15.2%, primary location right/left 12.1%/87.9% and the efficacy in previous Cmab, CR/PR/SD $\geq$6 months 3%/78.8%/18.2%, respectively. The primary endpoint; the rates of PR/SD/PD (95%CI) were PR 15.6% (5.3-32.7%)/SD 40.6% (23.6-57.6%)/ PD 43.8% (26.4-62.3%). Secondary endpoint; median PFS and OS (95%CI) were 88 days (62-113days) and 262 days (195-307days). There were no statistical significant difference of PFS stratified by median aEFI. New signals of adverse events were not identified.

Conclusions: Cmab rechallenge showed some activity in the salvage setting, in patients for whom Cmab was previously effective. The additional research of ctDNA may contribute to identify patients with benefit from Cmab rechallenge.

Clinical trial identification: UMIN 000016439.

Legal entity responsible for the study: Comprehensive Support Project for Oncological Research.

Funding: Merck Serono.

Disclosure: E. Shinozaki, H. Satake: Honoraria: Merck Serono. All other authors have declared no conflicts of interest.

482P RET rearrangements may arise following anti-EGFR therapy in advanced colorectal cancer

T.A. Rich[1], K. Clifton[2], A. Grothey[3], A. Hendifar[4], D.H. Henry[5], Y. Kagawa[6], Y. Nakamura[7], W. Okamoto[8], B.R. Tan[9], G. Sherrill[10], T. Yoshino[11], V.M. Raymond[1], Y. Shiotsu[1], R.B. Lanman[1], V. Morris[2]

[1]Medical Affairs, Guardant Health, Redwood City, CA, USA, [2]Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [3]Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA, [4]Department of Internal Medicine/ Hematology/Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [5]Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [6]Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [7]Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [8]Biobank Translational Research Support Section, Translational Research Management Division, Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [9]Department of Medicine, Washington University, Saint Louis, MO, USA, [10]Department of Hematology/Oncology, Cone Health Cancer Center, Greensboro, NC, USA, [11]Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: RET rearrangements (RETr) are uncommon yet emerging oncogenic targets found in RAS/BRAF wild-type colorectal cancers (CRCs), particularly right-sided, MSI-high tumors. We describe the molecular landscape of metastatic CRCs harboring a somatic RETr detected by next generation sequencing (NGS) of cell-free DNA (cfDNA). cfDNA data complement previous descriptions of RETr in tissue, which are limited by small series of patients (pts) and cfDNA also provides a summary of genomic alterations (alts) across multiple metastatic sites in pts typically exposed to one or more lines of therapy.

Methods: Between 2/2015-3/2018, somatic RETr were identified among 4,234 consecutive metastatic CRC pts with tumor DNA detected on a 68-73 gene cfDNA assay (Guardant360®, Redwood City, CA). This validated NGS assay evaluates single nucleotide variants, and select indels, fusions, and copy number gains with high sensitivity and analytic specificity. Relevant clinicopathologic correlates were obtained from clinicians.

Results: Seventeen RETr were detected in 16 pts (0.4%). Functionally significant alts in other cancer genes were found in 88% of samples with a RETr (median 9.5 additional alts, max 23). There was a high co-occurrence of canonical KRAS alts (14 alts in 7/16 pts), 5 of whom also had alts in NRAS (n = 4pts), the EGFR extracellular domain (ECD, n = 4), and/or BRAF V600E (n = 3). For 4 pts with available comprehensive tissue NGS results, the RETr was detected in cfDNA only. Two also had KRAS, NRAS, and EGFR ECD alts, one had an EGFR activating alt, and the fourth had a FGFR3 fusion, all detected only in cfDNA. Prior to cfDNA collection, all 4 had progressed on anti-EGFR therapy after a median of 12mo (range 8-16mo) of treatment. Four additional RETr/KRAS+ pts had either a KRAS alt that was not detected in tissue (n = 2) or co-occurred with an ALK fusion and/or BRAF V600E in pts who had prior anti-EGFR therapy (n = 2).

Conclusions: RETr commonly co-occur with RAS/RAF alts in cfDNA, a novel observation. The alt pattern and clinicopatholgoic history suggest RETr contribute to acquired resistance to anti-EGFR therapy in metastatic CRC. Our data also raise the question of whether driver RETr may be associated with primary resistance to anti-EGFR therapy.

Legal entity responsible for the study: Guardant Health.

Funding: Has not received any funding.

Disclosure: T.A. Rich, V.M. Raymond, Y. Shiotsu, R.B. Lanman: Employee, Stock owner: Guardant Health. Y. Kagawa, Y. Nakamura: Research support: Guardant Health. W. Okamoto: Research support: Guardant Health; Grant funding: MSD. T. Yoshino: Research support: Guardant Health; Grants: MSD KK, Sanofi KK, Sumitomo Dainippon Pharma Co Ltd, Chugai Pharmaceutical Co Ltd, GlaxoSmithKline KK, Nippon Boehringer Ingelheim Co Ltd; Consulting fees: Sanofi KK, Chugai Pharmaceuticals Co Ltd, Eli Lilly Japan, Merck Serono Co Ltd. All other authors have declared no conflicts of interest.

483P A biomarker study to validate predictors for clinical outcome of cetuximab based chemotherapy in first-line metastatic colorectal cancer (mCRC) patients: JACCRO CC-05/06AR and FIRE-3

Y. Sunakawa[1], S. Stintzing[2], S. Cao[3], J. Luecke[4], D. Thompson[4], M. Moran[5], S.H. Astrow[6], J. Hsiang[5], C. Stephens[5], W. Zhang[7], A. Tsuji[8], T. Takahashi[9], T. Denda[10], K. Shimada[11], M. Kochi[12], M. Takeuchi[13], M. Fujii[12], W. Ichikawa[9], V. Heinemann[14], H-J. Lenz[7]

[1]Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan, [2]Medical Oncology, Ludwig Maximilians University - Grosshadern, Munich, Germany, [3]Preventive Medicine, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [4]Biostatistics and Bioinformatics, HTG Molecular Diagnostics Inc., Tucson, AZ, USA, [5]R&D and Pharmaceutical Services, Cancer Genetics, Inc., Los Angeles, CA, USA, [6]Kite, Santa Monica, CA, USA, [7]Medical Oncology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [8]Clinical Oncology, Kagawa University Hospital, Kagawa, Japan, [9]Medical Oncology, Showa University Fujigaoka Hospital, Yokohama, Japan, [10]Gastroenterology, Chiba Cancer Center, Chiba, Japan, [11]Medical Oncology, Showa University Koto Toyosu Hospital, Tokyo, Japan, [12]Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan, [13]Clinical Medicine (Biostatistics), Kitasato University, Tokyo, Japan, [14] Department of Medical Oncology and Comprehensive Cancer Center, Ludwig Maximilians University - Grosshadern, Munich, Germany

Background: We conducted a biomarker study to identify significant genes to predict efficacy of cetuximab (cet) based treatment using tumor samples from mCRC patients (pts) enrolled in JACCRO CC-05/06AR (UMIN000010635) and FIRE-3 (NCT00433927), which evaluated 1st-line doublet plus cet therapy. There are no established predictive biomarkers beyond RAS mutations. We reported recently CDX2 gene expression levels as a promising biomarker for cet treatment in KRAS wild-type mCRC pts of the JACCRO trial (ASCO 2016, abst3592). Therefore, we performed the validation study using tumor samples from pts enrolled in the FIRE-3 trial.

Methods: We analyzed tissue samples of 77 pts of the JACCRO trial for discovery set and 250 pts of cet arm in the FIRE-3 trial for validation set. Gene expression levels were measured by HTG EdgeSeq Oncology Biomarker Panel, which is comprised of probes targeting 2560 genes implicated in numbers of pathways, using next generation sequencing for quantitative analysis of targeted RNAs. Univariate Cox regression analysis was conducted for all genes that passed QC filtering.

Results: Seventy-one pts (male/female, 39/32; median age, 63 yrs) and 102 pts (male/female, 75/27; median age, 63 yrs) were successful for gene expression analysis in the JACCRO and FIRE-3 set, respectively. The Cox regression analysis identified 24 genes for overall survival (OS) and 8 genes for progression-free survival (PFS), which all were significant ($p < 0.005$) in the JACCRO set. Among those genes, LYZ and RNF43 genes were found to be significantly associated with OS (coefficients, 0.21; $p = 0.013$) and PFS (coefficients, -0.20; $p = 0.037$), respectively, in the FIRE-3 set. In the JACCRO set, high expression ($\log2 > 9.07$) of CDX2 predicted a significantly longer PFS ($p = 0.002$). The same effect was found in the FIRE-3 set when applied the same cutoff value (median PFS 10.9 vs. 6.9 months, HR 0.39, 95%CI 0.22-0.72, $p = 0.002$).

Conclusions: Our biomarker study validated CDX2 as a novel predictor for clinical outcome of 1st-line cet based chemotherapy in mCRC. These data warrant further exploration of CDX2 as a biomarker or as a potential target for drug development.

Clinical trial identification: UMIN000010635.

Editorial acknowledgement: We acknowledge Sachika Koyama and Yasushi Ohtake (JACCRO) for editorial assistance.

Legal entity responsible for the study: Heinz-Josef Lenz.

Funding: JACCRO, the National Cancer Institute (grant number P30CA014089), The Gloria Borges WunderGlo Foundation-The Wunder Project, Dhont Family Foundation, San Pedro Peninsula Cancer Guild, and Daniel Butler Research Fund.

Disclosure: Y. Sunakawa: Honoraria for talks: Taiho Pharmaceutical, Chugai Pharma, Yakult Honsha, Takeda, Merck Serono, Bayer Yakuhin, Sanofi. S. Stintzing: Consulting or advisory role, travel expenses, honoraria: Merck KGaA. A. Tsuji: Honoraria: Taiho Pharmaceutical, Merck Serono. T. Denda: Honoraria: Yakult Honsha, Taiho Pharmaceutical. K. Shimada: Corporate-sponsored research fee: Yakult Honsha, Taiho Pharmaceutical. M. Takeuchi: Consulting fees: Hisamitsu Pharmaceutical, Kowa, Shionogi Pharma, Abbvie, Astellas. W. Ichikawa: Consulting fees: Ono Pharmaceutical; Research funding: Takeda, Taiho Pharmaceutical, Eisai, Chugai Pharma, Merck Serono, Shionogi Pharma, Daiichi Sankyo; Honoraria: Merck Serono, Taiho Pharmaceutical, Chugai Pharma, Takeda, Ono Pharmaceutical, Lilly. V. Heinemann: Consulting or advisory role, travel expenses, honoraria, research funding: Merck. H-J. Lenz: Consulting or advisory role, travel expenses, honoraria, Merck Serono. All other authors have declared no conflicts of interest.

484P Retrospective RAS analysis of the EPIC trial: Cetuximab plus irinotecan vs irinotecan in patients (pts) with second-line metastatic colorectal cancer (mCRC)

A. Sobrero[1], H-J. Lenz[2], C. Eng[3], W. Scheithauer[4], G. Middleton[5], W. Chen[6], R. Esser[7], J. Nippgen[8], H. Burris[9]

[1]*Medical Oncology, Policlinico San Martino IRCCS, Genoa, Italy,* [2]*Medical Oncology, University of Southern California, Los Angeles, CA, USA,* [3]*Department of Gastrointestinal Medical Oncology, M. D. Anderson Cancer Center, Houston, TX, USA,* [4]*Clinical Department of Oncology, Medical University of Vienna, Vienna, Austria,* [5]*Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK,* [6]*R&D Global Biostatistics & Epidemiology, EMD Serono, Beijing, China,* [7]*Global Medical Affairs Oncology, Merck KGaA, Darmstadt, Germany,* [8]*Medical Oncology, Merck KGaA, Darmstadt, Germany,* [9]*Drug Development, Tennessee Oncology, Nashville, TN, USA*

Background: The multicenter, open-label, randomized, phase 3 EPIC study (EMR 062202-025) investigated the addition of cetuximab to irinotecan vs irinotecan in pts with EGFR-expressing mCRC who had previously progressed on first-line fluoropyrimidine- and oxaliplatin-based chemotherapy. The primary endpoint was overall survival (OS). We present the extended RAS analysis (KRAS/NRAS exons 2, 3, and 4) for the EPIC study population.

Methods: 1298 RAS-unselected pts were enrolled from May 2003 to February 2006. Existing DNA samples were reanalyzed using BEAMing (beads, emulsion, amplification, magnetics) technology. RAS wild-type (wt) status was defined as having all alleles be analyzable and a sum of RAS mutations of $\leq 5\%$. Baseline characteristics, efficacy, safety, and post-study therapy were assessed. 10.3% had no RAS data available.

Results: Among the 452 (231 in the cetuximab + irinotecan arm and 221 in the irinotecan arm) pts with RAS wt mCRC, baseline characteristics were comparable to those of the unselected population. 67.5% had 1 prior line of therapy. In the cetuximab + irinotecan vs irinotecan arms, median progression-free survival (PFS) was 5.4 vs 2.6 months (HR, 0.57 [95% CI, 0.46-0.69]; $P < .0001$), median OS was 12.3 vs 12.0 months (HR, 0.91 [95% CI, 0.71-1.17; $P = .4645$]), and overall response rate (ORR) was 29.4% vs 5.0% (OR, 8.12 [95% CI, 4.04-17.40]; $P < .0001$), respectively. 76.4% and 61.8% of pts in the cetuximab + irinotecan vs irinotecan arms, respectively, experienced a grade ≥ 3 adverse event. 47.1% of pts in the irinotecan arm received cetuximab in a subsequent line of therapy vs 11.3% in the cetuximab + irinotecan arm.

Conclusions: This retrospective analysis confirms that cetuximab-based therapy is suitable as a standard, second-line treatment for pts with RAS wt mCRC. Specifically, the addition of cetuximab to irinotecan significantly improved PFS and ORR in this population. A large proportion of pts in the irinotecan arm crossed over to receive post-study cetuximab, potentially masking any OS benefit of the addition of cetuximab to irinotecan in this study. Benefits appear clinically relevantly higher than for pts with RAS-unselected or KRAS wt mCRC.

Clinical trial identification: EMR 062202-025.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA.

Funding: Merck KGaA.

Disclosure: R. Esser: Employee, stock ownership: Merck KGaA. J. Nippgen: Employee: Merck KGaA. H. Burris: Consultancy (Includes expert testimony): Mersana, AstraZeneca, Forma, Janssen, Novartis, Roche/Genentech, TG Therapeutics, Medimmune, Bristol-Myers Squibb; Research funding: Roche/Genentech, Bristol-Myers Squibb, Incyte, Tarveda Therapeutics, Mersana, AstraZeneca, Medimmune, Macrogenics, Novartis, Boehringer Ingelheim, Lilly, Seattle Genetics, Abbvie, Bayer, Celldex, Merck, Celgene, Agios, Jounce Therapeutics, Moderna Therapeutics, CytomX Therapeutics, GlaxoSmithKline, Verastem, Tesaro, Immunocore, Takeda, millennium, BioMed Valley Discoveries, Pfizer, PTC Therapeutics, TG Therapeutics, Loxo, Vertex, eFFECTOR Therapeutics, Janssen, Gilead Sciences, Valent Technologies. All other authors have declared no conflicts of interest.

485P Withholding Anti-EGFR: Impact on outcome of RAS wild-type metastatic colorectal tumours (WAIT OR ACT): A multicentric AGEO study

L-J. Palmieri[1], L. Mineur[2], D. Tougeron[3], B.J-C. Rousseau[4], V. Granger[5], J-M. Gornet[6], D. Smith[7], A. Lievre[8], M.P. Galais[9], S. Racine Doat[10], S. Pernot[11], A.L. Bignon Bretagne[12], J-P. Metges[13], N. Baba-Hamed[14], M. Hassine[15], S. Obled[16], C. Vitellius[17], O. Bouche[18], D. Vernerey[19], R. Coriat[20]

[1]*Gastroenterology, Hôpital Cochin, Paris, France,* [2]*Oncology, Institut Ste Catherine, Avignon, France,* [3]*Medical Oncology, CHU Poitiers, Jean Bernard Hôpital, Poitiers, France,* [4]*Medical Oncology, Centre Hospitalier Universitaire Henri-Mondor, Créteil, France,* [5]*Gastroenterology, Centre Hospitalier Universitaire Grenoble, Grenoble, France,* [6]*Gastroenterology, Hôpital St. Louis, Paris, France,* [7]*Service d'Oncologie, CHU Bordeaux Hopital St. André, Bordeaux, France,* [8]*Gastroenterology, CHU de Pontchaillou, Rennes, France,* [9]*Medical Oncology, Centre Francois Baclesse, Caen, France,* [10]*Gastroenterology, Groupe Hospitalier Pitié Salpetriere, Paris, France,* [11]*Department of Gastroenterology and Digestive Oncology, Hopital European George Pompidou, Paris, France,* [12]*Gastroenterology, CHU de Caen, Caen, France,* [13]*Medical Oncology, C.H.U. Brest - Hôpital Morvan, Brest, France,* [14]*Medical Oncology, Groupe Hospitalier Paris Saint-Joseph, Paris, France,* [15]*Gastroenterology, CHU de Rouen - Hôpital Charle Nicolle, Rouen, France,* [16]*Medical Oncology, Centre Hospitalier Universitaire Nimes, Nimes, France,* [17]*Gastroenterology, CHU Angers, Angers, France,* [18]*Medical Oncology, CHU de Reims - Hôpital Robert Debré, Reims, France,* [19]*Statistics, CHU Besançon, Hôpital Jean Minjoz, Besançon, France,* [20]*Gastroenterology, Hôpital Cochin, Paris, France*

Background: Two phases III studies (FIRE-3 and CALGB/SWOG80405) suggested higher response rate (RR) for doublet chemotherapy with an anti-EGFR (Epidermal Growth Factor Receptor) compared to an anti-VEGF (Vascular Endothelial Growth Factor), in first line RAS/BRAF wild-type (WT) unresectable metastatic colorectal cancer (mCRC). Unfortunately, in clinical practice the delay to obtain RAS/BRAF status may delay the chemotherapy start. No study has evaluated the impact of a delayed introduction of the anti-EGFR.

Methods: This retrospective multicentric AGEO (Association Gastro-Entérologues Oncologues) study included mCRC RAS/BRAF WT patients who received a doublet chemotherapy either with an anti-VEGF introduced immediately (control arm) or with an anti-EGFR introduced at cycle 2 or 3 (delayed group) between 2013 and 2016. The primary endpoint was the Progression Free Survival (PFS). The Overall Survival (OS) and the RR were secondary endpoints. Given different characteristics between the two groups, a propensity score was developed.

Results: A total of 262 patients were included: 129 in the control group and 133 in the delayed group. Compared to the delayed group, patients treated in the control group were more likely descendant mCRC (60% vs 44%) and had more metastatic sites (>1 site: 57% vs 40%). In the delayed anti-EGFR group, the time to obtain RAS status was 20.7 days $\pm$18.9. The anti-EGFR was introduced in 70% of cases at C2 and in 30% at C3. Using the propensity score, there was no more difference between the two groups. The median follow-up was 37.9 months. PFS and RR were significantly longer and higher in the delayed anti-EGFR group compared to the control anti-VEGF group (PFS: 13.8 vs 10.8 months, $p = 0.03$; RR: 67% vs 46%, $p = 0.0007$). Meantime, no difference was observed concerning OS (30.4 months vs 30.0 months, $p = 0.23$).

Conclusions: There is no deleterious effect of delayed anti-EGFR introduction at cycle 2 or 3 compared to the immediate introduction of anti-VEGF in patients with RAS/BRAF WT mCRC. Therefore, in current clinical practice, if the response rate is an important goal, it is possible to wait for RAS status and to initially start chemotherapy without targeted therapy.

Legal entity responsible for the study: Lola-Jade Palmieri.

Funding: Has not received any funding.

Disclosure: D. Tougeron: Consulting or advisory role: MSD, BMS, Sanofi, Roche; Speaker's bureau: Roche, Novartis, Servier; Travel, accomodations, expenses: MSD, BMS, Merck, Amgen. A. Lievre: Consulting or advisory role: Merck, Amgen, Bayer, Ipsen; Speaker's bureau: Roche, Merck, Ipsen, BMS, Novartis, Servier; Travel, accomodations, expenses: Merck, Novartis, Ipsen, Roche. S. Pernot: Honoraria: Amgen, Sanofi; Travel, accomodations, expenses: Amgen, Merck, Servier, Bayer. O. Bouche: Consulting or advisory role: Roche, Merck, Amgen, Bayer; Speaker's bureau: Lilly, Pierre Fabre, Novartis, Servier; Travel, accomodations, expenses: Lilly, Roche, Merck. R. Coriat: Amgen, Merck, Roche, Novartis, Ipsen, Keocyt, Bayer, Servier. All other authors have declared no conflicts of interest.

486P Prospective biomarker study in advanced RAS wild-type colorectal cancer: POSIBA trial

X. García Albéniz[1], V. Alonso[2], P. Escudero[3], M. Méndez[4], J. Gallego Plazas[5], J.R. Rodriguez[6], A. Salud Salvia[7], J. Fernández-Plana[8], H. Manzano Alemany[9], M. Zanui[10], E. Falcó[11], J. Feliu Batlle[12], M. Gil-Raga[13], C. Fernández-Martos[14], U. Bohn Sarmiento[15], M.C. Alonso López[16], V. Calderero Aragón[17], F. Rojo[18], M. Cuatrecasas[19], J. Maurel[20]

[1]Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA, [2]Medical Oncology Service, Hospital Miguel Servet, Zaragoza, Spain, [3]Medical Oncology, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain, [4]Medical Oncology Service, Hospital de Móstoles, Móstoles, Spain, [5]Medical Oncology, Hospital General Universitario de Elche, Elche, Spain, [6]Hospital Infanta Cristina, Madrid, Spain, [7]Medical Oncology, Hospital Arnau de Vilanova, Lleida, Spain, [8]Medical Oncology Service, Hospital Mútua de Terrasa, Terrassa, Barcelona, Spain, [9]Medical Oncology Service, Hospital Universitario Son Espases, Palma de Mallorca, Spain, [10]Medical Oncology Service, Hospital de Mataró, Mataró, Spain, [11]Medical Oncology Service, Hospital Son Llàtzer, Palma, Spain, [12]Medical Oncology Service, Hospital Universitario La Paz, Madrid, Spain, [13]Medical Oncology Service, Hospital de Sagunto, Sagunto, Spain, [14]Medical Oncology Service, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [15]Medical Oncology Service, Hospital de Gran Canaria Dr. Negrin, Las Palmas, Spain, [16]Medical Oncology Service, Complejo Hospitalario Universitario de Albacete, Albacete, Spain, [17]Medical Oncology Service, Hospital de Barbastro, Barbastro, Spain, [18]Pathology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [19]Department of Pathology, Hospital Clínic de Barcelona, Barcelona, Spain, [20]Medical Oncology, Hospital Clínic of Barcelona, Barcelona, Spain

Background: RAS testing is used to select patients sensitive to anti-EGFR therapies in metastatic colorectal cancer (mCRC) but other biomarkers such as BRAF, PIK3CA/PTEN and p-IGF-1R+/MMP7 + (DP phenotype) have not prospectively assessed to predict anti-EGFR resistance.

Methods: We designed a multicenter prospective trial (NCT01276379) to evaluate if the following biomarkers BRAF mutation, PIK3CA mutation/PTEN loss and DP phenotype can improve the prediction of 12-months progression-free survival (PFS) over the use of only clinical variables in patients with RAS WT mCRC treated with standard chemotherapy plus biweekly Cetuximab as first-line therapy. The planned sample size was 170 RAS WT patients to detect a 20% difference in 12-month PFR based on analysis of clinical and selected biomarkers (alpha=.05, beta=.2). The discriminatory capacity of the biomarkers was evaluated using ROC curves.

Results: We included 181 RAS WT patients. The biomarker distribution was: BRAF mutant 20 patients (11%), PIK3CA mutated/PTEN loss 98 patients (58%) and DP 23 patients (12.7%). Median PFS: BRAF WT 11.4 vs BRAF mutant 5.9 months ($p = 0.004$). PIK3CA/PTEN pathway and DP phenotype did not discriminate PFR (p=NS). Baseline clinical variables with good prognosis in a multivariable model were PS = 0, left sided tumor and resectable liver metastases (i.e. liver only metastases (<3 nodules and <5cm)).

Conclusions: A clinical score discriminates between two groups of patients who benefitted differently from chemotherapy plus cetuximab. The addition of BRAF, PIK3CA/PTEN and DP to the clinical score does not improve the prediction of 12m PFS.

Clinical trial identification: EudraCT: 2010-019236-12.

Legal entity responsible for the study: Grupo Español Multidisciplinar de Cáncer Digestivo.

Funding: Merck.

Disclosure: All authors have declared no conflicts of interest.

487P Patient selection for targeting integrin with abituzumab in patients with metastatic colorectal cancer (mCRC): A retrospective analysis of the randomized phase I/II Poseidon study

R. Laeufle[1], D. Arnold[2], S. Kopetz[3], J. Straub[4], R. Bruns[5], G. Massimini[6], R. Debenedetto[7], R. Linke[7], E. Elez Fernandez[8], J. Tabernero[9]

[1]Clinical Development and Medical Affairs, SFJ Pharmaceuticals, Pleasanton, CA, USA, [2]Med. Abteilung, Asklepios Klinik Altona, Hamburg, Germany, [3]Department of Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [4]Global Early Development, Merck KGaA, Darmstadt, Germany, [5]Biostatistics, Merck KGaA, Darmstadt, Germany, [6]Global Research and Development, Merck KGaA, Darmstadt, Germany, [7]Clinical Development and Medical Affairs, SFJ-Pharmaceuticals, Pleasanton, CA, USA, [8]Gastrointestinal Cancer and Drug Development, Vall d'Hebron University Hospital, Barcelona, Spain, [9]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Adding abituzumab (EMD 525797) a humanized monoclonal IgG2 antibody, targeting αv integrin subunit to the control arm (irinotecan+cetuximab) failed to demonstrate a statistically significant PFS benefit in a phase I/II in second line KRAS wild-type (KRAS wt exon-2) mCRC. A pre-planned explorative biomarker analysis suggested that high integrin αvβ6 expression may be negatively prognostic for OS in the control arm and predictive for prolonged OS with abituzumab treatment. {Elez et al Annals of Oncology, Volume 26, Issue 1, 1 January 2015, Pages 132–140}.

Methods: Further retrospective analysis of Poseidon study data were performed (n = 98 patients with high and n = 99 low αvβ6 expression) to correlate the impact of location of tumor (left n = 152 versus right n = 44, and one patient had both right and left colorectal cancer) and integrin αvβ6 expression (low versus high) on overall survival (OS), progression free survival (PFS) and objective response rate (ORR) of abituzumab added to irinotecan+cetuximab.

Results: This retrospective explorative analysis suggest that patients with left sided KRAS wt mCRC and high expression of αvβ6 showed the most benefit for median OS of 25.6 months versus 10.2 months (HR 0.36 [95% CI 0.17; 0.75]; median PFS of 8.6 months versus 4.2 months (HR 0.61 [95% CI 0.31; 1.22]); ORR. 9/20 (45.0%) versus 5/22 (22.7%), when treated with abituzumab 1000 mg + irinotecan+cetuximab versus irinotecan+cetuximab alone. No treatment benefit was observed in right sided mCRC with high expression of αvβ6 and in all mCRC with low expression of αvβ6.

Conclusions: Although the sample size is small, patients with left sided KRAS wt mCRC and high expression of αvβ6 integrin in their tumor seem to benefit most from the addition of abituzumab to irinotecan+cetuximab compared to irinotecan+cetuximab alone. A prospective study in 1L left sided RAS wild-type mCRC with high expression of αvβ6 is planned with the addition of abituzumab 1000mg to SOC.

Clinical trial identification: Explorative, retrospective data analysis of study NCT01008475; first release October 19, 2009.

Legal entity responsible for the study: Merck KGaA and SFJ Pharmaceuticals.

Funding: Merck KGaA and SFJ Pharmaceuticals.

Disclosure: R. Laeufle: Consultant: SFJ Pharmaceuticals. D. Arnold: Consultancy, honoraria: Roche, Merck Serono; Research funding to the Principal Investigator: Roche, Sanofi Aventis. S. Kopetz: Intellectual property rights: Amgen, Array, Bayer, Genentech, Taiho; Ownership interest: MolecularMatch. J. Straub, R. Bruns, G. Massimini: Employee: Merck KGaA. R. Debenedetto: CEO: SFJ Pharmaceuticals. R. Linke: CMO: SFJ Pharmaceuticals. J. Tabernero: Consulting or advisory role: Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai Pharma, Lilly, Merck Serono, MSD, Novartis, Pfizer, Roche, Sanofi, Symphony Evolution, Taiho Pharmaceutical, Takeda. All other authors have declared no conflicts of interest.

488P Histopathologic evaluation of patients with liver-limited metastatic colorectal cancer receiving mFOLFOX6 plus bevacizumab or mFOLFOX6 plus cetuximab: The ATOM trial

Y. Emi[1], T. Yamanaka[2], K. Muro[3], H. Uetake[4], E. Oki[5], T. Takahashi[6], Y. Katayose[7], K. Yoshida[6], M. Sakamoto[8], S. Aishima[9], K. Ishida[10], J. Imura[11], M. Unno[12], I. Hyodo[13], N. Tomita[14], K. Sugihara[4], Y. Maehara[5]

[1]Surgery, Saiseikai Fukuoka General Hospital, Fukuoka, Japan, [2]Department of Biostatistics, Yokohama City University Hospital, Yokohama, Japan, [3]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan, [4]Specialized Surgeries, Tokyo Medical and Dental University, Tokyo, Japan, [5]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [6]Surgical Oncology, Gifu University Hospital, Gifu, Japan, [7]Surgery, Tohoku Rosai Hospital, Sendai, Japan, [8]Pathology, Keio University School of Medicine, Tokyo, Japan, [9]Pathology and Microbiology, Saga University, Saga, Japan, [10]Molecular Diagnostic Pathology, Iwate Medical University, Morioka, Japan, [11]Diagnostic Pathology, University of Toyama, Toyama, Japan, [12]Surgery, Tohoku University Hospital, Sendai, Miyagi, Japan, [13]Department of Gastroenterology, University of Tsukuba, Tsukuba, Japan, [14]Surgery, Hyogo College of Medicine, Nishinomiya, Japan

Background: We previously reported the results of a randomized phase II controlled trial comparing mFOLFOX6 plus bevacizumab (Bmab) with mFOLFOX6 plus cetuximab (Cmab) for KRAS wild-type (wt) colorectal cancer (CRC) with liver-limited metastases that were not optimally resectable. The current study is the first to examine the role of histopathologic response based on the study data of anti-VEGF versus anti-EGFR antibody.

Methods: In the ATOM trial, KRAS wild-type CRC patients with liver-limited metastases were eligible if the number of lesions was more than 5 and/or the size of lesions was more than 5cm in the maximum diameter. The primary endpoint was progression-free survival (PFS). Of 116 eligible patients, patients who underwent liver metastasectomy were evaluated for histopathologic response in this study. Resected liver specimens were assessed by the independent pathological review committee. Preplanned pathological assessments included tumor regression grade (TRG), dangerous halo, and sinusoidal obstruction of resected liver specimens. Patients were categorized into major histopathologic response (MjHR) if they had TRG of 1 (viable tumor cells = 0%) or 2 (< 25%), partial histopathologic response (PHR) if they had TRG of 3 (< 50%), or no histopathologic response (NHR) if they had TRG of 4 (< 75%) or 5 (> 75%).

Results: A total of 59 patients had TRG evaluation based on resected specimens by liver metastasectomy. Of those, 55 (28 in Bmab arm, 27 in Cmab arm) were eligible for analysis. In the Bmab arm, the number of patients with MjHR/PHR/NHR was 12/1/15 (43/4/54%); in the Cmab arm, 13/10/4 (48/37/15%). Median PFS of patients with a MjHR or PHR/NHR was 8.3 or 4.4 months in the Bmab arm and Not Reached or 5.4 months in the Cmab arm. Patients with a MjHR had a longer PFS than those with a PHR/NHR in both the Bmab arm (hazard ratio [HR], 0.50 (95%CI, 0.19-1.28)) and the Cmab arm (HR, 0.17 (95%CI, 0.05-0.58)).

Conclusions: In the TRG assessment, the proportion of MjHR was similar between the two arms. The impact of MjHR on PFS as compared to PHR/NHR was observed in both arms. Further results regarding other assessments will be presented.

Clinical trial identification: NCT01836653.

Legal entity responsible for the study: ATOM study group.

Funding: Chugai Pharmaceutical.

Disclosure: All authors have declared no conflicts of interest.

489P Verification of guideline conform mCRC treatment with EGFR inhibitors with real-world evidence data from EU5 countries

L. Hoyer, N. Schmidt

BU Oncology, Real World Insights, IQVIA Commercial GmbH & Co. OHG, Frankfurt am Main, Germany

Background: The EGFR inhibitors cetuximab and panitumumab are indicated for patients suffering from metastatic colorectal cancer (mCRC), which are RAS wild-type. The aim of this analysis is to verify with real-world data whether the drug usage of those EGFR inhibitors reflects clinical guidelines with regards to their genomic profile.

Methods: Anonymized patients-level data collected through a large web-based survey between April 2017 and March 2018 was used. The study reported patient case history information across all cancer types in 5EU (France, Germany, Italy, Spain & UK). Treatment information and biomarker testing information on 5248 mCRC drug treated patients were analyzed.

Results: Evaluating KRAS and NRAS biomarkers status, real-world data analysis showed that 18,9% of mCRC patients were not tested for N-RAS mutation and 11,4% were not tested for K-RAS mutation. 16% of the mCRC population were RAS mutant. However, 3,2% of these patients received cetuximab and panitumumab even though they did not qualify for this treatment, due to their RAS mutation. Among all mCRC patients who were RAS wildtype, 49,4% of them received cetuximab or panitumumab.

Conclusions: This analysis of real-word data showed that biomarkers testing is not carried out in all mCRC patients. Secondly, the use of EGFR inhibitors in the RAS mutant mCRC patient population demonstrates a misalignment with clinical guidelines. Howver, most of patients receiving EGFR inhibitors are RAS wildtype, which implies that the majority of mCRC patients receiving EGFR inhibitors is treated according to medical guidelines regarding their genomic profile.

Legal entity responsible for the study: IQVIA Commercial GmbH & Co. OHG.

Funding: Has not received any funding.

Disclosure: L. Hoyer, N. Schmidt: Employee of IQVIA Commercial GmbH & Co. OHG.

491P Impact of delayed addition of anti-EGFR monoclonal antibodies on the outcome of first-line therapy in metastatic colorectal cancer patients: A retrospective registry-based analysis

T. Buchler[1], O. Fiala[2], V. Veskrnova[1], R. Chloupkova[3], A. Poprach[4], I. Kiss[4], K. Kopeckova[5], L. Dusek[3], L. Slavicek[6], M. Kohoutek[7], J. Finek[2], M. Svoboda[4], J. Dvorak[1], L.B. Petruzelka[8], B. Melichar[9]

[1]Oncology, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic, [2]Oncology, University Hospital Plzen, Plzen, Czech Republic, [3]Institute of Biostatistic and Analyses, Masaryk University Brno, Brno, Czech Republic, [4]Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic, [5]Oncology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic, [6]Oncology, Hospital Jihlava, Jihlava, Czech Republic, [7]Oncology, T Bata's Regional Hospital, Zlin, Czech Republic, [8]Oncology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic, [9]Oncology, Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic

Background: The addition of monoclonal antibodies against epidermal growth factor receptor (anti-EGFR Abs) to chemotherapy is commonly delayed in the real-world clinical practice, usually because of delays in obtaining RAS testing results. The aim of this retrospective registry-based analysis was to determine whether the delayed addition of anti-EGFR mAbs up to the fourth cycle of backbone chemotherapy adversely affects outcomes of mCRC patients treated with first-line regimens.

Methods: Clinical data of patients with RAS wild-type mCRC treated with first-line systemic therapy regimens containing anti-EGFR mAbs from a national database were analysed retrospectively. Patients were divided into three groups according to the timing of anti-EGFR mAbs addition to the chemotherapy backbone. Cohort A (n = 401) included patients with anti-EGFR mAbs added to chemotherapy from the first cycle, cohort B (n = 71) patients with anti-EGFR mAbs added to chemotherapy from the second cycle, and cohort C (n = 101) patients who had anti-EGFR mAbs added to chemotherapy from the third or fourth cycle. The chemotherapy backbone regimens consisted of FOLFOX or FOLFIRI regimens.

Results: 336 (58.6%) patients received panitumumab and 237 (41.4%) patients received cetuximab. The median progression-free survival (PFS) of the whole cohort was 12.2 months (95% confidence interval [CI] 10.9–13.5), and the median overall survival (OS) was 33.5 months (95% CI 27.6–39.4). Survival results for the cohorts defined by the time of addition of anti-EGFR MoAbs to chemotherapy are shown in the table. In a multivariate test, ECOG performance status and chemotherapy regimen were associated with PFS, whereas the site of primary tumour and chemotherapy regimen were associated with OS.

Table: 491P

Cohort	PFS (95% CI), months	Log-rank p-value	OS (95% CI), months	Log-rank p-value
A (n = 401)	12.9 (11.5–14.3)		30.6 months (25.2–36.1)	
B (n = 71)	9.7 (9.1–10.3)	A vs. B p = 0.185	Not reached	A vs. B p = 0.645
C (n = 101)	11.5 (9.8–13.2)	A vs. C p = 0.826	37.9 months (28.6–47.3)	A vs. C p = 0.052

Conclusions: Delayed addition of anti-EGFR mAbs up to the fourth cycle of first-line chemotherapy was not associated with inferior survival or response rates.

Legal entity responsible for the study: Tomas Buchler.

Funding: The institute of Biostatistics and Analysis, Faculty of Medicine, Masaryk University, Brno received financial support for the CORECT registry from Bayer, Amgen, Merck, and Roche.

Disclosure: T. Buchler, O. Fiala: Research funding, Travel grants, honoraria: Roche, Merck, Bayer, Servier, BMS, MSD, Sanofi, Amgen. A. Poprach: Honoraria, travel grants: Roche, Amgen. I. Kiss: Speakers' honoraria: Roche, Merck, Amgen. J. Finek: Lecture honoraria, travel grants: Roche, Merck, Pfizer, Novartis, Amgen. B. Melichar: Research funding, travel grants, Honoraria: Roche, Merck, Bayer, Servier, BMS, MSD, Sanofi, Amgen. All other authors have declared no conflicts of interest.

492P A multicenter phase II trial to evaluate the efficacy of mFOLFOX6+cetuximab as induction chemotherapy to achieve R0 surgical resection for advanced colorectal liver metastases (NEXTO trial)

Y. Nishioka[1], K. Hasegawa[1], A. Saiura[2], M. Oba[1], J. Yamamoto[3], Y. Nomura[4], T. Takayama[5], Y. Hashiguchi[6], M. Shibasaki[7], H. Sakamoto[8], S. Yamagata[9], N. Aoyanagi[10], H. Kaneko[11], H. Koyama[12], S. Miyagawa[13], Y. Mise[2], E. Shinozaki[14], S. Yoshida[15], H. Nozawa[16], N. Kokudo[1]

[1]Hepatobiliary-Pancreatic Surgery Division, Department of Surgery, The University of Tokyo, Graduate School of Medicine, Tokyo, Japan, [2]Department of Surgery, Cancer Institute Hospital of JFCR, Tokyo, Japan, [3]Department of Surgery, National Deffence Medical College, Tokorozawa, Japan, [4]Department of Surgery, Asahi General Hospital, Chiba, Japan, [5]Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan, [6]Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan, [7]Department of Surgery, JCHO Tokyo Yamate Medical Center, Tokyo, Japan, [8]Gastrointestinal Surgery, Saitama Cancer Center, Saitama, Japan, [9]Department of Surgery, JCHO Tokyo Shinjuku Medical Center, Tokyo, Japan, [10]Department of Surgery, Kohnodai Hospital, National Center for Global-Health and Medicine, Chiba, Japan, [11]Department of Surgery, Toho University Faculty of Medicine, Tokyo, Japan, [12]Department of Surgery, JCHO Tokyo Takanawa Hospital, Tokyo, Japan, [13]First Department of Surgery, Shinshu University, School of Medicine, Matsumoto, Japan, [14]Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan, [15]Department of Gastroenterology, The University of Tokyo, Graduate School of Medicine, Tokyo, Japan, [16]Department of Surgical Oncology, Tokyo University Hospital, Tokyo, Japan

Background: Hepatic resection is known to be the standard treatment for patients with colorectal liver metastasis (CRLM). The recent advancement in chemotherapy has led to the extended surgical indication and better outcome in patients with advanced CRLM. This phase II trial was designed to prospectively evaluate the validity of induction chemotherapy using mFOLFOX with cetuximab for advanced CRLM, which has been reported to provide early tumor shrinkage in CRLM with KRAS wild type.

Methods: Patients having advanced CRLM (tumor number > =5 and/or technically unresectbale) with KRAS wild type were included to this study. The induction of mFOLFOX with cetuximab was followed by the evaluation of surgical indication every 4 cycles (2 months). If all the tumors were regarded as technically resectable, we performed surgical resection after the waiting period of 1 month and postoperative chemotherapy was added until 12 cycles in total. If they were unresectable, we continued the regimen within the upper limit of 12 cycles. The primary endpoint was R0 resection rate. The secondary endpoints included recurrence free survival (RFS), progression free survival (PFS), and overall survival (OS).

Results: Between May 2012 and May 2015, total 50 patients were enrolled to this trial in 14 centers. The induction was not done in 2 patients, who were excluded. The median age of the 48 patients was 62.5 (range: 45 to 79) including 36 men and 12 women. The median tumor number detected by CT before the induction was 12 (1 to 57). R0 and R1 resections were performed in 26 and 5 patients, respectively (R0 resection rate: 54.2%), and there was no mortality. Under the median follow-up of 2.5 years, the 3-year RFS was 14.4%, 3-year PFS was 8.2%, 3-year OS was 60.0%, and median survival time was 3.4year.

Conclusions: For advanced CRLM with KRAS wild type, mFOLFOX with cetuximab induction therapy provided the sufficient R0 resection rate and favorable outcome.

Clinical trial identification: UMIN Clinical Trials Registry; C000007923.

Legal entity responsible for the study: The Institutional Review Board of each participating institutions.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

493P Initial report of a phase I/II study of S-1 and irinotecan (IRIS) in combination with cetuximab in patients with wild-type RAS metastatic colorectal cancer

E. Oki[1], H. Samura[2], H. Okumura[3], T. Ohchi[4], H. Orita[5], K. Kobayashi[6], T. Kinjo[7], S. Mori[8], T. Touyama[9], K. Ohgaki[10], H. Kawanaka[11], A. Makiyama[12], N. Ureshino[13], M. Kotaka[14], T. Shimose[15], H. Saeki[16], T. Nishimaki[17], H. Baba[18], Y. Maehara[19]

[1]Surgery and Science, Kyushu University Hospital, Fukuoka, Japan, [2]Surgery, Urazoe General Hospital, Okinawa, Japan, [3]Surgery, Kagoshima kouseiren hospital, Kagoshima, Japan, [4]Surgery, Social Insurance Tagawa Hospital, Kurume, Japan, [5]Department of Surgery, Nakatsu Municipal Hospital, Nakatsu, Japan, [6]Department of Surgery, Nagaski University Hospital, Nagasaki, Japan, [7]Surgery, Ryukyu University, Okinawa, Japan, [8]Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University, Kaghosima, Japan, [9]Surgery, Nakagami Hospital, Okinawa, Japan, [10]Surgery, Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuoka, Japan, [11]Surgery, National Beppu Medical Center, Beppu, Japan, [12]Medical Oncology, Japan Community Healthcare Organization Kyushu Hospital, Fukuoka, Fukuoka, Japan, [13]Medical Oncology, Saga-Ken Medical Center Koseikan, Saga, Japan, [14]Surgery, Sano Hospital-Gastrointestinal Cancer Centre, Kobe, Hyogo, Japan, [15]Biostatistics, Clinical Research Support Center Kyushu, Fukuoka, Japan, [16]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [17]Unit of OrganOriented Medicine Division of Digestive and General Surgery First Depertment of Surgery, Ryukyu University, Okinawa, Japan, [18]Gastrointestinal Surgery, Kumamoto University, Kumamoto, Japan, [19]Kyushu Central Hospital of the Mutural Aid Association of Public School Teachers, Fukuoka, Japan

Background: Combination therapy with oral fluoropyrimidine and irinotecan with cetuximab has not yet been established as first-line treatment of metastatic colorectal cancer (mCRC). This study was designed to assess the tolerability of different doses of tri-weekly intravenous infusion of irinotecan in combination with S-1 (IRIS) and weekly cetuximab (phase I) and explore the efficacy and safety of the IRIS in combination with cetuximab in patients with mCRC (phase II).

Methods: Main eligibility was RAS (exon 2) wild-type mCRC and without any prior chemotherapy except for adjuvant therapy. S-1 was given orally at a dose of 40 mg/m^2 (40-60mg) twice for 2 weeks, followed by a 1-week rest. Irinotecan (150mg/m^2) was given on days 1. Cetuximab was administered on days 1 (400 mg/ m^2), 8 (250 mg/ m^2) and 15 (250 mg/ m^2), followed by every week (250 mg/ m^2) thereafter. A standard 3 + 3 phase I dose de-escalation design was utilized to decide maximum tolerant dose (MTD) and recommend dose (RD) of irinotecan. Primary endpoint of Phase II part was overall response rate (ORR). We set the expected and threshold RRs at 60% and 40%, respectively. ORR was assessed by central office according to RECIST version 1.1 criteria.

Results: Between December 2014 and September 2017, 58 patients were enrolled. Seven patients were excluded owing to ineligibility. No dose limiting toxicity was observed in phase I part and RD irinotecan was decided at 150mg/m^2. In phase II part, the treatment response with confirmation was complete response (CR) in 1, and partial response (PR) in 28, stable disease (SD) in 15, progressive disease (PD) in 6, not evaluated (NE) in 1, final response rate was 56.9% (90 %; CI 44.4 – 68.7 %, p = 0.011). The safety profile revealed the common Grade 3/4 adverse events to be neutropenia (31.4%), appetite loss (27.5%), hypokalemia (11.8%) and diarrhea (11.8%). Grade 3/4 HFS occurred in 9 patients (9.8%).

Conclusions: This study showed the efficacy and safely was comparable to other first line treatment regimens. The results support IRIS/cetuximab is more convenient and provide treatment flexibility in first line treatment with metastatic colorectal cancers.

Clinical trial identification: UMIN000015835.

Legal entity responsible for the study: This work was supported by CReS Kyushu with funding from Merck Serono, Japan, under a research contract.

Funding: Merck Serono.

Disclosure: E. Oki: Honoraria for lecturing: Bayer Yakuhin, Ltd, Japan; Eli Lilly Japan K.K.; Taiho Pharmaceutical Co., Ltd.; Yakult Honsha Co., Ltd.; Merck Serono Co., Ltd.; Takeda Pharmaceutical Co., Ltd.; Johnson & Johnson K.K.; and Chugai Pharmaceutical Co., Ltd. M. Kotaka: Honoraria lecturing: Chugai Pharmaceutical Co., Ltd. H. Baba, Y. Maehara: Lecture fees: Taiho Pharm; Grant research funding: Taiho Pharm, Merck Serono, Yakult Honsha, Japan. All other authors have declared no conflicts of interest.

494P A multi-institutional randomized phase II study on the timing of oxaliplatin plus 5-fluorouracil (FOLFOX) for patients (pts) with operable stage III rectal cancer: The KIR study

P. Kavan[1], I. Barrera[1], L. Azoulay[1], A-G. Martin[2], C. Vasilevsky[1], M. Boutros[1], E. Ferland[3], G. Batist[1], T. Vuong[1]

[1]Oncology, Jewish General Hospital McGill University, Montreal, QC, Canada, [2]Oncology, CHU de Quebec Laval, Montreal, QC, Canada, [3]Oncology, CHUM, Montreal, QC, Canada

Background: Recent randomized studies have shown low compliance to adjuvant chemotherapy in stage III rectal cancer pts who received preoperative combined chemotherapy and external beam radiation (CT/EBRT) with total mesorectal excision (TME surgery). We examined whether giving part of the chemotherapy prior to radiotherapy (delivered by brachytherapy (HDRBT)) and surgery (instead of chemotherapy after RT and surgery, which is the current standard of care) for pts with node positive operable rectal cancer, would result in higher pt compliance to chemotherapy.

Methods: Between 2010-2017, 180 eligible pts were randomly assigned (2:1) to two arms, 6 cycles of FOLFOX prior to radiotherapy and surgery following by 6 cycles of FOLFOX in adjuvant (Arm A, (AA)), or 12 cycles of FOLFOX in adjuvant (Arm B, (AB)). The primary end point was compliance to chemotherapy (pts receiving at least 85% of full-dose CT prescribed at each cycle (x 12 cycles), 1 yr post-diagnosis); secondary end points were disease free survival rate (DFS), pT0N0, local recurrence rate and overall survival (OS), 5 yrs post-surgery.

Results: All pts were randomly assigned to either AA (n = 120; 84 pts were male (M), median age (MA) was 65 years) or AB (n = 60; 35 pts were M, MA was 63.5 years). Compliance on AA was 78% and 51.9% on AB. Levels of G3/G4 toxicity were 30.8% in AA and 28.3% in AB respectively. 174 of 178 pts completed HDRBT as planned (97.7%). In AA, 3 pts progressed locally under CT. 1 pt refused HDRBT after randomization in AB. pT0N0 for AA and AB were 35pts (30.1%) and 15 pts (25%). The 3-year DFS was 80% with AA and 76% with AB (p = 0.6511). The 3-year OS for AA and AB were 94% and 85%, respectively (p = 0.8219).

Conclusions: The safety and improved compliance to neoadjuvant CT is confirmed in this study using HDRBT as a neoadjuvant modality for rectal cancer. There is no statistical difference in pT0N0 rate, local recurrence, and DFS between the two arms in the early result analysis, but favorable oncological outcomes are observed. At the time of this reporting, pelvic nodal recurrence is seldom isolated, asymptomatic and preceded by systemic failure.

Clinical trial identification: NCT01274962.

Legal entity responsible for the study: Jewish General Hospital-McGill.

Funding: Sanofi.

Disclosure: All authors have declared no conflicts of interest.

495P Tumor regression grading after preoperative hyperfractionated radiotherapy/chemoradiotherapy for locally advanced rectal cancers: A phase III clinical study

A. Idasiak[1], K. Galwas-Kliber[1], K. Behrendt[1], I. Wziętek[2], M. Zeman[3], E. Stobiecka[4], E. Chmielik[4], T. Dworzecki[2], R. Suwiński[1]

[1]Radiotherapy and Chemotherapy Clinic and Teaching Hospital, Maria Sklodowska Curie MSC Memorial Cancer Institute in Gliwice, Gliwice, Poland, [2]Radiotherapy Department, Maria Sklodowska Curie MSC Memorial Cancer Institute in Gliwice, Gliwice, Poland, [3]Department of Surgery, Maria Sklodowska Curie MSC Memorial Cancer Institute in Gliwice, Gliwice, Poland, [4]Department of Pathology, Maria Sklodowska Curie MSC Memorial Cancer Institute in Gliwice, Gliwice, Poland

Background: We investigated tumor regression grading (TRG) as a prognostic marker for disease-free survival (DFS) in patients with advanced rectal cancer treated within phase III randomized study. The study was prospective trial of preoperative hyperfractionated radiotherapy (HART) compared with concomitant hyperfractionated radiotherapy with co-administration of chemotherapy based on 5FU (HART-CT) in patients with T2/N+ or T3/any N resectable mid-low primary rectal cancer.

Methods: The 136 patients were randomly assigned to HART (n = 69) and HART-CT (n = 67). The pelvis was irradiated twice a day (28 fractions of 1.5 Gy), with a minimal interfraction interval of 8 hrs to total dose 42 Gy over 18 days (HART) or mentioned scheme with concurrent chemotherapy: 5FU-325mg/m^2 (bolus) on days 1-3 and days 16-18 (HART-CT). Surgery was performed 5-6 weeks after HART/HART-CT. The TRG was recorded using 4-point scale: TRG0 (pCR) denoted no cancer cells; TRG1 - cancer cells less than 10% of a tumor mass; TRG2 cancer cells in 10-50% or TRG3 - cancer cells in more than 50% of tumor mass. Multivariable analysis was performed using Cox regression models adjusted for treatment arm, resection status and pathologic stage. Cox proportional hazard model was used in survival analysis.

Results: The crude rate of patients with any serious adverse events during the follow-up was 12% vs. 17% for HART and HART-CT. Anterior resection was performed in 52% vs. 62% for HART and HART-CT respectively (p = 0.06). Of the 136 patients evaluable for pathologic response there were 3(4%) vs. 9(13%), 16(23%) vs. 24(36%), 40(58%) vs. 30(45%), and 10 (15%) vs. 4(6%) patients with TRG 0, 1, 2 and 3, respectively in HART vs. HART-CT, the difference was statistically significant p = 0.002. The actuarial 2-year cumulative loco-regional relapse free survival control rates (LRC) for HART vs.

HART-CT were 86% vs. 91% and actuarial DFS control rates were 70% vs. 76%, respectively.

Conclusions: Significant differences in the tumor regression grading (TRG) were found. Both LRC and DFS of rectal cancer patients treated with HART vs. HART-CT had favorable outcomes in those allocated to HART-CT. Also the sphincter preservation rate tended to favor HART-CT.

Clinical trial identification: NCT01814969.

Legal entity responsible for the study: Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, 44-100 Gliwice, Poland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

496P Short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR): A planned interim analysis

J. Jin[1], Y. Tang[1], S. Liu[2], Y. Zhu[3], W. Wang[4], G. Li[5], X. Wang[6], J. Wang[7], J. Yang[8], S. Li[1], N. Li[1], W. Liu[1], Y. Li[1], Y. Chi[9], A. Zhou[10], J. Huang[9], X. Wang[11], L. Jiang[12], J. Jiang[12], S. Zou[13]

[1]Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China, [2]Radiation Oncology, Jilin Provincial Cancer Hospital, Changchun, China, [3]Radiation Oncology, Zhejiang Provincial Cancer Hospital, Hangzhou, China, [4]Radiation Oncology, Guizhou Provincial Cancer Hospital, Guiyang, China, [5]Radiation Oncology, Beijing Hospital, Beijing, China, [6]Radiation Oncology, West China Hospital, Sichuan University, Chengdu, China, [7]Radiation Oncology, Hebei Provincial Cancer Hospital, Shijiazhuang, China, [8]Radiation Oncology, Sichuang Provincial Cancer Hospital, Chengdu, China, [9]Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China, [10]Department of Medical Oncology, National Cancer Center/Cancer Hospital,Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [11]Colorectal Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China, [12]Radiology Department, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China, [13]Pathology Department, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

Background: At present, distant metastasis remains the main cause of failure for locally advanced rectal cancer (LARC), efficient short-course radiotherapy (SCRT) combined with neoadjuvant chemotherapy is an attempt of optimizing pre-operative treatment.

Methods: We did this randomized, phase III study in multiple centers in China. Patients with middle or lower rectal adenocarcinomas, staged cT_{3-4} and/or N_{1-2} by MRI, were randomly assigned to receive 5Gy × 5 and 4 courses of CAPOX (experimental group) or 50 Gy in 25 fractions concurrently with capecitabine (control group). TME in both groups was performed 6-8 weeks later, then two or six courses of CAPOX as postoperative chemotherapy was prescribed in experimental or control group, respectively. The purpose of this interim analysis was focusing on the compararison of primary enrolled 100 patients.

Results: Initially enrolled 100 patients, 51 in experimental group and 49 in control group were analyzed, with MRF+ 27.5% vs. 30.6%, MRI based T_{3-4} 92.2% vs. 98.0%, N_{1-2} 74.5% vs. 77.6%, and EMVI $scores_{3-4}$ 52.9% vs. 65.3% in each group. The completion rates of neoadjuvant treatment were 98.0% vs. 100% ($p = 0.325$), with incidences of grade III-IV toxicity 17.6% vs. 4.1% ($p = 0.076$) in each group, respectively. 80 patients completed surgery and 7 patients (all in experimental group) chose "watch-and-wait" policy due to clinical complete remission (cCR) after neoadjuvant treatment. 92.9% and 89.5% of patients in experimental and control group had R_0 resection ($p = 0.593$), while 26.2% and 5.3% of them achieved $_{yp}T_0N_0$ ($p = 0.011$), respectively. The completion rates of adjuvant chemotherapy were 76.2% vs. 65.8% ($p = 0.305$) in each group, respectively. On the whole, the patients who had received 6 cycles of chemotherapy accounted for 62.7% vs. 49.0% ($p = 0.000$) in experimental and control group, and there were 76.5% and 49.0% of patients who could complete all planned treatments in each group, respectively.

Conclusions: The interim analysis revealed the acute toxicity and surgical complication were acceptable and comparable in both groups, however, the people in experimental group showed better treatment completion.

Clinical trial identification: NCT02533271.

Legal entity responsible for the study: National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College.

Funding: Collaborative Innovation Center for Cancer Medicine [No. XT2015-03].

Disclosure: All authors have declared no conflicts of interest.

497P mFOLFOXIRI versus mFOLFOX6 as neoadjuvant chemotherapy in locally advanced rectal cancer: A propensity score analysis from two prospective trials

J. Zhang, Y. Deng, Z. Wu, H. Hu, Y. Cai, J. Ling

Medical Oncology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Neoadjuvant chemoradiotherapy (CRT) is the standard of treatment for locally advanced rectal cancer, but it delays administration of systemic chemotherapy, leading to high incidence of distant metastases. To enhance systemic chemotherapy and avoid the damage of radiation, full dose of neoadjuvant chemotherapy regimens with mFOLFOXIRI or mFOLFOX6 were both under investigation. Here, we aimed to compare the safety and efficacy of preoperative chemotherapy with mFOLFOXIRI versus mFOLFOX6 in locally advanced rectal cancer.

Methods: Prospectively maintained databases of patients from two clinical trials (NCT01211210 and NCT02217020) underwent preoperative treatment for locally advanced rectal cancer in a single center were included. Those had received mFOLFOXIRI or mFOLFOX6 chemotherapy alone preoperatively was selected for this study, including 90 patients with mFOLFOXIRI and 119 patients with mFOLFOX6. All patients had undergone total mesorectal excision. A comparative analysis was performed after the implementation of propensity score matching on the 2 main cohorts (mFOLFOXIRI and mFOLFOX6).

Results: A total of 209 patients were enrolled in the study. After propensity score matching, 180 patients were selected. 90 patients were comparable in the two groups. Higher pathologic complete response rate was observed in mFOLFOXIRI group than that of mFOLFOX6 group (16.7% vs. 5.6%, $p = 0.03$), although the tumor downstaging (ypT0-2N0M0) rate was comparable in this two group (41.1% vs. 37.8%, $P = 0.76$). The anal preservation rate was similar between the two groups (87.8% vs. 89.2%). Higher incidence of grade 3/4neutropenia (42.2% vs. 10%, $P < 0.001$) was shown in mFOLFOXIRI group than that of mFOLFOX6 group.

Conclusions: Preoperative mFOLFOXIRI chemotherapy showed higher pCR rate than that of mFOLFOX6. The tumor downstaging rate was comparable between the two regimens. But the adverse events were more common in mFOLFOXIRI group. Whether the intensive regimen would improve the survival is unknown. Further follow-up is needed.

Clinical trial identification: NCT01211210 and NCT02217020.

Legal entity responsible for the study: Yanhong Deng.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

498P Phase I/II study of valproic acid (VPA) and short-course radiotherapy (SCRT) plus capecitabine (CAP) as preoperative treatment in low-moderate risk rectal cancer (V-shoRT-R3)

A. Budillon[1], P. Delrio[2], B. Pecori[2], F. Tatangelo[3], E. Di Gennaro[1], C. Romano[2], V. D'Angelo[2], P. Marone[2], C. Granata[4], E. Cavalacanti[5], A. De Stefano[2], U. Pace[2], F. Bianco[2], A. Petrillo[6], S. Lastoria[6], G. Botti[3], P. Muto[7], F. Perrone[8], M.C. Piccirillo[8], A. Avallone[9]

[1]Experimental Pharmacology Unit, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [2]Abdominal Oncology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [3]Pathology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [4]Radiology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [5]Clinical Pathology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [6]Radiology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy, [7]Radiotherapy, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [8]Translational Research, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [9]Abdominal Oncology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy

Background: Recurrence with distant metastases is the predominant pattern of failure in locally advanced rectal cancer (LARC), thus the integration of new agents into preoperative fluoropyrimidine-based chemo-radiotherapy represents a clinical challenge to intensify the therapeutic strategy. We have recently reported synergistic antitumor interaction between valproic acid (VPA), an histone-deacetylase inhibitor, capecitabine (CAP) and radiotherapy in colorectal cancer preclinical models.

Methods: We planned two parallel phase-1 studies in low-moderate risk LARC patients (pts) to assess the safety of preoperative short-course radiotherapy (SCRT) (5 Gy/day on days 1 to 5 days) combined with (a) CAP alone (4 increasing dose levels: 500 to 825 mg/m2/bid, on days -1 to 20), or (b) CAP as above plus VPA (orally on days -14 to 21, with an intra-patient titration for a target serum level of 50-100 μg/ml), followed by surgery 8 weeks after the end of SCRT. Within each of the two phase-1 trials, maximum tolerated dose (MTD) was defined as the dose level that produces a dose-limiting toxicity (DLT) occurring within 5 weeks from day 1 of treatment in more than one-third of pts. Correlative studies on pharmacokinetic and pharmacodynamics biomarkers on both tumor and peripheral blood samples as well as FDG-PET were also planned.

Results: From Apr 2013 and Oct 2018, 28 pts were enrolled in the two phase-1 studies. Median age was 61 (range 46-71), 100% were PS 0. No DLT occurred with CAP alone, but a symptomatic angina occurred in a patient at the first dose level of CAP plus VPA. However, no DLT was observed within the further 3 pts enrolled at the same level, nor

at the following dose levels. All but one pts underwent R0 resection. TRG1 was obtained in 6 pts, TRG2 in 11 pts, TRG3 in 8 pts and TRG4 in 3 pts.

Conclusions: The addition of CAP to preoperative SCRT +/- VPA is feasible and 825 mg/m2/bid is the recommended dose that will be used in an ongoing phase-2 trial, aimed to explore whether the addition of VPA and/or CAP to preoperative SCRT might increase TRG1 rate in low-moderate risk LARC pts.

Clinical trial identification: NCT01898104.

Legal entity responsible for the study: Istituto Nazionale Tumori Fondazione G. Pascale.

Funding: Italian Ministry of Health, Grant RF-2011-02346914 to AB.

Disclosure: All authors have declared no conflicts of interest.

499P A classifier of 53BP1, immune score and texture analysis of MRI images can predict pathological response to chemoradiotherapy in locally advanced rectal cancer

H. Ma, J. Yao, A. Huang, Y. Xiao, L. Fan

Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Preoperative chemoradiotherapy is the standard care for advanced rectal cancer. Yet, predicting the response remains a challenge. Our previous studies found that 53BP1 protein deletion leaded to chemoradiotherapy resistance.53BP1 deficiency played pivotal role in inducing lymphocyte mature. As the development of functional imaging, texture analysis can predict response to chemoradiotherapy. Our study aims to explore the relationship among 53BP1 protein, immune score, texture analysis and radiation sensitivity, then set a new classifier to predict response in advanced rectal cancer.

Methods: We enrolled 57 advanced rectal cancer patients who received neoadjuvant chemoradiotherapy in Wuhan Union hospital from January 2015 to January 2018. The expression of 53BP1, CD3, CD8, CD45RO was detected by immunohistochemistry. Immune score were calculated, which are based on the combination of two lymphocyte populations (CD3/CD45RO, CD3/CD8 or CD8/CD45RO) both in the center (CT) and the invasive margin (IM) of tumors. T2W MRI images studies obtained in 34 patients before treatments, texture analysis by manually delineating a region of interest. The response rate, anus preservation rate were collected. The relationship among 53BP1 protein, immune score, texture analysis parameters and radiation sensitivity were explored by t-test. A new classifier was set to predict pathological response.

Results: The results indicated that the response rate in 53BP1 deletion group was significantly lower than that in 53BP1 high expression group (25.00% vs.84.44%, $P < 0.005$). "CD3+CD8" is the most reasonable immune score, the patients of 53BP1 deletion had lower immune score. The response rate in lower immune score group was lower than higher immune score group (54.54% vs.88.57%, $P < 0.005$). Texture analysis parameters were related with response rate. We set a new classifier to predict response in advanced rectal cancer, we randomly selected 10 patients as training group, others were selected as predict group, the accuracy is 83.33%.

Conclusions: A classifier of 53BP1, immune score and texture analysis of MRI can predict response in advanced rectal cancer.

Legal entity responsible for the study: Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Funding: 2015CFB659.

Disclosure: All authors have declared no conflicts of interest.

500P Mismatch repair deficient rectal cancer is resistant to induction combination chemotherapy

A. Cercek[1], G. Dos Santos Fernandes[2], C. Roxburgh[3], S. Ng[4], R. Yaeger[1], N. Segal[1], K. Ganesh[1], D. Reidy[1], J.J. Smith[5], G. Nash[5], J. Guillem[5], P. Paty[5], J. Shia[6], J. Garcia-Aguilar[5], L. Diaz[1], C. Crane[4], K. Goodman[4], L. Saltz[7], M. Weiser[5], Z. Stadler[2]

[1]Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]GI Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3]Surgical Oncology, MSKCC, New York, NY, USA, [4]Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [5]Surgery, MSKCC, New York, NY, USA, [6]Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [7]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: Although most rectal cancers are responsive to combination induction chemotherapy, the sensitivity of mismatch repair deficient (MMR-D) rectal cancers to chemotherapy remains uncertain.

Methods: MMR-D rectal tumor cases were retrospectively reviewed with tabulation of baseline characteristics, treatment modalities and clinical outcomes. Prevalence of germline mutations in the MMR genes, diagnostic of Lynch syndrome (LS), was compared to LS-associated colon cancer patients. We also assessed somatic mutational status for a subset of these patients.

Results: Twenty of the 49 patients received induction chemotherapy with 5FU and oxaliplatin, 15 received standard neoadjuvant chemoradiation, and 14 proceeded directly to surgery. Of the 15 patients treated with induction chemoradiation, 93% ($n = 14$) experienced radiographic response and tumor downstaging; and none of these patients showed evidence of disease progression. In contrast, of the 18 patients treated with induction chemotherapy alone, only 61% ($n = 11$) experienced tumor response and 28% ($n = 5$) of patients demonstrated progressive disease while on therapy. The majority of these cases, 82% (41/50) harbored germline mutations in the MMR genes and the observed prevalence of germline MSH2 and MSH6 mutations was significantly higher in the rectal ($n = 41$) versus colon ($n = 244$) cancer patients (rectal vs colon: MSH2: 57% vs 37%; MSH6: 20% vs 11%; p-value <0.0005).

Conclusions: Patients with MMR-D rectal tumors appear to have a high chance of disease progression on induction chemotherapy. As opposed to LS-associated colon cancers, LS-associated rectal cancers are more likely to harbor MSH2 or MSH6 germline mutations. Upfront testing for MMR status and initial treatment with chemoradiation in MMR-D rectal tumors should be undertaken until better therapies are available.

Legal entity responsible for the study: Andrea Cercek.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

501P Outcomes of chemoradiotherapy plus local excision in patients with clinical T1 or T2, N0 rectal cancer

T. Suzuki, S. Sadahiro, T. Ogimi, H. Miyakita, G. Saito, K. Okada, A. Tanaka

Surgery, Tokai University School of Medicine, Isehara, Japan

Background: NCCN guidelines recommend local excision (LE) as a standard treatment for selected patients with cT1/T2,N0,M0 rectal cancer. However, the rates of local recurrence after LE alone were 12.5% in cT1 disease and 22.1% in cT2 disease and those after total mesorectal excision (TME) were 6.9% and 15.1%, respectively. In pathological T1 disease, adding (chemo)radiotherapy (CRT) to LE decreased the rate of local recurrence to 5%, which was comparable to the rate after TME (4%). In pT2 disease who underwent LE, the local recurrence rate decreased slightly but remained high (14%) even after CRT.

Methods: In our institution, patients with cT1, N0 disease with a tumor diameter of less than 30 mm underwent transanal full thickness LE and additionally receive CRT (40/45Gy plus UFT or S-1). Patients with poorly differentiated adenocarcinoma or mucinous carcinoma should additionally undergo TME. Patients with cT2, N0 disease underwent transanal LE after CRT. Patients whose tumors include poorly differentiated adenocarcinoma or mucinous carcinoma should receive TME.

Results: In accordance with these treatment policy, LE was performed in 65 patients with cT1, N0 disease, 50 of whom additionally received CRT. The median follow-up was 71 months. Local recurrence occurred in 1 patient (2%), and distant metastasis occurred in 3 patients (6%). The 5-year disease-free survival rate (5y DFS) was 86%, and the 5-year overall survival rate (5y OS) was 92%. Patients with pT1 disease who had local nodal recurrence underwent abdominoperineal resection and are still alive with no recurrence. In 53 patients with cT2, N0 disease, LE was performed after CRT. Four patients had pT3 disease and additionally underwent TME. In the other 49 patients, six patients (12%) had local recurrence at the anastomotic site, and 7 (14%) had distant metastasis. The 5y DFS was 70%, and the 5y OS was 87%.

Conclusions: These results suggested that multidisciplinary treatment combining chemoradiotherapy with local excision is a treatment option in some patients with a preoperative diagnosis of clinical T1, N0 or T2, N0 rectal cancer. However, further studies are needed to determine the optimal treatment for patients with clinical T2, N0 rectal cancer.

Legal entity responsible for the study: Sotaro Sadahiro.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

502P Comparison of immune microenvironment between different neoadjuvant radiotherapy regimens for rectal cancer

J. Wu, Q. Peng, J. Li, L. Tang, Y. Huang, X. Zhang

Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, China

Background: Conventionally neoadjuvant radiotherapy regimens for rectal cancer are long-course radiotherapy in combination with chemotherapy (LCRT) and short-course radiotherapy (SCRT). We aimed to compare the different immune microenvironment in patients between two the different radiotherapy regimens.

Methods: The expression of LAG-3, CD8 and CD3 was detected by immunohistochemistry on specimen of 76 rectal cancer patients following neoadjuvant treatment. The expression of proteins was assessed as the percentage of positive cells (PP). The variation of proteins expression was compared by Mann-Whitney U test analysis.

Results: LCRT was given in 40 (52.6%) patients and the rest 36 (47.4%) patients were SCRT. The median PP of immune cells LAG-3 expression was 15% (range, 0% - 80%) in all patients. The expression of CD8 and CD3 were 10% (range, 0 - 80%) and 30% (range, 0 - 90%), respectively. The LAG-3 expression was high in patients with SCRT

compared to LCRT (22.5% vs. 8.0%, P = 0.0440). On the contrary, CD8+ cells were high in LCRT (15% vs. 8%, P = 0.0146). No difference was observed in CD3+ cells.

Conclusions: Tumor microenvironment might be modified by different fractions and dose. Immune cells LAG-3 expression were high with respect to SCRT. The diverse expression pattern of LAG-3 between SCRT and LCRT supporting the different combination strategies of immune checkpoint blockade and neoadjuvant radiotherapy.

Legal entity responsible for the study: Junxin Wu.

Funding: National Clinical Key Specialty Construction Program, The Fujian Province Natural Science Foundation (2017J01260).

Disclosure: All authors have declared no conflicts of interest.

503P Prognostic factors of chemo-radiotherapy efficacy in patients with locally-advanced rectal cancer

M. Fedyanin[1], A. Tryakin[1], I. Pokataev[1], A. Bulanov[1], O. Sekhina[1], D. Chekini[1], S. Gordeev[2], V. Aliev[2], D. Kuzmichev[2], Z. Mamedli[2], Y. Barsukov[2], V. Glebovskaya[3], S. Tkachev[3], M. Chernykh[4], N. Kozlov[5], S. Tjulandin[1]

[1]Clinical Pharmacology and Chemotherapy, Federal State Budgetary Institution «N.N. Blokhin National Medical Research Center of Oncology» of the Ministry of Health of the Russian Federation, Moscow, Russian Federation, [2]Surgery, Federal State Budgetary Institution «N.N. Blokhin National Medical Research Center of Oncology» of the Ministry of Health of the Russian Federation, Moscow, Russian Federation, [3]Radiotherapy, Federal State Budgetary Institution «N.N. Blokhin National Medical Research Center of Oncology» of the Ministry of Health of the Russian Federation, Moscow, Russian Federation, [4]Radiotherapy and Surgery, Federal State Budgetary Institution «N.N. Blokhin National Medical Research Center of Oncology» of the Ministry of Health of the Russian Federation, Moscow, Russian Federation, [5]Morphology, Federal State Budgetary Institution «N.N. Blokhin National Medical Research Center of Oncology» of the Ministry of Health of the Russian Federation, Moscow, Russian Federation

Background: We decided to evaluate preoperative clinical factors associated with progression free survival, overall survival and tumor regression in patients with locally-advanced rectal cancer after chemo-radiotherapy.

Methods: we analyzed prospective database of patients with locally-advancded rectal cancer (cT3-4N0-2M0) who received preoperative chemo-radiotherapy followed by surgery in our center from 2004 to 2013. Multivariate regression analyses was performed to evaluate odds of absent morphological response (Dworak tumo regression rate system 0-2) and hazards of progression and deaths. Statistical analyses was performed with SPSS v.20.

Results: Chemo-radiotherapy followed by surgery was performed in 457 patients with locally-advanced rectal cancer. The median f.-up was 46 months (2-141), 3-year progression free survival and overall survival were 79% and 91%, respectively. Multivariate regression analyses revealed factors associated with tumor regression rate 0-2 as high level (above normal range) CEA (carcinoembryonic antigen) before chemo-radiotherapy (OR 1.49 95%CI 1.11-2.02, p = 0.008), neutrophils count ≥ 7,000/µl (OR 2.29, 95%CI 1.0-5.2, p=0.05) and cT4 (OR 3.73, 95%CI 2.03-6.86, p < 0.001). Independent negative prognostic factors for progression free survival were perineural invasion (HR 3.1, 95% CI 1.43-6.89, p<0,001), neutrophil/lymphocyte ratio before surgery ≥ 3 (HR 1.8, 95%CI 1.37-2.42, p=0.01) and ypT3-4 or/and N + (HR 1.82, 95%CI 0.45-0.92, p<0.01). For overall survival: ypT3-4 or/and N + (HR 1.9, 95%CI 1.3-2.65, p<0.01), lymphatic vessel invasion (HR 2.4, 95%CI 1.27-4.59, p<0.01) and leucocytes count before surgery ≥11,000/µl (HR 3.1, 95%CI 1.33-7.33, p<0.01).

Conclusions: ypTNM after preoperative chemo-radiotherapy more effective than cTNM predicts progression free and overall survival in patients with localy-advanced rectal cancer.

Legal entity responsible for the study: Mikhail Fedyanin.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

504P Association of systemic and local inflammation with prognosis in rectal cancer treated with neoadjuvant radiotherapy

J. Li[1], X. Zhang[2], Y. Huang[2], L. Tang[2], Q. Peng[2], J. Wu[1]

[1]Department of Radiation Oncology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, Fujian, China, [2]Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fuzhou,Fujian, China

Background: To explore the characteristics of cancer-associated systemic and local inflammation and its impact on overall survival (OS) in locally advanced rectal cancer (LARC) treated with neoadjuvant radiotherapy (RT).

Methods: A consecutive cohort of 76 LARC patients underwent neoadjuvant RT were retrospectively analyzed from February 2012 to September 2015. Peripheral neutrophil to lymphocyte ratio (NLR) was calculated at diagnosis, and tumor-infiltrating lymphocyte was examined in postoperative tumor tissue by immunohistochemistry. The association between clinicopathological features and inflammation was explored through chi-square test. The prognostic factors in terms of OS were investigated through uni- and multivariate Cox regression. SPSS 22.0 was used for statistical analyses.

Results: The median follow-up time was 29.0 months (range, 2-59). The 1-, 3- and 5-year OS rates were 93.4% (95%CI 87.91-98.89), 80.0% (95%CI 69.81-90.19) and 68.6% (95%CI 46.06-91.14), respectively. High NLR (≥2.0) and low CD8+ T-cells (<9%) were more common in 76 patients (53.9% and 59.2%, respectively). For patients with high NLR and low CD8+ T-cells, 5-year OS was significantly worse than those with low NLR and high CD8+ T-cells (P = 0.005). Also, NLR ≥ 2.0 was associated with poor tumor regression after neoadjuvant RT (P = 0.039), while no significant association was found between CD8+ T-cells and tumor regression. In addition, NLR was related to lymphovascular invasion (P = 0.031). CD8+ T-cell was related to neural invasion (P = 0.048) and mucinous adenocarcinoma (P = 0.045). Furthermore, NLR (HR 7.71, 95%CI 1.30-45.71, P = 0.025), CD8+ T-cells (HR 0.09, 95%CI 0.01-0.67, P = 0.018) , age (HR 16.1, 95%CI 1.56-167.15, P = 0.020), lymphovascular invasion (HR 7.17, 95%CI 1.12-46.05, P = 0.038) and T stage (HR 0.03, 95%CI 0.00-0.45, P = 0.011) were independent risk factors for prognosis according to multivariate Cox regression.

Conclusions: High NLR and low CD8+ T-cells were significantly associated with dismal survival. Systemic combined with local inflammation might help to predict prognosis of LARC with neoadjuvant RT.

Legal entity responsible for the study: Jun-xin Wu.

Funding: National Clinical Key Specialty Construction Program.

Disclosure: All authors have declared no conflicts of interest.

505P Early prediction of histopathological response by PET/CT after two weeks of neoadjuvant chemoradiotherapy for rectal cancer: Wishful thinking or reality?

Y. Kundel[1], G. Natalia[2], H. Berenshtain[2], J. Prus[3], B. Brenner[3]

[1]Radiation Oncology, Rabin Medical Center Davidoff Cancer Centre, Beilinson Campus, Petah Tikva, Israel, [2]Radiology, Rabin Medical Center Beilinson Campus, Petah Tikva, Israel, [3]Oncology, Institute of Oncology, Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petach Tiqva, Israel

Background: Neoadjuvant chemoradiotherapy (CRT) is standard in locally advanced rectal cancer (LARC). Current data on the predictive value of early PET/CT, i.e. the correlation between the tumor's early metabolic response, manifested by the reduction of its ^{18}F-FDG uptake after two weeks of CRT compared with baseline, and histopathological response, are conflicting.

Methods: Patients (pts) with histologically confirmed LARC who were planned to receive standard CRT regimen of 50.4 Gray radiotherapy with concurrent fluoropyrimidine–based chemotherapy followed by radical surgery were eligible for the study. Baseline PET/CT was done within 4 weeks prior to CRT and the investigational scan was done two weeks+/-two days after its initiation. Maximum standardized uptake value (SUV-MAX) and the changes in FDG uptake between the two scans (ΔSUV-MAX) were compared with the histopathological response at surgery. Response was classified by tumor regression grade (TRG) and presence of pathological complete response (pCR).

Results: Twenty pts were included in the study, 65% with clinical stage II and 35% with stage III. Ninety percents of tumors were located at least 5 cm from the anal verge. Pts underwent surgery within a median of 8.6 weeks (4.5-12.8) after the completion of CRT. Six pts (30%) achieved pCR and 7 (35%) had TRG I-II. Absolute SUV-MAX values at both time points did not correlate with pCR (p = 0.099) nor with TRG (p = 0.670). Histopathological response also did not correlate with ΔSUV-MAX: pts who achieved pCR had median ΔSUV-MAX of -45%, while those who did not had median ΔSUV-MAX of -41% (p = 0.617). Similarly, pts with TRG I-II and those with TRG III-IV had the same median ΔSUV-MAX of -42% (p = 0.882). In addition, using ROC analysis we did not find any cutoff of any the PET-CT parameters that will predict pCR or TRG I-II.

Conclusions: In the current study, early PET/CT done after two weeks of neoadjuvant CRT for LARC, failed to predict histopathological response to treatment.

Legal entity responsible for the study: Rabin Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

506P Association between obesity and efficacy of chemoradiotherapy in rectal cancer patients

C. Diaz Romero[1], R.G. Calderillo[1], M. Herrera-Martínez[2], R.G. Erika[1], J.M. Flores Castro[1]

[1]Oncology, Instituto Nacional de Cancerologia - Mexico, Mexico City, Mexico, [2]Medical Oncology, Instituto Nacional de Cancerologia - Mexico, Mexico City, Mexico

Background: Obesity is a major public health problem, in Mexico there is a high prevalence of obesity. However, there have been few studies that have reported association between obesity and rectal cancer outcomes in the Mexican population. Many studies have recently revealed the relationship between obesity and cancer. Controversy remains as to whether obesity has a harmful prognostic effect in advanced stage rectal cancer patients. There is a report that obesity was associated with lower pathologic complete response rates in rectal cancer patients after neoadjuvant chemoradiotherapy. In their study, complete response was associated with better disease-free survival.

Therefore, we hypothesized that obesity influenced the local treatment outcomes in patients with rectal cancer after surgery and RT.

Methods: A total of 312 eligible patients were retrospectively analyzed; from 1999 to 2014 at National Cancer Institute Mexico, they received chemo-radiotherapy concomitant before surgery for rectal cancer.

The patients were categorized as obese, overweight, normal weight, or underweight based on BMI according to World Health Organization (WHO) criteria. Pathological complete response (pCR) was defined as no invasive cancer in the rectal or lymph tissue. Chi-squared tests were used for detecting the predictors of pCR and determining the relationship between BMI category and pCR rate in the subgroup analysis with respect to other variables.

Results: Median age was 54 years (18-82), 24% of patients were obese, 31% were overweight, and 45% normal or underweight. 22% (n = 68) of patients were pCR. In multivariate analysis, there was statistical trend in pCR between treatment groups: pCR for obese 16/75 patients, overweight 21/97 and normal or underweight was 31/140 patients (p = 0.057). Nevertheless, obese patients compared with normal weight patients (OR = 0.81; 95% CI, 0.69 to 1.33 p = 0.039) were significantly less likely to have a pCR.

Conclusions: These results show an association between obesity and a poor pathological response in rectal cancer patients. This analysis suggests that higher BMI should be considered, and the mechanism of influence of BMI and obesity, on treatment response in patients with rectal cancer.

Legal entity responsible for the study: Diaz Romero Maria del Consuelo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

507P Treatment outcomes of patients with localized anal squamous cell carcinoma and HIV infection: Systematic review and meta-analysis

M. Camandaroba[1], R. Riechelmann[1], V. Silva[1], C. Mello[1], R. Araujo[2]

[1]*Oncology, A. C. Camargo Cancer Center, Sao Paulo, Brazil,* [2]*Upper GI and HPB Surgery, Barretos Cancer Hospital, São Paulo, Brazil*

Background: Definitive chemoradiation (CRT) is the standard treatment for localized squamous cell carcinoma of the anus (SCCA). Because most phase III trials in SCCA have excluded patients with HIV, the evidence on treatment outcomes of these patients is lacking. We performed a systematic review and meta-analysis on the efficacy and toxicity profiles of HIV-positive SCCA patients treated with definitive CRT.

Methods: The systematic search was conducted Embase, Medline, Cochrane Libary, Scopus, Lilacs and Opengrey, from inception until September 2017. Eligible studies were clinical trials, prospective or retrospective cohorts studies. The main outcome variables were 3-year disease-free (DFS) and overall survival (OS) rates and frequency of grade 3 or 4 (G3/4) treatment-related toxicities, according to HIV status. Meta-analyses using pooled risk ratios were performed for binary outcomes from comparative studies from the antiretroviral therapy era with random and fixed effects models.

Results: Out of 3,951 studies, 40 were deemed eligible, with a total of 3,720 patients. One third (N = 1,298; 34%) were HIV-positive and their median pre CRT CD4 count was 347 um/L. HIV-positive patients presented trends for higher risk of G3/4 cutaneous toxicities (Risk Ratio [RR]: 1.56,95% [CI] 0.98-2.48;p0.061; I2= 77%), G3/4 leukopenia (RR: 1.28, 95% [CI] 0.96-1.70; p = 0.088; I2= 0%) and inferior 3-year DFS rate (RR: 1.52, 95% [CI] 0.99-2.33, p = 0.057; I2= 52.19%), and significantly worse 3-year OS rate (RR: 1.64, 95% [CI] 1.27-2.11,p< 0.001; I2= 0%).

Conclusions: Patients with localized SCCA and HIV infection treated with CRT tend to experience higher risk of toxicities and worse DFS and OS rates. Our findings suggest that future trials should be tailored to HIV-positive patients.

Legal entity responsible for the study: Rachel Riechelmann.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

508P p16 and PD-L1 expression in locoregional squamous cell carcinoma of the anal canal: A single center retrospective analysis in Japan

R. Takahashi[1], T. Wakatsuki[1], N. Yamamoto[2], S. Taguchi[3], E. Shinozaki[1], H. Osumi[1], M. Ogura[1], T. Ichimura[1], D. Takahari[1], M. Suenaga[1], K. Chin[1], M. Oguchi[3], M. Ueno[1], K. Yamaguchi[1]

[1]*Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan,* [2]*Department of Pathology, Cancer Institute Hospital of JFCR, Tokyo, Japan,* [3]*Department of Radiotherapy, Cancer Institute Hospital of JFCR, Tokyo, Japan*

Background: Squamous cell carcinoma of the anal canal (SCCA) is a rare malignancy especially in Asia. It is widely known that SCCA is linked to prior infection with human papillomavirus (HPV) in western countries. However, it is unclear whether HPV is associated with SCCA in Japan. In addition, expression of PD-L1, potential predictive marker for anti-PD-1 antibody, and its prognostic impact on locoregional SCCA remain to be elucidated. The aim of this study is to examine expression rates and prognostic impact of p16 and PD-L1 in Japanese patients with SCCA.

Methods: 34 patients with locoregional SCCA were treated by concurrent CRT at the Cancer Institute Hospital between 2007 and 2017. Among them, 28 patients whose biopsy specimens were available were enrolled. Radiation consisted of 45.0-59.4 Gy. Chemotherapy was given during radiation: 1000mg/m^2 daily fluorouracil on day 1-4 and 29-32, and a single dose of mitomycin C 10mg/m^2 administered on day 1 and 29. Data on relapse and death were obtained until March 2018. p16 positive was defined as p16 was stained on tumor nuclei. PD-L1 positive was also defined as PD-L1 was overexpressed on tumor membrane with more than 2+ score and the area was more than 5%.

Results: Of 28 patients, the median age was 59 (range 35-82) years. Male to female sex ratio was 1:6. 6 (21.4%) were clinically staged as I, 4 (14.3%) as II, 5 (17.9%) as IIIA, and 13 (46.4%) as IIIB. SCCA remained or recurred in 1 with cStage II, 1 with cStage IIIA and 7 with cStage IIIB. 3-year disease free survival (DFS) was 65.8% (95%CI, 44.3-80.6%), and 3-year overall survival (OS) was 79.2% (95%CI, 53.4-91.7%). Of 28 cases, 27 (96.4%) were positive for p16, and 6 (21.4%) were positive for PD-L1. In univariate analysis for DFS and OS, lymph node metastasis was significantly related to poor outcomes (DFS, p = 0.0289; OS, p < 0.0001). T factor (p < 0.0001) and tumor stage (p = 0.0035) significantly influenced OS. No significantly difference was found in terms of PD-L1 expression (DFS, p = 0.595; OS, p = 0.544).

Conclusions: High expression rate of p16 was observed in Japanese patients with locoregional SCCA. Lymph node metastasis, advanced T factor and tumor stage were negative prognostic factors for CRT, but no prognostic impact of PD-L1 was found.

Legal entity responsible for the study: Ryo Takahashi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

509P Factors influencing conversion to resectability and survival after resection of metastases in RAS WT metastatic colorectal cancer (mCRC): A FIRE-3 analysis

D.P. Modest[1], V. Heinemann[2], G. Folprecht[3], T. Denecke[4], J. Pratschke[5], H. Lang[6], M. Bemelmans[7], T. Becker[8], M. Rentsch[9], D. Seehofer[10], C. Bruns[11], B. Gebauer[12], S. Held[13], U. Neumann[14], I. Ricard[15]

[1]*Medical Department III, Ludwig Maximilians University - Grosshadern, Munich, Germany,* [2]*Department of Medical Oncology and Comprehensive Cancer Center, Ludwig Maximilians University - Grosshadern, Munich, Germany,* [3]*University Cancer Center, Medical Dept. I, Universitätsklinikum Dresden, Dresden, Germany,* [4]*Klinik f. Radiologie, Charite, Berlin, Germany,* [5]*Chirugie, Charite, Berlin, Germany,* [6]*Chirugie, Uniklinik Mainz, Mainz, Germany,* [7]*Chirurgie, Maastricht University Medical Center (MUMC), Maastricht, Netherlands,* [8]*Klinik f. Allgemeine-, Viszeral-, Thorax-, Transplantations- und Kinderchirurgie, Uniklinikum Schleswig-Holstein, Kiel, Germany,* [9]*Chirurgie, LMU Großhadern, Munich, Germany,* [10]*Chirugie, Uniklinik Leipzig, Leipzig, Germany,* [11]*Chirurgie, Uniklinik Köln, Cologne, Germany,* [12]*Radiologie, Charite, Berlin, Germany,* [13]*Statistik, Clinassess, Leverkusen, Germany,* [14]*Chirurgie, Universitaetsklinikum Aachen (UKA), Aachen, Germany,* [15]*Biometrie, IBE München, Munich, Germany*

Background: Paired tumor evaluations before randomization and at best response (nadir) of 270 patients with RAS WT tumors treated with first-line therapy with cetuximab (cet) vs. bevacizumab (bev)- in combination with FOLFIRI were reviewed for resectability of metastates. We assessed parameters influencing resectability, conversion to resectability and survival after nadir.

Methods: Baseline information and resectability were correlated with Fisher's exact tests. Conversion to resectability was defined as unresectable disease before randomization and resectable disease at nadir. Univariate and multivariate logistic models were fitted with resectability at nadir as response variable. A Cox model comparing the survival from nadir was used to measure the influence of treatment, resectability at nadir and resection (time dependent variable). Interaction of resection and treatment arm on survival was tested by likelihood ratio test.

Results: Initial Lung metastases (OR = 0.35 95% CI = (0.19 - 0.63), p = 0.001), BRAF mutation (OR = 0.33 95% CI = (0.12-0.82), p = 0.03) and high alkaline phosphatase (OR = 0.51, 95% CI = (0.31-0.81), p = 0.006) were associated with less chance of conversion to resectability and in case of lung metastases also of being resected if resectability at nadir was observed (OR = 0.33, 95% CI = (0.08-1.04) p = 0.046). Early tumor shrinkage (=ETS: -20% tumor diameter after 6 weeks therapy) and depth of response (DpR) were associated with conversion to resectability (ETS: OR = 1.86, 95% CI = (1.06-3.3), p = 0.034, DpR: OR = 1.02, 95% CI = (1.01-1.03), p < 0.001). Metastatic resection improved post-nadir survival (HR = 0.53, 95% CI = (0.29- 0.97), p = 0.04). This was pronounced in cet-treated patients as compared to bev-treated patients (HR (cet)=0.17, 95% CI = (0.04-0.69), p = 0.01; HR (bev)=0.89, 95% CI = (0.47-1.69), p = 0.73; interaction test p = 0.02).

Conclusions: Conversion to resectability is associated with baseline characteristics like lung metastases and BRAF mutation as well as with early efficacy parameters (ETS, DpR). In FIRE-3, resection of metastases was associated with improved post-nadir survival, this effect originated predominantly from the cetuximab-based study arm.

Clinical trial identification: NCT00433927.

Legal entity responsible for the study: Klinikum der Universität (LMU), Munich, Germany.

Funding: Merck Serono.

Disclosure: D.P. Modest: Grants: Merck KGaA, Pfizer, Visage Imaging, during the conduct of the study; Grants and personal fees: Merck KGaA, Amgen, Roche, Bayer; Grants: Sanofi, outside the submitted work. V. Heinemann: Grants: Merck, Pfizer during the conduct of this study, Grants: Amgen, Roche, Sanofi Sirtex outside the

submitted work. G. Folprecht: Honoraries: Roche/Genentech, Bayer, Amgen, Lilly and Servier, Study grant, Honoraries: Merck-Serono, outside the submitted work. T. Denecke: Grants and personal fees: Bayer and B.E Imaging; Personal fees: Toshiba, Novartis, Ipsen and Parexel; Grants, personal fees and non-financial support: Siemens, GE; Grants: Guerbet; Non-financial support: Visage Imaging, outside the submitted work. C. Bruns: Personal fees: Merck, Sirtex, Grant: Celgene, outside the submitted work B. Gebauer: Personal fees: Merck KGaA, Pfizer; Personal fees, Study support: Visage Imaging, during the conduct of the study; Personal fees: Parexel, C.R. Bard, Sirtex Medical, Roche, Merck, Bayer, Icon, Ipsen, Siemens outside the submitted work; Travel support: Cook Medical, 3M, St Jude Medical; Travel and study support: AngioDynamics; Study support: Philips, outside the submitted work U. Neumann: Study grant: Merck during the conduct of the study; Study grant and personal fees: Merck outside the submitted work; Personal fees: Roche, Amgen, Novartis, Chiesi and Astellas during the submitted work. All other authors have declared no conflicts of interest.

510P Targeted therapies in conversion therapy in mCRC: A systematic review and meta-analysis

B. Xing[1], B. Cui[2], Z. Gu[3], H. Peng[4]

[1]Department of Gastrointestinal Surgery, Xiangya Hospital of Central South University, Changsha, China, [2]Oncology, Third Affiliated Hospital of Harbin Medical University, Harbin, China, [3]Merck Serono Co. Ltd, Darmstadt, Germany, [4]Hepatopancreatobiliary Surgery, Peking University Cancer Hospital, Beijing, China

Background: Chemotherapy (CT) plays a vital role as conversion treatment for initially unresectable or borderline resectable colorectal cancer (CRC). Targeted therapies are recommended with CT for conversion therapy; however, their role in conversion of initially unresectable tumours has not been elucidated. This meta-analysis evaluated the role of targeted therapies for conversion aimed at R0 resection in KRAS WT mCRC.

Methods: We conducted a literature search for randomized controlled trials (RCTs) in PubMed, Embase and Cochrane library evaluating the role of anti EGFR and anti VEGF as conversion therapies. A comparison was performed for anti-EGFR + CT vs. anti-VEGF + CT (Gp. A) and anti-EGFR + CT vs. CT (Gp. B). R0 resection rate and objective response rate (ORR) were the primary outcomes; with overall survival (OS), progression free survival (PFS) and safety evaluated as the secondary outcomes. Primary outcomes and safety were presented as relative risk (RR) and 95% confidence interval (CI), whereas survival was presented as hazard ratio (HR) and 95%CI.

Results: We identified 8 RCTs from the potential 81 studies. In Gp. A, a fixed effects model was used for analysis; and showed that although non-significant, anti EGFR + CT had better R0 resection rate (RR 1.44, 95% CI 0.91,2.27; $p = 0.1156$; $I^2 = 0\%$) and ORR (RR 1.05, 95% CI 0.88, 1.24; $p = 0.6039$; $I^2 = 0\%$) compared with anti VEGF + CT. OS with anti EGFR + CT was significantly longer than anti VEGF + CT (HR: 0.64; CI 0.47, 0.86; $p = 0.0036$; $I^2 = 0\%$); however, PFS was numerically better in anti EGFR + CT. Compared with CT alone, anti EGFR + CT resulted in significantly higher R0 resection rate (RR 1.85, 95% CI 1.15,2.98; $p = 0.0107$; $I^2 = 57.16\%$) and ORR (RR 1.19, 95% CI 1.11, 1.28; $p < 0.0001$; $I^2 = 0\%$). In Gp. B, only PFS was significantly longer with anti EGFR + CT vs. CT (HR: 0.85; 95% CI 0.74, 0.98; $p = 0.0015$; $I^2 = 45.60\%$), and not OS. Safety evaluation showed anti EGFR + CT with significantly greater adverse events than CT alone (RR: 1.26; 95% CI: 1.18, 1.35; $p < 0.0001$).

Conclusions: In conclusion, anti EGFR + CT was an effective conversion therapy compared with anti VEGF + CT and CT in patients with initially unresectable mCRC; however, frequency of AEs was more with targeted therapy.

Legal entity responsible for the study: Merck Serono Co. Ltd.

Funding: Merck Serono Co. Ltd.

Disclosure: All authors have declared no conflicts of interest.

511P Morphologic response to chemotherapy containing bevacizumab in patients with colorectal liver metastases (CLM): A post hoc analysis of the WJOG4407G phase III study

A. Hosokawa[1], K. Yamazaki[2], C. Matsuda[3], S. Ueda[4], H. Fujii[5], E. Baba[6], S. Okamura[7], M. Tsuda[8], T. Tamura[9], K. Shinozaki[10], T. Tsushima[11], T. Tsuda[12], T. Shirakawa[13], H. Yamashita[14], S. Morita[15], K. Muro[16]

[1]Department of Medical Oncology, University of Miyazaki, Miyazaki, Japan, [2]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [3]Department of Surgery, Osaka General Medical Center, Osaka, Japan, [4]Department of Medical Oncology, Kindai University Nara Hospital, Nara, Japan, [5]Clinical Oncology, Jichi Medical University, Shimotsuke, Japan, [6]Comprehensive Clinical Oncology, Kyushu University Hospital, Fukuoka, Japan, [7]Department of Surgery, Suita Municipal Hospital, Suita, Japan, [8]Department of Gastroenterological Oncology, Hyogo Cancer Center, Hyogo, Japan, [9]Department of Medical Oncology, Kindai University Faculty of Medicine, Osakasayama, Japan, [10]Division of Clinical Oncology, Hiroshima Prefectural Hospital, Hiroshima, Japan, [11]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [12]Department of Clinical Oncology, St Marianna University School of Medicine, Kawasaki, Japan, [13]Department of Chemotherapy, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan, [14]Department of Gastroenterology and Hepatology, National Hospital Organization Okayama Medical Center, Okayama, Japan, [15]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [16]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Background: The phase III WJOG4407G study showed non-inferiority of FOLFIRI plus bevacizumab to mFOLFOX6 plus bevacizumab in progression-free survival, as the first-line chemotherapy for patients with metastatic colorectal cancer. The aim of this study was to evaluate the predictive and prognostic value of morphologic response to first-line chemotherapy containing bevacizumab in patients with CLM.

Methods: This study is a post hoc analysis of patients from the WJOG4407G study. Morphologic response was assessed with the comparison of baseline and week 8 contrast-enhanced CT images. Three blinded radiologists evaluated CT images and classified as optimal, incomplete or none response according to the morphologic criteria. RECIST response, early tumor shrinkage (ETS) and depth of response (DpR) were also evaluated. The Cox proportional hazards model was used to investigate the association between radiological variables and progression-free survival (PFS) and overall survival (OS).

Results: Of 395 patients who were eligible for efficacy analysis in the WJOG4407G study, 70 patients had liver-limited disease. Enhanced CT images of 57 of these patients from 22 participating centers were collected. Two patients were excluded from this analysis because their post-chemotherapy metastases were too small. Optimal morphologic response was identified in 19 of 55 patients (34.5%). The median PFS was 10.7 months for patients with optimal response and 10.1 months in those with incomplete/no response (log-rank $p = 0.96$). The median OS was 26.2 and 35.5 months, respectively (log-rank $p = 0.062$). According to univariate analysis, morphologic response was not associated with PFS or OS, whereas RECIST response was significantly associated with both PFS and OS, with ETS and DpR being associated with significantly longer PFS.

Conclusions: Morphologic response might be neither predictive nor prognostic factor in patients with CLM undergoing chemotherapy containing bevacizumab, whereas RECIST response was significantly associated with both PFS and OS.

Clinical trial identification: UMIN000022171.

Legal entity responsible for the study: West Japan Oncology Group.

Funding: West Japan Oncology Group.

Disclosure: A. Hosokawa: Honoraria: Taiho, Chugai, Takeda, Ono, Novartis, Eisai, Eli Lilly; Research funding: Taiho, Chugai, Ono, Eisai, Yakult. K. Yamazaki: Speakers' bureau: Chugai, Takeda, Taiho, Yakult, Merck Serono, Eli Lilly, Sanofi, Bayer E. Baba: Speakers' bureau: Chugai, Eli Lilly; Research funding: Ono, Chugai, Eli Lilly, Takeda, Taiho, Merck Serono. K. Shinozaki: Honoraria: Chugai, Takeda, Mochida, Merck Serono, Taiho, Yakult, Astellas, Novartis, Eisai, Eli Lilly, Shionogi, Kyowa Hakko Kirin, Asahi Kasei, MSD. S. Morita: Honoraria: Chugai Pharma, Daiichi Sankyo. K. Muro: Honoraria: Chugai, Taiho, Bayer, Ono, Eli Lilly, Takeda; Research funding: Ono, MSD, Daiichi Sankyo, Kyowa Hakko Kirin, Gilead Sciences, Shionogi. All other authors have declared no conflicts of interest.

512P KRAS mutations as a prognostic factor after metastasectomy in colorectal cancer patients

M. Domenech Viñolas[1], C. Santos[1], J. Pérez[2], M. Varela[3], M. Martinez Villacampa[1], A. Teule[1], J.C. Ruffinelli Rodriguez[1], N. Mulet Margalef[1], G. Soler[1], A. Ortega[1], M.S. Bergamino[1], X. SanJuan[3], J. Torras[4], E. Ramos[4], R. Salazar[1]

[1]Medical Oncology, Catalan Institute of Oncology, Hospitalet de Llobregat, Spain, [2]Research Unit, Catalan Institute of Oncology, Hospitalet de Llobregat, Spain, [3]Pathology, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain, [4]Surgical, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain

Background: Different clinicopathological factors have been associated with survival after liver metastasis resection in metastatic colorectal cancer (mCRC) patients. However, there is a need to better identify those patients who may benefit from metastasis resection. In this retrospective study we aimed to analyse clinical outcomes according to KRAS mutational status in a prospective collected series of mCRC patients.

Methods: We evaluated mCRC patients with exon 2 KRAS mutational status assessed between 2010 and 2014. Exon 2 KRAS mutational analysis was performed by therascreen® or cobas® assays. We excluded patients (pts) with no clinical data available. Disease-free survival (DFS) and overall survival (OS) were calculated using the Kaplan-Meier method.

Results: KRAS mutational status was assessed in 395 mCRC patients, but clinical data were only available in 348 patients. Median age was 66 years old. Two hundred and twenty-six patients were male (65%) and 210 pts (60%) had synchronous metastases at diagnosis. KRAS mutations were detected in 175 tumours (51%). Liver was the most common site of metastasis (210 pts, 60%), followed by lung (133 pts, 33%), lymph nodes (56 pts, 16%) and peritoneum (44 pts, 11%). Lung metastases at diagnosis were more frequent in KRAS mutant tumours (38% vs 27%, p-value = 0.022). We observed different metastasis spread pattern between pts with KRAS mutant and KRAS wt tumours. Risk of lung metastasis after 50 months of follow-up was higher in KRAS mutant tumours (77% vs 60%, p=.023). Risk of brain metastasis was also higher (18% vs 2%, p=.012). Median OS was 37 months, with no differences observed between KRAS mutant and KRAS wt tumours (34 vs 41 months, p-value = .70). One hundred thirty-nine patients underwent metastases resection (39.9%). In this subgroup of patients, KRAS mutations were associated with worse DFS (13.3 vs 24.5 months, p-value=.024).

Conclusions: KRAS mutations were associated with lung metastasis in CRC patients and different pattern spread. Although KRAS mutations were not a prognostic biomarker in the metastatic setting, patients with KRAS mutant tumours had a shorter DFS after metastasis resection.

Legal entity responsible for the study: Catalan Institute of Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

513P Impact of response to preoperative chemotherapy on the outcome of pulmonary metastasectomy for colorectal cancer: Results of a retrospective multicenter study

T. Okumura[1], N. Boku[2], T. Hishida[3], Y. Ohde[4], Y. Sakao[5], K. Yoshiya[6], M. Higashiyama[7], K. Kameyama[8], H. Adachi[9], K. Shiomi[10], M. Kanzaki[11], M. Yoshimura[12], M. Matsuura[13], Y. Hata[14], F. Chen[15], K. Yoshida[16], H. Sasaki[17], I. Hyodo[18], K. Mori[19], H. Kondo[20]

[1]Surgery, Teikyo University School of Medicine, University Hospital Mizonokuchi, Kanagawa, Japan, [2]Gastrointestinal Medical Onclogy, National Cancer Center Hospital, Tokyo, Japan, [3]Thoracic Surgery, Keio University School of Medicine, Tokyo, Japan, [4]Thoracic Surgery, Shizuoka Cancer Center, Shizuoka, Japan, [5]Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, [6]Chest Surgery, Niigata Cancer Center Hospital, Niigata, Japan, [7]Thoracic Surgery, Osaka International Cancer Center, Osaka, Japan, [8]Thoracic Surgery, Kurashiki Central Hospital, Okayama, Japan, [9]Thoracic Surgery, Hokkaido Cancer Center, Hokkaido, Japan, [10]Thoracic Surgery, Kitasato University School of Medicine, Kanagawa, Japan, [11]Surgery I, Tokyo Women's Medical University, Tokyo, Japan, [12]Thoracic Surgery, Hyogo Cancer Center, Hyogo, Japan, [13]Chest Surgery, Hiroshima City Hospital, Hiroshima, Japan, [14]Surgery, Toho University School of Medicine, Tokyo, Japan, [15]Thoracic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, [16]Thoracic Surgery, Shinshu University School of Medicine, Nagano, Japan, [17]Immunology, Oncology and Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [18]Gastroenterology, University of Tsukuba, Tsukuba, Japan, [19]Clinical Trial Coordination Office, Shizuoka Cancer Center Hospital, Shizuoka, Japan, [20]Thoracic Surgery, Kyorin University, Tokyo, Japan

Background: The benefit of preoperative chemotherapy (pre-CT) and metastasectomy for pulmonary metastasis (PM) from colorectal cancer (CRC) (PM-CRC) are unclear due to a lack of enough studies. However, there are some patients who receive chemotherapy after PM detection and subsequently undergo metastasectomy in clinical practice. The aim of this study was to investigate the impact of response to pre-CT on the outcome of pulmonary metastasectomy for PM-CRC.

Methods: The subjects were 92 patients, who received pre-CT before metastasectomy for PM-CRC, identified from the 1237 patients whose PM-CRC were curatively resected at 46 institutions in Japan between 2004 and 2008.

Results: Twenty-six (28%) patients initially judged to have inoperable PM underwent chemotherapy leading to conversion to be resectable and subsequently received metastasectomy. The remaining 66 patients initially judged to have operable PM received pre-CT and subsequently underwent metastasectomy. Fifty-six (61%) patients received fluoropyrimidine based regimens combined with oxaliplatin or irinotecan, and most of the remaining 26 received tegafur/uracil. Pre-CT yielded partial response (PR), stable disease (SD) and progressive disease (PD) in 28 (30%), 26 (28%) and 38 (42%) patients, respectively. At metastasectomy, the proportions of patients with extrathoracic lesion, multiple PMs, and abnormal carcinoembryonic antigen level were 34, 58, and 40%, respectively. Wedge resection was the most frequent (62%) surgical procedure. The five-year disease-free (DFS) and overall survival (OS) rate of the all 92 patients were 25.1% (95% CI 16.4-34.7) and 45.4% (33.4-56.7). The five-year DFS rates of the patients with PR/SD and PD during pre-CT were 28.2% (16.5-41.1) and 20.6% (9.2-35.2), and those of OS were 58.1% (40.8-71.9) and 27.5% (12.9-44.3), respectively. By multivariate analysis, independent prognosticators were two or less PMs (HR = 0.56, 95% CI 0.33-0.94; p = 0.029) for DFS, and performance status 0 (0.44, 0.22-0.90; 0.024) and PR/SD during pre-CT (0.33, 0.18-0.61; < 0.001) for OS.

Conclusions: Response to Pre-CT had some impacts on OS after metastasectomy for PM-CRC: better in the patients with PR/SD compared to PD.

Legal entity responsible for the study: Nonprofit Organization Tsukuba Cancer Clinical Trial Group.

Funding: Non-profit organization Tsukuba Cancer Clinical Trial Group.

Disclosure: N. Boku: Honoraria: Ono, BMS, Chugai, Merck Serono, Yakult, Eli Lilly companies. I. Hyodo: Honoraria: Taiho, Chugai, Daiichi-Sankyo, Yakult-Honshya companies. All other authors have declared no conflicts of interest.

514P Long-term outcomes with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in peritoneal carcinomatosis: 10-year experience in a developing country

F. Arias[1], E. Londoño-Schimmer[1], J. Otero[2], C.E. Cétares[1], G.E. Herrera[1], M. Mora[1], P. Rodriguez[3], M. Mejía[3], J.D. Guerra[4], A. Ruiz-Patiño[5], A.F. Cardona Zorrilla[5]

[1]Department of Surgery, Peritoneal Neoplasms Clinical Care Center, Fundacion Santa Fe de Bogotá, Bogotá, Colombia, [2]Clinical Oncology Group, Institute of Oncology, Fundacion Santa Fe de Bogotá, Bogotá, Colombia, [3]Department of Pathology, Fundacion Santa Fe de Bogotá, Bogotá, Colombia, [4]Facultad de Medicina, Universidad de Los Andes, Bogotá, Colombia, [5]Translational Research, Foundation for Clinical and Applied Cancer Research, Bogotá, Colombia

Background: Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a comprehensive treatment of peritoneal malignancies and it is currently a viable option in the increasing number of specialized centers all around the world.

Methods: A review of 119 CRS/HIPEC patients operated between 2007-2017 in a tertiary referral center of Bogotá, Colombia was performed. Patient characteristics, surgical variables, and postoperative outcomes were prospectively collected and analyzed.

Results: Median age at diagnosis was 51-yo (r, 22-78) and 73% (n = 87) were female. Primary origin of the peritoneal carcinomatosis was the appendix in 64%, advanced ovarian and primary peritoneal carcinomas (PC) in 17%, colorectal cancer (CRC) in 10.1%, peritoneal mesothelioma (PM) in 9%, and others in 1.6%. Prior surgical Peritoneal Cancer Index (PCI) was 19 (r, 2-39) and 25.2% were exposed to preoperative chemotherapy. Complete cytoreduction rate (CCR) was 81.5% (75% appendiceal tumors, 94% OC, 83% CRC, and 100% PM [p = 0.81]). Grade III, IV, and V complications were reported in 10%, 12%, and 4% of patients, respectively. Progression-free survival (PFS) was 38.4 months (95%CI 12.6-64.3) and 5-year PFS was 64%. PFS was positively influenced by appendiceal and mesothelioma histology (p = 0.035) as well as complete cytoreduction (p = 0.0001). At 42-month median follow-up 26 patients have died and the median overall survival (OS) was 108.5 months (95%CI 77.5-139.5). OS of patients with t relapse was 78.6 months (95% CI 36.1-121.1) and NR (p = 0.002), respectively, and only this variable adversely affected the multivariate analysis (RR 3.7, 95% CI 1.4-9.5; p = 0.007).

Conclusions: CRS/HIPEC is an effective treatment for patients with PC providing long-term survival and should be considered as standard of care. Our results, from a specialized center in a developing Latin-American country, are comparable to those from first-world centers, implying the importance of group experience in providing high-quality outcomes. Results showed that patients without relapse at the 5th year follow-up could be considered cured, but should always resume observation.

Legal entity responsible for the study: Fundacion Santa Fe de Bogotá.

Funding: Fundacion Santa Fe de Bogotá.

Disclosure: All authors have declared no conflicts of interest.

515P Clinical impact of 18F-FDG-PET/CT (PET) in patients (P) with oligometastatic disease (OMD) at a skin and gastrointestinal tumour section

J.J. Garcia-Mosquera, L. Layos Romero, C. Buges, S. España Fernandez, S. Chen, J.M. Velarde, E. Felip, C. Erasun Lecuona, L. Angelats, M. Cucurull Salamero, J.L. Manzano

Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

Background: Is important to avoid aggressive treatments in P with OMD with undetected metastasis. Previous data demonstrated that PET can have a significant clinical impact, especially in colorectal cancer.

Methods: Retrospectively, we review the history of P studied with PET at our unit, from October 2013 to December 2017. We included only P with OMD with a PET done to complete disease extension study in addition to conventional imaging and previously to undergo a potential curative management. Baseline data (age, sex, primary and stage), disease extension and initial strategy before PET were collected. After PET, disease extension, definitive strategy and overall survival (OS) was determined.

Results: Overall, 93 P met the inclusion criteria: 72 (77%) colorectal (CRC), 13 (14%) melanoma, 4 (4%) biliary tract, 2 (2%) oesophageal and 2 (2%) other primaries. The mean age was 64 years (range: 24-83) and 58 (62%) P were male. At debut, 64 (79%) P were non-metastatic, and PET was done at the recurrence. After PET, 47 (51%) P were restaged: 35 (38%) were upstaged and 12 (13%) were downstaged. Final strategy was changed in 43 (46%) P, leading to a non-radical plan in 32 (34%) P. On the radical plan group there was 2 (2.2%) p with no malignant disease after surgery (pulmonary

tuberculosis and aspergillosis). Median OS after PET in CRC cohort with changed strategy was significantly lower (28m, CI 95% 23-32) versus cohort without changes (47m, CI 95% 29-65); p-value 0.03.

Conclusions: After PET approximately half of P were restaged, consequently avoiding aggressive strategies in one-third of P. PET seems to be effective in selecting P with poor overall survival outcomes that need a palliative rather than a radical management. PET has relevant advantages compared with conventional imaging in the selection of P with OMD disease who may be eligible for surgery or local techniques.

Legal entity responsible for the study: Catalan Institute of Oncology (ICO Badalona).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

516P Simultaneous resection of colorectal primary tumor and liver metastasis after neoadjuvant therapy: A propensity score matching analysis

Y. Xu

Department of Colorectal Cancer, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Considering the surgical safety and presentation of perioperative complications, simultaneous resection of colorectal cancer and liver metastasis after neoadjuvant treatment is not regularly conducted in many centers. Herein, we assessed and compared the surgical safety and incidences of postoperative complications in patients with and without neoadjuvant treatment.

Methods: A total of 257 patients who underwent simultaneous resection were included in this single-center, retrospective study. Comparison of the short-term outcomes was performed after propensity score adjustment.

Results: No postoperative death occurred. After matching, the differences from colorectal cancer and liver metastasis were well-balanced. The median operative time, and blood loss and intraoperative transfusion rates did not differ between Group A (without neoadjuvant treatment) and Group B. The morbidity (Group A vs. Group B, 15.4% vs. 19.2%, $p = 0.420$), and Clavien-Dindo grade of complications ($p = 0.632$) were also similar. No difference was found when the complications were divided according to the origin (general, colorectal and hepatic). The length of the hospital stays also did not differ between the groups. Ratios of patients with the elevation of some important blood indices related to liver function did not differ, and there was no increase in the number of patients with delayed adjuvant treatment after surgery in Group B.

Conclusions: Simultaneous resection after neoadjuvant treatment was found to be comparably safe. It did not increase morbidity and influence subsequent adjuvant treatment, and may be a treatment option for patients with synchronous liver metastasis.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

517P Clinical factors are unable to accurately predict the absence of benefit of surgery in patients operated for resection of colorectal liver metastasis

A. Bohlok[1], H. Tessely[2], E. Naets[2], F. Bouazza[1], D. Germanova[3], J.L. Van Laethem[3], A. Hendlisz[4], V. Lucidi[3], V. Donckier[1]

[1]Surgery, Institute Jules Bordet, Brussels, Belgium, [2]Chirurgie, Institut Jules Bordet, Bruxelles, Belgium, [3]Digestive Surgery, Erasme University Hospital ULB, Brussels, Belgium, [4]Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Background: A substantial proportion of patients operated of resection for colorectal liver metastases (CRLM) with curative-intent will rapidly recur after surgery, emphasizing the need to improve the current selection process for surgery. The aim of the study is to analyze clinicopathologic prognostic factors that could better identify patients that wouldn't benefit of surgery.

Methods: A prospective database including patients operated of hepatectomy for CRLM between 2005 and 2017 was analyzed. Within this population, we selected and compared 2 groups: early relapsers (ER), defined as patients with unresectable recurrence $\leq$1 year postoperatively considered as having not benefited of surgery and long-term survivors (LTS), defined as patients without recurrence $\geq$5 years after first hepatectomy. In the entire population and in the 2 subgroups, we analyzed potential predictive factors, using uni- and multivariate analysis.

Results: In total population ($N = 357$), 5 and 10-year disease-free survival (DFS) and overall survival (OS) are 26 and 21.5% and 44 and 25% respectively. In univariate analysis, Fong's Clinical Risk Score (CRS) >2, mutated-KRAS, major hepatectomy and positive resection margins are significant poor prognostic factors for DFS and OS. In multivariate analysis only mutated-KRAS remains a significant poor prognostic factor for DFS (HR = 1,5 Ci:1,06-2,12 p = 0,02) and OS (HR = 1,8 Ci:1,19-2,70 p = 0,005). Comparing the 2 subgroups ER-group (77 patients) and LTS-group (64 patients), representing respectively 21 and 18% of entire population the univariate analysis showed significantly more synchronous CRLM, multiple metastases, mutated-KRAS and CRS>2 in the ER group. Of note, 25% of LTS had CRS>2. In multivariate analysis, only multiple metastases remain significantly increased in ER ($p = 0.016$).

Conclusions: Clinical factors are unable to discriminate preoperatively the patients who will benefit of surgery for CRLM from those in whom surgery will be futile. This strongly underlines the need to identify other markers of tumor biology for better individualization of the therapeutic decision.

Legal entity responsible for the study: Vincent Donckier.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

518P Hepatic arterial infusion (HAI) of oxaliplatin with capecitabine in first line treatment of patients (pts) with liver limited metastases from colorectal cancer (LLmCRC)

B.V. Vittrup[1], H.H. Nørgaard[2], M. Bergenfeldt[3], F.O. Larsen[1], E. Høgdall[4], J.S. Johansen[1], J.S. Sidenius Johansen[1], H.K. Hermann[2], D.L. Nielsen[1]

[1]Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [2]Radiology, Herlev and Gentofte Hospital, Herlev, Denmark, [3]Surgery, Herlev Hospital and Skåne Hospital, Herlev, Denmark, [4]Pathology, Herlev and Gentofte Hospital, Copenhagen, Denmark

Background: The hepatic artery accounts for the primary blood supply of liver metastases from CRC.

Methods: First-line therapy with up to 12 series of HAI with oxaliplatin 100 mg/m^2 day 1 and capecitabine 3500 mg/m^2 day 1-7 every second week. When the hepatic arterial anatomy did not permit a permanent catheter pts had intravenous oxaliplatin 130 mg/m^2 day 1 every third week combined with capecitabine 2000 mg/m^2 day 1-14 (CAPOX). RAS mutations were retrospectively determined by next generation sequencing of KRAS Exon (E) 2, codon (C) 12 and 13, E3C59 and 61, E4C117 and 146 and NRAS E2C12 and 13, E3C59 and 61, E4C117 and 146. Pts had a baseline PET/CT scan and was evaluated by liver surgeons for resectability.

Results: Included were 93 pts, 66 had HAI and 27 CAPOX. The groups were comparable with an equal distribution of RAS wildtype (RAS-W) and mutants (RAS-M) tumours. Follow-up was 95-154 mths. Overall response rate (ORR) with complete (CR) and partial remission (PR) was 89% vs 59% in the HAI vs. CAPOX group ($P = 0.0008$). Progression-free survival (PFS) was independent of RAS status and treatment. Median overall survival (OS) was 6 mths. longer in the HAI vs CAPOX group (HR 1.62, 95% Confidence Interval (CI) 1.0-2.6, $P = 0.05$). OS was independent of RAS status in the CAPOX group and equal to OS in the HAI RAS-M group. Pts with RAS-W tumours treated with HAI survived double that of all the other groups (HAI-RAS-W vs HAI-RAS-M: HR 1.88, 95%CI 1.1-3.2, $P = 0.023$, HAI-RAS-W vs. CAPOX-RAS-W: HR 1.60 95%CI 1.12-2.27, $P = 0.009$). Toxicity of HAI was comparable to CAPOX with abdominal pain, neuropathy, and hand foot syndrome as the most common adverse events.

Table: 518P

	HAI-CAPOX			Systemic-CAPOX		
	All	RAS-W	RAS-M	All	RAS-W	RAS-M
No	66	31	35	27	14	13
NA	2		2	3	1	2
CR	8 (12%)	6	2	0		
PR	51 (77%)	25	26	16 (59%)	10	6
SD	4		4	6 (22%)	3	3
PD	1		1	2		2
mOS [1]	36 (28-44)	64 (45-81)	29 (24-35)	30 (24-35)	30 (20-41)	22 (16-29)
mPFS [1]	12 (10-15)	14 (11-17)	11 (8-15)	11 (9-13)	12 (7-17)	10 (8-13)

Mths with 95%CI in brackets. NA=not applicable, SD =stable disease and PD=progressive disease.

Conclusions: ORR and OS was significantly higher when pts with LLmCRC was treated with Capecitabine and HAI with oxaliplatin compared to CAPOX. Survival benefit is limited to pts with RAS-W tumours treated with HAI.

Legal entity responsible for the study: Benny Villars Vittrup.

Funding: The Danish Cancer Society.

Disclosure: All authors have declared no conflicts of interest.

519P Microsatellite instability is associated with distinct clinical and molecular characteristics in early colon cancer: Analysis of a molecular registry of the AIO colorectal study group - Colopredict Plus

A. Reinacher-Schick[1], H. Juette[2], S. Noepel-Duennebacke[1], D. Arnold[3], N. Basara[4], H. Boehner[5], T. Dahm[1], I. Feder[2], T. Herzog[6], W. Hiller[7], L. Mueller[8], L. Engel[9], M. Senkal[10], C. Teschendorf[11], G. Trenn[12], B. Verdoodt[2], H. Wolters[13], W. Uhl[14], A. Tannapfel[2]

[1]Department of Hematology, Oncology and Palliative Care, St. Josef-Hospital Bochum, Ruhr-University Bochum, Bochum, Germany, [2]Institute of Pathology, Ruhr-University Bochum, Bochum, Germany, [3]Hematology, Internal Medicine and Palliative Care, Asklepios Klinik Altona, Hamburg, Germany, [4]Hematology/Oncology/Internal Medicine, St. Franziskus Hospital Malteserkrankenhaus, Flensburg, Germany, [5]Surgical Clinic, Katholisches Krankenhaus Dortmund West, Dortmund, Germany, [6]General and Visceral Surgery, Katholisches Klinikum Bochum - St. Josef-Hospital, Bochum, Germany, [7]General, Visceral and Thoracic Surgery, Klinikum Lippe GmbH, Detmold, Germany, [8]Onkologie UnterEms Leer Emden Papenburg, Onkologische Schwerpunktpraxis Leer-Emden, Leer, Germany, [9]Intestinal Centre, Klinikum Nürnberg Nord, Nürnberg, Germany, [10]General and Visceral Surgery, Marien Hospital Witten, Witten, Germany, [11]Internal Medicine, Katholisches Krankenhaus Dortmund West, Dortmund, Germany, [12]Internal Medicine/Hemato-oncology, Knappschaftskrankenhaus Bottrop Medizinische Klinik, Bottrop, Germany, [13]General and Visceral Surgery, St.-Josefs-Hospital Dortmund-Hoerde, Dortmund, Germany, [14]Department of Surgery, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany

Background: High microsatellite instability (MSI-H) is a prognostic marker in early colon cancer (CC) identified in retrospective analysis of many trials. However, broad validation in real-life cohorts and its association with clinical and molecular markers is lacking.

Methods: In Sep 2013 the molecular registry trial Colopredict Plus was intiatied in 70 German community cancer centers recruiting patients with UICC stage II and III CC. MSI was tested by immunohistochemistry (IHC) of mismatch repair proteins MLH1, MSH2, MSH6 and PMS2. In case of any loss of protein expression fragment length analysis (FLA) was performed, defining MSI high tumors (MSI-H) and MS stable tumors (MSS). Moreover, mutations in known prognostic factors in CC such as RAS, BRAF, PI3K and others were determined by next generation sequencing (NGS).

Results: By April 2018, 2102 patients have been recruited: median age 72 yrs., stage II/III: 1108/994 pts. So far, tissue was analysed in 1342 pts. Of these, 377 pts. were IHC neg with 290 pts. subsequently tested MSI-H upon FLA (21.6%). Median age was 73 yrs. female/male: 677/665 pts., stage II/III: 736/606 pts. Association of MS status with clinical and molecular factors is shown in the table. Upon NGS analysis we found 18.9% BRAF mutations, 41.5% KRAS mutations, 3.2% NRAS mutations and 25.1% PI3K mutations. MSI-H status was significantly associated with BRAF mutation and wild-type status of RAS.

Conclusions: MSI-H was more frequent in this community based registry compared to randomised trials, possibly related to a higher median age in our cohort. MSI-H was associated with female sex, right-sided primary tumor and BRAF mutations representing a heterogeneous subgroup of CC. First survival data will be presented at the meeting. Table: Association of clinical features with MSI-H in patients with CC (MS status determined by FLA).

Table: 519P

	All	MSI-H (%)	MSS (%)
	1342	290 (21,6)	1052 (78,4)
Median age	73	76	73
Male	677	78 (11,5)	599 (88,5)
Female	665	212 (31,9)	453 (68,1)
Stage II	736	181 (24,6)	555 (75,4)
Stage III	606	109 (18)	497 (82)
Right Colon	793	242 (30,5)	551 (69,5)
Left Colon	536	47 (8,8)	489 (91,2)

Clinical trial identification: DRKS Registry number: DRKS00004305 Release Date: 09-JAN-2013.

Legal entity responsible for the study: Ruhr-University Bochum, Institute of Pathology; Department of Hematology, Oncology and Palliative Care, St. Josef-Hospital.

Funding: State of North-Rhine Westfalia, Roche Pharma GmbH.

Disclosure: A. Reinacher-Schick: Honoria: Amgen, Roche, Pfizer, Sanofi-Aventis, Merck-Serono, Shire, Calgene, Lilly, BMS; Advisory board member: Amgen, Roche, Pfizer, Sanofi-Aventis, Celgene, Lilly, BMS, Merck-Serono; Studies sponsored by: Roche, Sanofi-Aventis, Calgene, Ipsen. H. Juette: Honoria: Roche, MSD, BMS, AstraZeneca, Amgen. S. Noepel-Duennebacke: Advisory board member: Bexalta, BMS; Studies sponsored by: Roche, Sanofi-Aventis, Celgene, Ipsen. D. Arnold: Honoraria: Bayer, Biocompatibles, Lilly, Merck, MSD, Roche, Sanofi, Servier, Sirtex; Advisory board member: Bayer, Lilly, Merck, Roche, Sanofi, Servier, Sirtex, Termuno; Studies sponsored by: Mologen, Roche, Sanofi. C. Teschendorf: Advisory board member: Roche. A. Tannapfel: Honoraria: Amgen, Roche, Pfizer, Merck-Serono, Celgene, BMS; Advisory board member: Amgen, Roche, Pfizer, Sanofi-Aventis, Celgene, BMS, Merck-Serono; Studies sponsored by: Roche, Celgene, Ipsen. All other authors have declared no conflicts of interest.

520P Prognostic impact of MSI and 18qLOH in stage II colon cancer: A prospective biomarker study in the SACURA trial

T. Ishikawa[1], M. Ishiguro[2], E. Nakatani[3], H. Ueno[4], H. Uetake[5], K. Murotani[6], S. Matsui[7], N. Tomita[8], Y. Shimada[9], K. Takahashi[10], K. Kotake[11], M. Watanabe[12], H. Mochizuki[13], S. Teramukai[14], K. Sugihara[15]

[1]Department of Specialized Surgeries, Tokyo Medical and Dental University, Tokyo, Japan, [2]Department of Translational Oncology, Tokyo Medical and Dental University, Tokyo, Japan, [3]Division of Medical Statistics, Translational Research Informatics Center, Foundation for Biomedical Research and Innovation at Kobe, Hyogo, Japan, [4]Department of Surgery, National Defense Medical College, Saitama, Japan, [5]Specialized Surgeries, Tokyo Medical and Dental University, Tokyo, Japan, [6]Biostatistics Center, Kurume University, Graduate School of Medicine, Fukuoka, Japan, [7]Department of Biostatistics, Nagoya University, Aichi, Japan, [8]Division of Lower GI Surgery, Department of Surgery, Hyogo College of Medicine, Hyogo, Japan, [9]Division of Clinical Oncology, Kochi Health Sciences Center, Kochi, Japan, [10]Deparment of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [11]Department of Surgery, Tochigi Cancer Center, Tochigi, Japan, [12]Department of Surgery, Kitasato University School of Medicine, Kanagawa, Japan, [13]Deparment of Surgery, National Defense Medical College, Saitama, Japan, [14]Department of Biostatistics, Kyoto Prefectural University of Medicine, Kyoto, Japan, [15]Deparment of Surgery, Tokyo Medical and Dental University, Tokyo, Japan

Background: The SACURA trial is a phase III study to evaluate the superiority of 1-year adjuvant treatment with oral tegafur-uracil (UFT) to surgery alone in stage II colon cancer, in which survival benefit of 1-year UFT was not demonstrated (Eur J Cancer 96:54-63, 2018). In an additional biomarker study, we studied MSI status and 18qLOH of cancer tissues and evaluated their clinical value in stage II colon cancer patients.

Methods: A total of 1026 samples were collected from patients enrolled in the SACURA trial. MSI was evaluated by 5 markers; BAT25, BAT26, D2S123, D5S346, and D17S250. MSI-high (MSI-H) was defined as the presence of instability in more than 20% of the markers. 18qLOH was evaluated by 3 markers; D18S69, D18S74E, and D18S851. 18qLOH positivity was defined as the presence of LOH in any of the 18q markers. 18q LOH negativity was strictly defined as the presence of at least one informative markers and the absence of LOH.

Results: MSI-H was observed in 74 (7.2%) patients. The 18q LOH was present in 526 patients (51.3%) and LOH negativity was observed in 354 (34.5%). Informative LOH data was not available in 146 patients (14.2%). Relapse free survival (RFS) in MSI-H patients was better than that in non MSI-H (HR: 0.40, 95%CI: 0.17-0.98, p = 0.045). RFS in 18qLOH positive patients was significantly worse than in 18qLOH negative patients (hazard ratio: 1.44, 95%CI: 1.01-2.07, p = 0.047). When the patients were divided into 3 groups using MSI status and 18qLOH, approximately 5% differences of RFS were observed among the subgroups (Table). In the group 1 and 2, 5-year RFS rates were favorable and there were no differences in RFS between the treatment arms. In the group 3, 5-year RFS rate in the UFT group was +3% better than in the surgery-alone group although the difference was not significant.

Table: 520P

5yRFS in the subgroups divided by MSI status and 18qLOH

Subgroup divided by MSI status and 18qLOH	5yRFS		
	Overall	Surgery-alone group	UFT group
group 1: MSI-H	92.9% (N = 74)	94.3% (N = 36)	91.7% (N = 38)
group 2: non MSI-H and 18qLOH negative	87.2% (N = 327)	87.5% (N = 153)	87.0% (N = 174)
group 3: non MSI-H and 18qLOH positive/non-informative	82.5% (N = 625)	81.0% (N = 320)	84.0% (N = 305)

Conclusions: In stage II colon cancer, adjuvant chemotherapy might be unnecessary for MSI-H or 18qLOH negative patients. MSI status and 18qLOH might be useful biomarkers in stage II colon cancers.

Clinical trial identification: NCT00392899.

Legal entity responsible for the study: Sacura Study Group.

Funding: The Foundation for Biomedical Research and Innovation, Translational Research Informatics Center (TRI), under the funding contract with Taiho Pharmaceutical Co. Ltd.

Disclosure: T. Ishikawa: Honoraria: Chugai Pharma, Merck Serono, Takeda, Sanofi, Taiho Pharmaceutical; Research funding: Taiho Pharmaceutical. M. Ishiguro: Honoraria: Chugai Pharma, Merck Serono, Takeda, Sanofi, Taiho Pharmaceutical; Advisory role: Taiho Pharmaceutical; Research funding: Yakult, Taiho Pharmaceutical. H. Ueno: Honoraria: Chugai Pharma, Yakult, Eazai, Taiho Pharmaceutical. H. Uetake: Honoraria: Chugai Pharma, Merck Serono, Takeda, Taiho Pharmaceutical; Advisory role: Sanofi; Research funding: Taiho Pharmaceutical. N. Tomita: Research funding: Chugai Pharma, Taiho Pharmaceutical. Y. Shimada: Honoraria: Chugai Pharma, Yakult, Takeda, Lilly, Taiho Pharmaceutical; Research funding Merk Serono, Lilly, MSD, Taiho Pharmaceutical. K. Kotake: Honoraria: Chugai Pharma, Bristol-Myers Squibb, Taiho Pharmaceutical. M. Watanabe: Honoraria: Taiho Pharmaceutical: Research funding: Taiho Pharmaceutical: Travel and accommodations: Taiho Pharmaceutical. H. Mochizuki: Honoraria: Becton, Dickinson and Company, Taiho Pharmaceutical; Advisory role: Otsuka Pharmaceutical. K. Sugihara: Honoraria: Chugai Pharma, Lilly, Novertis, Bayer, Taiho Pharmaceutical; Advisory role: Otsuka Pharmaceutical; Research funding: Chugai Pharma, Takeda, Taiho Pharmaceutical. All other authors have declared no conflicts of interest.

521P miR-31 as a prognostic and predictive marker of disease-free survival (DFS) in resected stage III colon cancer: A retrospective analysis of the PETACC-8 trial

Y. Gaston Mathe[1], S. Martin-Lannerée[2], C. Vazart[2], K. Fontaine[2], C. Mulot[3], A. Caumont[4], F. Montestruc[4], K. Le Malicot[5], C. Lepage[6], J. Taieb[7], P. Laurent-Puig[8]

[1]Molecular Diagnostics, IntegraGen SA, Évry, France, [2]R&D, IntegraGen, Évry, France, [3]U1147, INSERM, Paris, France, [4]Biostatistics, EXYSTAT, Malakoff, France, [5]Biostatistics, FFCD-, Dijon, France, [6]Clinical Oncology, CHU Dijon, Dijon, France, [7]Department of Gastroenterology and Digestive Oncology, Hopital European George Pompidou, Paris, France, [8]UMR1147, Paris Descartes University, Paris, France

Background: In RAS wild type metastatic colorectal cancer patients (pts), high tumor expression of microRNA miR-31-3p and miR-31-5p has been associated with poorer benefit of anti-EGFR therapy. miR-31-3p expression has been shown to be predictive of treatment effect in the FIRE-3 trial. The PETACC-8 phase III trial assessed the efficacy of cetux addition to FOLFOX compared to FOLFOX only in pts with resected stage III colon cancer (CC). The primary end point was negative, but a trend towards benefit of cetux on disease free survival (DFS) was observed in pts with RAS/BRAF wild type (WT) tumors. The current study aimed at assessing miR-31-3p and 5p tumor levels as prognostic and predictive biomarkers of adjuvant cetux benefit in these pts.

Methods: miR-31-3p and 5p levels were measured by RT-qPCR from 477 WT pts tumor RNA. The primary objective was to demonstrate a benefit of cetux on DFS for low miR-31-3p expressers. Cox regression model was used for univariate and multivariate analyses. Optimal cut-off values for low and high expressers were determined post hoc.

Results: In the studied population, cetux benefit was significant for DFS (HR = 0.71 [0.50;1.00] p = 0.05) but not for Overall Survival (OS) (HR = 0.79 [0.53;1.18] p = 0.25). Expression of miR-31-3p and miR-31-5p were highly correlated (R > 0.9). Higher miR-31-3p and 5p expression were associated with shorter DFS and OS (p < 0.01). Pts with low miR-31-3p levels (n = 218/435, 50%) had a non-significant benefit from cetux on DFS (HR 0.61 [0.33; 1.11] p = 0.10) and OS (HR = 0.67 [0.33; 1.35] p = 0.26). Pts with low miR-31-5p levels (n = 233/477, 49%) benefited from cetux on DFS (HR = 0.46 [0.25; 0.84] p = 0.01) and OS (HR = 0.50 [0.25; 0.99], p = 0.047) whereas high expressers did not (DFS: HR = 0.87 [0.56; 1.34] ; OS: HR = 1.01 [0.61; 1.67]). miR-31-5p was predictive of treatment effect on DFS at the 10% level (interaction tests: p = 0.09 for DFS and p = 0.103 for OS). Results were still significant after adjustment for clinical covariates.

Conclusions: In pts with resected stage III WT CC, miR-31-3p and 5p were prognostic of DFS and OS. Pts with low miR-31 expression benefited from cetux addition to FOLFOX for adjuvant therapy, and miR-31-5p was predictive of cetux efficacy.

Clinical trial identification: NCT03362684.

Legal entity responsible for the study: IntegraGen SA.

Funding: IntegraGen.

Disclosure: Y. Gaston Mathe: Ex employee: IntegraGen. S. Martin-Lannerée, C. Vazart, K. Fontaine: Employee: IntegraGen. A. Caumont, F. Montestruc: Consultant: IntegraGen. J. Taieb: Honoraria: Lilly, Celgene, Servier, Amgen, Roche, Merck, Sirtex, Sanofi. P. Laurent-Puig: Honoraria: IntegraGen, Merck-Serono, Amgen, Boehringer-Ingelheim, Roche, Lilly, Sanofi. All other authors have declared no conflicts of interest.

522P Prognostic value of neutrophil-lymphocite ratio in resected high risk colorectal cancer: An analysis of adjuvant TOSCA trial

F. Petrelli[1], G. Rosati[2], M. Banzi[3], M.G. Zampino[4], N. Pella[5], M. Di Bartolomeo[6], E. Maiello[7], P. Bidoli[8], D. Ferrari[9], L. Rimassa[10], R. Labianca[11], M. Scartozzi[12], S. Lonardi[13], S. de Placido[14], A. Zaniboni[15], A. Sobrero[16], L.G. Frassineti[17], N. Silvestris[18], D. Corsi[19], F. Galli[20], S. Barni[21]

[1]Oncology, Azienda Ospedaliera Treviglio-Caravaggio, Treviglio, Italy, [2]Oncology, Ospedale San Carlo, Potenza, Italy, [3]Oncology, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy, [4]Oncology, Istituto Europeo di Oncologia, Milan, Italy, [5]Oncology, Azienda Ospedaliero Universitaria Santa Maria della Misericordia, Udine, Italy, [6]Istituto Nazionale dei Tumori, Fondazione IRCCS, Milan, Italy, [7]Oncology, Hospital Casa Sollievo della Sofferenza-IRCCS, San Giovanni Rotondo, Italy, [8]Oncology, San Gerardo dei Tintori Hospital, Monza, Italy, [9]Oncology, Azienda Ospedaliera San Paolo, Milan, Italy, [10]Humanitas Clinical and Research Center, Rozzano, Italy, [11]Oncology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy, [12]Oncology, University Hospital and University of Cagliari, Cagliari, Italy, [13]Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [14]Oncology, AOU Policlinico Federico II, Naples, Italy, [15]Oncology, Casa di Cura Poliambulanza, Brescia, Italy, [16]Medical Oncology, IRCCS Ospedale San Martino IST, Genoa, Italy, [17]Oncology, Istituto Tumori della Romagna I.R.S.T., Meldola, Forlì-Cesena, Italy, [18]Oncology, Ospedale Oncologico "Giovanni Paolo II"- IRCCS, Bari, Italy, [19]Oncology, Ospedale S.Giovanni Calibita FBF, Rome, Italy, [20]Laboratory of Clinical Research Methodology, IRCCS Laboratorio Ricerche Farmacologiche Mario Negri, Milan, Italy, [21]Oncology, ASST Bergamo Ovest, Treviglio, Italy

Background: Prognostic factors in resected colon cancer (CC) guide adjuvant therapy and intensity of follow up. Inflammation parameters as C-reactive protein and neutrophil counts in relation to lymphocyte number (neutrophil/lymphocyte ratio: NLR) have been correlated with poor prognosis in advanced tumors. To confirm the prognostic value of a prechemoterapy NLR in adjuvant setting, we performed a retrospective analysis of high risk stage II and stage III resected CC patients randomized into the TOSCA phase 3 trial comparing 3 or 6 months of adjuvant chemotherapy.

Methods: patients randomized in TOSCA trial with data available for NLR analysis before chemotherapy were included. A recursive partitioning analysis was performed to identify the best cut-off that better discriminates patients in terms of relapse-free survival (RFS). According to this cut-off, RFS and overall survival (OS) hazard ratios (HR) for NLR were calculated and adjusted for age, sex, treatment type (XELOX vs FOLFOX) and duration (3 vs 6 months), grade, stage, performance status (PS), site and CEA level.

Results: Out of 3759 subjects randomized in the TOSCA trial, 1590 were included in the efficacy analysis. Mean NLR was 2.1 (median 1.8; range 0.3-24.0). Among patients analysed, 17.4% relapsed and 12.2% died. The best NLR cut off detect in this analysis population is 2.33. However, only age, PS, stage III and CEA levels were associated with RFS and OS in multivariate analysis, but not NLR>2.33 (RFS: HR = 1.17, 95%CI 0.90-1.51; P = 0.24, OS: HR = 1.16 95%CI 0.84-1.61; P = 0.38). Site was also correlated with poor OS.

Conclusions: Prechemotherapy NLR is not significantly associated with poor prognosis in patients with CC undergoing adjuvant chemotherapy. Resection of primary tumor and the associated reduced inflammatory stimulus may explain the lack of correlation with prognosis of NLR. Baseline evaluation, before surgery, likely represents the better timing to collect this information in cancer patients.

Legal entity responsible for the study: GISCAD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

523P Distribution of lymph node metastases can have an impact on survival benefit of oxaliplatin-containing chemotherapy in stage III colon cancer

Y. Chae[1], J.G. Kim[2], J.H. Baek[3], S.J. Lee[2], D.W. Baek[2], B.W. Kang[2]

[1]Oncology, Kyungpook National University Medical Center, Daegu, Republic of Korea, [2]Oncology, Kyungpook National University Hospital, Daegu, Republic of Korea, [3]Oncology, Ulsan University Hospital, Ulsan, Republic of Korea

Background: This study investigated the effect of oxaliplatin-containing adjuvant chemotherapy according to the distribution of lymph node (LN) metastases for patients with stage III colon cancer (CC).

Methods: Among 1554 patients with CRC who underwent surgical resection between 2010 and 2014, 254 patients were diagnosed with stage III CC, and adjuvant chemotherapy was administered. Patients were treated with either oxaliplatin-containing chemotherapy or non-oxaliplatin-containing chemotherapy according to each investigator decision. LN distribution was classified on the basis of the Japanese classification of colorectal carcinoma. The patients were grouped into two categories: pericolic LN-positive and extrapericolic LN-positive.

Results: Among the 254 patients enrolled in this study, 175 belonged to the PLN group, whereas the remaining 79 patients to the ELN group. The PLN group was also divided into two groups based on the regimen: 79 patients were included in the non-oxaliplatin-containing chemotherapy group, while 96 in the oxaliplatin-containing chemotherapy group. The characteristics were similar between two groups, except for age and body mass index. During the median follow-up duration of 48.5 months

(range 4.7-94.0), 39 (15.4%) patients died and 47 (30.5%) patients experienced recurrence and the estimated DFS and OS at 3 years was 82.8% and 90.1%, respectively. In the univariate analysis, oxaliplatin chemotherapy was not significantly associated with DFS (p = 0.457) and OS (p = 0.147). In the multivariate analysis, the addition of oxaliplatin showed no prognostic significance on DFS (p = 0.073) and OS (p = 0.594).

Conclusions: In conclusion, oxaliplatin-containing adjuvant chemotherapy was not found to have a significant effect on survival for stage III CC patients with only PLN. Accordingly, the current study can provide a novel strategy for subgroups with limited LNs distribution, considering that the state of the LN distribution is a critical factor for therapeutic success.

Legal entity responsible for the study: Jong Gwang Kim.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

524P Implications of thymidylate synthase gene polymorphisms, KRAS and BRAF mutations in the survival of patients with colorectal cancer treated with adjuvant chemotherapy

A. Ntavatzikos[1], A. Spathis[2], P. Patapis[3], G. Peros[4], I. Panayiotides[5], I. Papadopoulos[4], A. Koumarianou[1]

[1]Hematology Oncology Unit, Fourth Department of Internal Medicine, Athens Greece, Attikon University Hospital, Athens, Greece, [2]Department of Cytopathology, Attikon University Hospital, Athens, Greece, [3]Third Department of Surgery, Attikon University Hospital, Athens, Greece, [4]Fourth Department of Surgery, Attikon University Hospital, Athens, Greece, [5]Pathology, Attikon University Hospital, Athens, Greece

Background: Fluoropyrimidine-based adjuvant chemotherapy in colorectal cancer (CRC) is associated with a reduction of recurrence in only 25% of patients (pts) with stage III disease. The aim of this study was to investigate thymidylate synthase (TYMS) gene polymorphisms, KRAS and BRAF as possible factors affecting therapeutic outcome in pts with stage III CRC.

Methods: Formalin-fixed paraffin-embedded tissues of 130 consecutive pts treated with FABC between 2005-2007 were analysed with PCR for the detection of TYMS polymorphisms, mKRAS and mBRAF. Patients were classified into three groups of 5'UTR TYMS polymorphisms according to the predicted expression profile (high, medium and low). Based on the presence or absence of the 3'UTR polymorphism ins/LOH pts were allocated into two groups (high and low risk). Cox regression models examined factors associated with survival outcome.

Results: The 5-year DFS and OS rate was 61.6% and 73.9% respectively. Patients who had tumors with 5'UTR polymorphisms of intermediate TYMS expression profile (2RG/3RG, 2RG/LOH, 3RC/LOH) when compared to those with low (2RG/2RG, 2RG/3RC, 3RC/3RC) or high expression (3RG/3RG, 3RG/LOH, 3RG/3RC) had lower risk for relapse (HR 0.320, p = 0.02 and HR 0.343, p = 0.013 respectively) and death (HR 0.368, p = 0.031 and HR 0.394, p = 0.029 respectively). The 3'UTR polymorphism ins/LOH was independently associated with increased risk for disease recurrence (p = 0.001) and death (p = 0.005). Presence of mBRAF (3.8% pts) was associated with an increased risk of death (HR 4.500, p = 0.022), whereas mKRAS (39% of pts) was not found to correlate with survival.

Conclusions: The group of TYMS polymorphisms 2RG/3RG, 2RG/LOH, 3RC/LOH, the absence of ins/LOH and absence of mBRAF were associated with better prognosis of pts with early stage CRC. Mutated KRAS was not found to affect relapse or risk of death in the adjuvant setting. Further prospective studies investigating the role of TYMS polymorphisms and mBRAF are warranted to identify pts who could benefit from 5FU-based cytotoxic chemotherapy.

Legal entity responsible for the study: Anna Koumarianou.

Funding: National and Kapodistrian University of Athens.

Disclosure: All authors have declared no conflicts of interest.

526P Results of the national organised colorectal cancer screening program with FIT in Paris

A. Pellat[1], R. Coriat[2], S. Chaussade[2]

[1]Medical Oncology, Hôpital Saint-Antoine, Paris, France, [2]Gastroenterology and Digestive Oncology, Hôpital Cochin, Paris, France

Background: In France, colorectal cancer (CRC) benefits from a nationwide screening program. The faecal immunochemical test (FIT) is being used since April 2015. The test is recommended in asymptomatic patients followed by a colonoscopy if positive for identification and treatment of colorectal lesions. We investigate the CRC national organised screening program using FIT in Paris.

Methods: We performed a retrospective observational study, collecting data from the screening program in Paris using the ADECA75 database. Rates of participation, numbers of positive FIT, detection rates and positive predictive values (PPV) for advanced adenomas (AA) and/or CRC were determined.

Results: Between 01/01/2016 and 30/06/2017, 620.227 Parisians were eligible and 409.340 were invited to participate to the program. A total of 88.796 participants (23%) performed the test with 3.839 positive tests (4.3%). In the positive test population, 2.706 out of 3.839 individuals (70.5%) performed the required colonoscopy with available reports. Histology reports were only available for 2.401 participants (88,7%). Regarding lesions, 733 (30,5%) and 205 patients (8.5%) had AA and CRC, respectively.

Conclusions: Over 18 months of screening with FIT in Paris, the PPV is in line with expected results while the participation rate is below European recommendations.

Legal entity responsible for the study: Gastroenterology and Digestive Oncology Department, Cochin Hospital, Paris.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

527P Screening strategy of Lynch syndrome for Chinese colorectal cancer patients with MLH1-immunoloss

W. Wang, L. Dong, S. Zou, N. Lu

Pathology Department, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

Background: Inactivation of MLH1 due to promoter hypermethylation strongly suggests a sporadic origin, and nearly half sporadic colorectal cancer patients harbor BRAF mutation, providing exclusion criteria for Lynch syndrome (LS). However, there was little evidence from Chinese population. The aim of this study was to compare the utility of two tests, and explore the possibility of substituting BRAF immunohistochemical staining (IHC) for real-time PCR.

Methods: We reviewed MMR expression status of consecutive patients who had undergone surgery for colorectal cancer between 2012.1.1 and 2014.12.30 in Chinese National Cancer Center. Among 317 patients who were identified as dMMR, 170 patients with MLH1 immunoloss were taken into final analysis. MLH1 methylation status was evaluated by MS-PCR(methylation – specific PCR) ,BRAF mutation was tested by IHC and real-time PCR.

Results: 52.9%patients display MLH1 promoter hypermethylation. As for BRAF status, the mutation rate tested by IHC and real-time PCR was 14.1% and17.1%, respectively, and the concordance rate was 92.1%. BRAF mutation did better on ruling out patients whose relatives had CRC history. Although patients who had unmethylated CRCs had a notably stronger family history of CRC, there were still 13.3% patients in the hypermethylation group having family history of CRC, indicating a likelihood of LS.

Table: 527P

Feature	MLH1 methylated n = 90	MLH1 unmethylated n = 80	P	BRAF mutation n = 24	BRAF wild-type n = 146	p
Median age	62y	50y		64y	54y	
Synchronic CRC	3(3.3)	8(10.0)	0.078	1(4.2)	10(6.8)	0.962
FDR or SDR with LS-related tumor	17(18.9)	14(17.5)	0.815	3(12.5)	28(19.2)	0.617
FDR or SDR with CRC	12(13.3)	32(40)	0.000	0	44(30.1)	0.002
FDR with CRC	9(10.0)	27(35.0)	0.000	0	36(24.7)	0.016
Revised Bethesda guidelines	43(47.8)	69(86.3)	0.000	8(33.3)	104(71.2)	0.000

Conclusions: The mutation rate of BRAF in Chinese population with MSI CRCs was significantly lower than that in western countries, leading to a decreased specificity. Thus, BRAF mutation alone was not efficient to be a negative predictor of LS. Due to the high specificity of MLH1 methylation test and the high concordance rate of IHC and real-time PCR for BRAF mutation, patients who have MLH1 hypermethylation, BRAF wild-type tested by IHC and family history of CRC should be recommended for germline mutation test additional to those with MLH1 unmethylated CRCs.

Legal entity responsible for the study: National Cancer Center, China.

Funding: Chinese Academy of Medical Science.

Disclosure: All authors have declared no conflicts of interest.

528P Early detection of colorectal cancer using breath biomarkers: Preliminary study

G. Woodfield[1], I. Belluomo[1], H. Panesar[1], G.P. Lin[1], P. Boshier[1], A. Romano[1], J. Martin[2], C. Groves[3], B. Saunders[4], W. Atkin[1], G.B. Hanna[1]

[1]Department of Surgery and Cancer, Imperial College London, London, UK, [2]Gastroenterology, Imperial College Healthcare NHS Trust, London, UK, [3]Gastroenterology, St George's Healthcare NHS Trust, London, UK, [4]Gastroenterology, St Mark's Hospital, London, UK

Background: Colorectal cancer (CRC) is the 2nd most common UK cause of cancer death. The bowel cancer screening programme (BCSP) has saved lifes through early cancer diagnosis. However, it only targets those aged 60-74, and leads to many potentially unnecessary colonoscopies. A breath test could be used as a more specific non-invasive screening tool, or to triage/reassure symptomatic patients. Prior studies have shown promising results using exhaled propanal for detecting CRC (96% sensitivity/76% specificity). The Colorectal BReath Analysis (COBRA) study aims to determine the diagnostic accuracy of breath volatile organic compounds for detecting CRC, first by analysing breath of known colorectal cancer patients, then by testing the resultant diagnostic model on a prospective BCSP population, target 2000 patients.

Methods: Clinical data was collected from patients attending for colonoscopies or CRC surgery across 4 London centres July 2017 to May 2018. Exhaled breath (500mls) was collected using the ReCIVA™ breath sampling device, onto thermal desorption tubes. Analysis by gas chromatography mass spectrometry and proton transfer reaction (PTR) mass spectrometry identified and quantified breath compounds.

Results: 426 patients were recruited for this preliminary dataset. 80 samples were excluded due to inadequate colonoscopies, instrument faults or inadequate quality measures. This left 346 patients; 20 with known CR adenocarcinoma were sampled pre-operatively, the rest from endoscopy units pre-colonoscopy. All were nil by mouth having had bowel preparation. Colonoscopy results showed: 29 CR adenocarcinoma, 84 normal, 35 benign pathology, 31 IBD, 83, 20 and 57 with low, intermediate and high risk polyps, and 7 with polyposis syndromes. PTR data analysis so far indicates that there are discriminatory breath compounds between pathology groups, but analysis is ongoing to investigate potential confounders.

Conclusions: Further analysis of this preliminary dataset is expected to reveal compounds of interest for colorectal cancer diagnosis. The true diagnostic accuracy of breath testing is expected to be revealed once these compounds are tested on the larger population dataset for COBRA (recruitment ongoing since January 2018).

Legal entity responsible for the study: Imperial College London.

Funding: Imperial College Charity - Rosetrees.

Disclosure: All authors have declared no conflicts of interest.

529P Survival of stage IV colorectal cancer: Interaction of cancer location, microsatellite instability and KRAS mutation

J. Uhlig[1], S. Stein[2], J. Lacy[3], C.S. Fuchs[3], H.S. Kim[1]

[1]Section of Interventional Radiology, Yale School of Medicine - Interventional Radiology Yale Cancer Center, New Haven, CT, USA, [2]Medical Oncology, Yale School of Medicine, New Haven, CT, USA, [3]Yale Cancer Center, Yale University, New Haven, CT, USA,

Background: The current literature on stage IV colorectal cancer (CRC) indicates a survival advantage for left-sided CRC. Still, the biological basis remains unclear. We assessed the interaction of cancer location with microsatellite instability (MSI) and KRAS mutation to elaborate how key molecular features modify the effect of cancer location on overall survival.

Methods: The 2010-2015 United States National Cancer Database was searched for stage IV colorectal adenocarcinomas. Overall survival (OS) was assessed via Cox models, implementing 2/3-way interaction terms.

Results: A total of 73,685 patients were included, of which n = 11,720/n=25,433 had data on microsatellite and KRAS status. Left-sided CRC was an independent predictor of improved OS (vs. right: HR = 0.75, $p < 0.001$). Rectal cancer had highest OS (2/5-year OS: 43%/10%) compared to cancers of the rectosigmoid junction (HR = 1.07), sigmoid (HR = 1.12), descending colon (HR = 1.19), transverse colon (HR = 1.41), ascending colon (HR = 1.45) or cecum/appendix (HR = 1.45, $p < 0.001$ respectively). Patients with stable microsatellites (MSS) had improved OS versus MSI (HR = 0.93, $p = 0.027$); KRAS wildtype showed superior OS over KRAS mutation (HR = 0.88, $p < 0.001$). CRC location interacted with microsatellite status and KRAS mutation: the prognostic impact of MSS was more pronounced in rectal cancers versus other locations (interaction $p < 0.001$); the prognostic impact of KRAS wildtype was larger in rectal cancers (interaction $p < 0.001$). In a 3-way interaction model, the largest prognostic impact of MSS and KRAS wildtype was noted for rectal cancer (interaction term $p < 0.05$). The table summarizes 2/4-year OS rates.

Table: 529P Adjusted 2-year and 4-year OS rates by cancer location and mutational status

Location / mutational status	Two year OS	Four year OS
rectal CRC, MSS, KRAS wildtype	68%	38%
rectal CRC, MSS, KRAS mutation	56%	29%
rectal CRC, MSI, KRAS wildtype	66%	39%
rectal CRC, MSI, KRAS mutation	43%	18%
other CRC, MSS, KRAS wildtype	60%	31%
other CRC, MSS, KRAS mutation	52%	24%
other CRC, MSI, KRAS wildtype	47%	25%
other CRC, MSI, KRAS mutation	48%	20%

Conclusions: Survival for stage IV CRC shows marked variation depending on location, MSI and KRAS mutation. The prognostic effects of molecular features varies by CRC location, demonstrating largest impact in rectal cancers.

Legal entity responsible for the study: Hyun S. Kim, MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

530P Influence of primary tumour sidedness on survival after upfront primary tumour resection (PTR) in synchronous metastatic colon cancer (mCC)

K.L. van Rooijen[1], S.A. Kurk[1], D.E.W. van der Kruijssen[1], S. Elias[2], A.M. May[3], A. Cats[4], G-J.M. Creemers[5], F.L.G. Erdkamp[6], O.J. Loosveld[7], C.J. Rodenburg[8], P.J. Tanis[9], G.R. Vink[10], J.H.W. de Wilt[11], C.J.A. Punt[12], M. Koopman[1]

[1]Medical Oncology, University Hospital Utrecht, Utrecht, Netherlands, [2]Epidemiolgy, Julius Center of Health Academy, Utrecht, Netherlands, [3]Julius Center, University Hospital Utrecht, Utrecht, Netherlands, [4]GI Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [5]Department of Medical Oncology, Catharina Hospital, Eindhoven, Netherlands, [6]Medical Oncology, Zuyderland Medical Center-Sittard-Geleen, Sittard, Netherlands, [7]Medical Oncology, Amphia Ziekenhuis-location Molengracht, Breda, Netherlands, [8]Medical Oncology, Meander Medical Center, Amersfoort, Netherlands, [9]Surgical Oncology, Academic Medical Center, Amsterdam, Netherlands, [10]General Oncology, Netherlands Comprehensive Cancer Organisation, Utrecht, Netherlands, [11]Surgical Oncology, University Medical Center St Radboud, Nijmegen, Netherlands, [12]Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background: Retrospective data suggest a survival benefit for PTR in synchronous mCC, which is the topic of ongoing prospective trials. Whether outcome after PTR varies by primary tumour sidedness, an important prognostic factor in colorectal cancer (CRC), is currently unknown. We investigated the impact of upfront PTR followed by systemic treatment in synchronous mCC according to sidedness within two randomized phase 3 trials (CAIRO and CAIRO2).

Methods: A total of 408 synchronous mCC patients, with available data on both PTR status and sidedness, were included (CAIRO n = 279; CAIRO2 n = 129, excluding patients treated with both bevacizumab and cetuximab). We used mixed effect Cox regression models to study the association between PTR and overall survival (OS) and to estimate hazard ratios (HR). Models were adjusted for age, treatment arm, WHO performance status (PS), serum lactate dehydrogenase (LDH) and year of enrollment as potential confounders. To analyze whether PTR effect was modified by sidedness, we tested the interaction term of PTR status and sidedness.

Results: A total of 191 patients (46.8%) had right-sided mCC and 217 patients (53.2%) had left-sided mCC. The rate of PTR was comparable in right-sided (69.1%) and left-sided (65.0%) mCC. Patients who underwent PTR had better PS and LDH level compared to patients without PTR. Univariable and multivariable analyses demonstrated significant and comparable ($p_{interaction} > 0.05$) survival benefits after upfront PTR for both right-sided and left-sided mCC (Table).

Table: 530P

HR (95%CI) for OS after PTR versus no PTR

	Right-sided mCC (n = 191)	Left-sided mCC (n = 217)	pinteraction	Overall effect (n = 408)
Univariable	0.53 (0.38-0.73)	0.66 (0.49-0.87)	0.31	0.61 (0.50-0.76)
Multivariable	0.60 (0.42-0.84)	0.72 (0.53-0.96)	0.43	0.69 (0.55-0.87)

Conclusions: The previously reported better survival after PTR among synchronous mCRC patients included in the CAIRO and CAIRO2 trials was significant for all mCC patients in our analysis, independent of sidedness. Prospective randomized trials on the prognostic effect of PTR in synchronous mCC, i.e. the CAIRO4 trial, remain valid for mCC patients with both right- and left-sided primary tumours.

Clinical trial identification: CAIRO: NCT00312000, published: July 14, 2007 (Lancet) CAIRO2: NCT00208546, published: February 5, 2009 (N Engl J Med).

Legal entity responsible for the study: University Medical Center Utrecht, Utrecht, The Netherlands.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

531P The clinical features and genomic landscape of elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) in patients with colorectal cancer

M-H. Chen[1], S-C. Chang[2], P-C. Lin[3], S-H. Yang[4], C-C. Lin[4], Y-T. Lan[4], H-H. Lin[4], C-H. Lin[5], W-Y. Liang[6], W-S. Chen[4], J-K. Jiang[7], J-K. Lin[7]

[1]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, [2]Department of Surgery, Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan, [3]Department of Health and Welfare, University of Taipei, Taipei, Taiwan, [4]Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, [5]Division of Genomic Medicine, National Health Research Institutes, Taipei, Taiwan, [6]Pathology, Taipei Veterans General Hospital, Taipei, Taiwan, [7]Taipei Veterans General Hospital, Department of Surgery, Taipei, Taiwan

Background: The form of microsatellite instability (MSI) affecting tetranucleotide repeats known as EMAST (elevated microsatellite alterations at selected tetranucleotide repeats) has emerged as a new potential biomarker in multiple cancers. In colorectal cancer (CRC), the clinical implications and mutation spectrum of EMAST mutations remain inconclusive.

Methods: We evaluated 1,505 CRC cases using five EMAST markers (D20S82, D20S85, D8S321, D9S242 and MYCL1) and the Bethesda panel of MSI markers. Most commonly mutations involved in CRCs were identified by MassArray Assay and DNA repair genes were analyzed by Next-Generation Sequencing (NGS). Clinical characteristics and prognostic relevance were correlated with EMAST. SPSS software (version 16.0) was used to perform all statistical analyses.

Results: Tumors with EMAST-positivity were detected in 159 (10.6%) out of 1,505 CRC cases and associated with unique clinical features including female predominance ($p = 0.017$), higher prevalence of proximal colon tumors ($p < 0.001$), early stage tumors ($p = 0.002$), poorly differentiated tumors ($p < 0.001$), mucinous histology ($p = 0.001$), and MSI ($p < 0.001$) and higher incidence of mutations in PI3KCA ($p = 0.003$), BRAF ($p < 0.001$), TGFßR ($p < 0.001$), PTEN ($p = 0.001$), and AKT1 ($p = 0.04$) compared with EMAST-negative tumors. Compared with EMAST-positive alone or MSI-H alone tumors, EMAST-positive MSI-H tumors had higher rates of MSH6, MSH3, PMS2, and EXO1 gene mutation ($p < 0.001$, $p = 0.005$, $p = 0.001$, and $p = 0.027$) and MLH1, MSH6, and EXO1 gene mutation ($p = 0.019$, $p = 0.005$, and $p = 0.046$), respectively. Finally, EMAST-positivity was a good prognostic indicator in early stage CRC ($p = 0.002$) but not in late CRC ($p = 0.920$).

Conclusions: The EMAST defines a unique molecular subtype of CRC.

Legal entity responsible for the study: Taipei Veterans General Hospital.

Funding: Taipei Veterans General Hospital, Ministry of Science and Technology.

Disclosure: All authors have declared no conflicts of interest.

532P Identification of positively and negatively selected driver gene mutations associated with colorectal cancer with microsatellite instability

V. Jonchere[1], L. Marisa[2], M. Greene[3], A. Guilloux[4], A. Collura[1], A. De Reynies[2], A. Duval[1]

[1]Centre De Rercherche (CdR) Saint-Antoine INSERM - UMR S 938, Hôpital Saint-Antoine, Paris, France, [2]Programme 'Cartes d'Identité des Tumeurs', Ligue Nationale Contre le Cancer, Paris, France, [3]UMRS 938, INSERM, Paris, France, [4]UMR 8071, Évry University, Évry, France

Background: Recent studies have shown that cancers arise due to the positive selection of driver somatic events in tumor DNA, with negative selection playing only a minor role. However, these investigations were concerned with alterations at non-repetitive sequences and did not take into account mutations in repetitive sequences that have very high pathophysiological relevance in the tumors displaying Microsatellite Instability (MSI) due to mismatch repair deficiency investigated in the present study.

Methods: We performed whole exome sequencing of 47 MSI CRC and confirmed results in an independent cohort of 53 MSI CRC. We used probabilistic model of mutational events within microsatellites, while adapting preexisting models to analyze non-repetitive DNA sequences. Negatively selected coding alterations in MSI CRC were investigated for their functional and clinical impact in CRC cell lines and in a third cohort of 164 MSI CRC patients.

Results: Both positive and negative selection of somatic mutations in DNA repeats was observed, leading us to identify the expected driver genes associated with the MSI-driven tumorigenic process. Several Coding negatively selected, MSI-related mutational events (n = 5) were demonstrated to have deleterious effects on tumor cells. In the tumors in which deleterious MSI mutations are observed despite the negative selection, they were associated with worse survival in MSI CRC patients (hazard ratio [HR], 3; 95% confidence interval, 1.1-7.9; $p = 0.03$), suggesting their anticancer impact should be offset by other as yet unknown oncogenic processes that contribute to poor prognosis.

Conclusions: The present results shed new light on the main driver somatic mutations acting in MSI-driven tumorigenesis, suggesting that genomic instability in MSI CRC plays a dual role in achieving tumor cell transformation.

Legal entity responsible for the study: INSERM.

Funding: This work was supported by grants from the 'Institut National du Cancer' (INCa, PRTK MICROSPLICOTHER, SIRIC, and HTE CoLi, to AD), the Fondation ARC (to AC) and the Canceropole Ile de France (to AC). AD group has the label 'La Ligue Contre le Cancer'. This work is part of the Cartes d'Identité des Tumeurs (CIT) research program, funded and developed by the Ligue Nationale Contre le Cancer.

Disclosure: All authors have declared no conflicts of interest.

533P Distinct clinico-pathological features of hypermutant colorectal cancers with POLE pathogenic mutations, Lynch syndrome and sporadic MSI analyzed over 1,000 colorectal cancer patients

T. Nagasaka[1], A. Nyuya[1], H. Tanioka[1], Y. Katata[1], M. Yokota[2], F. Taniguchi[3], T. Kawai[4], Y. Mori[4], K. Shigeyasu[4], M. Okawaki[1], M. Yamamura[1], Y. Umeda[4], A. Tsuruta[5], T. Ueno[5], Y. Yamaguchi[1]

[1]Medical Oncology, Kawasaki Medical School Hospital, Kurashiki, Japan, [2]General Surgery, Kurashiki Central Hospital, Kurashiki, Japan, [3]Surgery, Iwakuni Clinical Hospital, Iwakuni, Japan, [4]Gastroenterological Surgery, Okayama University Hospital, Okayama, Japan, [5]Digestive Surgery, Kawasaki Medical School Hospital, Kurashiki, Japan

Background: POLE proofreading mutations cause ultrahypermutant-phenotype in colorectal cancer (CRC) but the characters of POLE mutations are still obscure in contrast to Lynch syndrome or sporadic microsatellite instability (MSI). Herein, we examined mutation profiles of POLE in 1,039 CRC Japanese patients, and tried to clarify clinico-pathological features of hypermutant CRC patients with respect to POLE mutations, Lynch syndrome and sporadic MSI.

Methods: We analyzed POLE pathogenic hotspot (exon9, 13 and 14), BRAF codon 600 and KRAS exon 2 mutations by Sanger sequencing. MSI status was confirmed by a multiplex PCR assay. MSI positive cases were confirmed the four mismatch repair (MMR) proteins (MLH1, MSH2, PMS2, and MSH6) expression. Germline mutations were analyzed by Sanger sequencing and a TruSight One Sequencing Panel using a next generation sequencer.

Results: Of 1,039 CRC patients, only four cases showed POLE pathogenic mutations (two P286R, one V411L and one S459F). The four POLE-mutant CRCs showed no MSI. CRC with MMR deficient (=MSI) were observed in 58 cases (5.6%). Of CRCs with MSI, Lynch syndrome was found in 17 cases and the rest of 41 cases were sporadic MSI. Therefore, we divided 1,039 CRCs into the four subsets; POLE-mutant (POLE; n = 4, 0.4%), Lynch syndrome (LS; n = 17, 1.6%), sporadic MSI (MSI; n = 41, 4.0%), and non-hypermutant CRCs (NH; n = 997, 94.0%). Mean age at diagnosis in POLE/LS/MSI/NH was 52.5/55.7/73.6/65.9 years, respectively ($P < .0001$). Frequency of female in POLE/LS/MSI/NH was 50/23.5/61/41% ($P = 0.03$). The primary tumor located at the right colon was observed in 100/35/80.5/30% of POLE/LS/MSI/NH ($P < .0001$). BRAF mutation was observed in 49% of MSI and 4% of NH while KRAS mutation was in 35% of LS and 32% of NH ($P < .0001$). Interestingly, 100/82/78% of POLE/LS/MSI tumors were diagnosed at the earlier stage, I or II, while 46% of NH ($P < .0001$). The recurrence free survival rate at 5-years was better in POLE (100%)/LS (86%)/MSI (94%) compared with that in NH (74%).

Conclusions: POLE-mutant CRC was rare, observed in the younger without family history, located at the right colon, and diagnosed at the earlier stage.

Legal entity responsible for the study: The authors.

Funding: The Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Disclosure: All authors have declared no conflicts of interest.

534P Patterns of germline and somatic mutations in 16 mismatch repair associated genes analyzed with next generation sequencing (NGS) in colorectal cancer with EMAST (+) and/or MSI-high

S-C. Chang[1], P-C. Lin[2], C-C. Lin[1], J-K. Lin[3], Y-T. Lan[1], J-K. Jiang[3], S-H. Yang[1], C-H. Lin[4], W-S. Chen[1]

[1]Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, [2]Department of Clinical Pathology, Taipei City Hospital, Taipei, Taiwan, [3]Taipei Veterans General Hospital, Department of Surgery, Taipei, Taiwan, [4]Division of Genomic Medicine, National Health Research Institutes, Taipei, Taiwan

Background: We assume that besides mismatch repair (MMR) genes, next generation sequencing (NGS) of MMR associated genes could improve detection of driver mutattors and clarify the somatic mutation patterns of subtypes CRC classfied by EMAST and MSI-high.

Methods: Extracted from a 1505 CRC cases database,81 cases with MSI-high and EMAST+,78 cases with EMAST+ and MSS, and 72 cases with MSI-high but EMAST- were identified. The tumor and WBC DNA were applied and got from Biobank of Taipei-Veteran General Hospital afer approval of IRB. The germline and somatic mutations were analyzied with 16- genes NGS (illumina HiSeq2500 system).

Results: Totally 284 pathological germline mutations were identified in 161 patients with MSI-high or EMAST+. The most common gene mutations were EPCAM (17.3%), MSH6 (16.9%), followed by MLH1 (15.2%), and AXIN2(15.2%). Majority of EMAST and MSI resulted from not only MMR dysfunction, but also germline mutations of AXIN2, POLD1 and TGFBR2. After deduction of 284 germline mutations, there were 1,090 somatic mutations in 161 cases with germline mutations, 445 mutations in 70 cases without germline mutations. Tumors with EMAST+ and MSI-high had signifcantly higher mutation number than those of tumors with only EMAST+ or only MSI-high. Besides germline mutations of AXIN2, germline mutations of other genes were similar. With AXIN2 germline mutations, somatic mutation rate was 187.7 ± 97.8 mut/MB significantly higher than those of without germline mutations (137.8± 84.5 mut/MB $p = 0.002$). Besides five major MMR genes, Eleven Axin2, eight POLE and six TGFbR2 germline mutations resulted in following MSI-high or EMAST (+) genotype without other accompany germline mutation. Clinically, patients with germline mutation had significantly higher frequency of proximal tumor location and early stage disease.

Conclusions: Our result showed that NGS could enhance detection of familial CRC. Somatic mutation burden might be through MSI or EMAST but not only germline mutation genes themselves. Several genes with germline mutations could explain origin of the familiar CRC. AXIN2 gene deserved to do futher experiment to confirm its role in WNT pathway and as a hypermutator.

Legal entity responsible for the study: The Institutional Review Board of Taipei Veterans General Hospital (number 2017-06-004BC).

Funding: Taipei-Veterans General Hospital, Taiwan.

Disclosure: All authors have declared no conflicts of interest.

535P Lower tumor mutational burden (TMB) and hepatic metastases may predict for lack of response to PD-1 blockade in MSI-H metastatic colorectal cancer (MCRC)

I. Amanam[1], J. Chao[1], D. Lim[1], S. Rahmanuddin[1], A.B. Schrock[2], S.M. Ali[2], C. Lau[1], D. Chevalier[1], E. Harris[1], J. Saluja[1], C. Wang[1], M. Fakih[1]

[1]Department of Medical Oncology and Therapeutics, City of Hope, Duarte, CA, USA, [2]Genetics, Foundation Medicine, Cambridge, MA, USA

Background: MCRC with microsatellite instability (MSI-H) are associated with cytotoxic lymphocytic infiltration that is counterbalanced by multiple checkpoints. Several prospective clinical trials in chemotherapy-resistant MSI-H MCRC have demonstrated a high rate of disease control and a favorable progression free survival (PFS) with PD-1 inhibitors. However, there is a significant discrepancy in response rates (RR) with pembrolizumab and nivolumab (28% to 52%), likely reflecting patient heterogeneity. We sought to determine the RR to PD-1/PD-L1 targeting in a single center setting.

Methods: All MCRC patients (pts) with MSI-H tumors (by CLIA certified PCR, IHC, or NGS assays) who were treated at City of Hope with PD-1 or PD-L1 inhibitors starting Jan 2016 were identified. RR and PFS were determined by RECIST 1.1. BRAF status, primary tumor location, and metastatic sites were collected on all pts. TMB as determined by FoundationOne® on 0.83-1.1 megabases (Mb) of sequenced DNA was collected, when available.

Results: 17 pts with MSI-H tumors were identified (16 treated with pembrolizumab and 1 with darvulumab). Pts characteristics were: males (10, 59%), age (median 53.7 years, range 33-78), BRAF mutant (6, 35%), right sided (11, 65%), and liver-sparing (8, 47%). 7 (41%) had an objective response, 2 (12%) had stable disease. The median PFS was 9.97 months (mo), and the 6 and 12 mo PFS rates were 53% and 35%, respectively. TMB was available for 9 MSI-H cases (range 8 – 73 mutations/Mb): 1 CR (TMB 73), 1 PR (TMB 71), and 1 SD (TMB 31), and 6 PD (TMB: 6, 13, 16, 18, 25, 36). We categorized our patients based on the lowest 10% (TMB < 23.5) and 25% (TMB < 33.06) TMB cut points identified from a large Foundation Medicine database of MSI-H MCRC. All 4/4 patients in the lowest TMB decile and 5/6 in the lowest TMB quartile experienced PD. On univariate analysis, only hepatic metastases ($p = 0.01$) and low TMB ($p = 0.02$) were associated with poor PFS.

Conclusions: A substantial percentage of pts with MSI-H tumors will progress with PD-1/PD-L1 inhibitors; these patients appear to be enriched for a low TMB status and hepatic metastases. Additional studies should explore TMB as a predictive marker of response to checkpoint inhibition in MSI-H CRC.

Legal entity responsible for the study: City of Hope.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

536P Comparison of microsatellite status detections in colorectal carcinoma

M. Chen, L. Yu, B. Liu, X. Qian, M. Yang

The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University& Clinical Cancer Institute of Nanjing University, Nanjing, China

Background: There are two commonly accepted methods for detecting microsatellite status: the one is to detect amplified microsatellite loci by polymerase chain reaction (PCR), and the other is to detect mismatch repair gene (MMR) proteins expression by immunohistochemistry(IHC). The PCR detection is considered to have accuracy in clinic, while the IHC is widely used because of its easier operation and cheaper expense.

Methods: In order to compare IHC with PCR in detecting the microsatellite status in colorectal carcinoma, A total of 569 samples of colorectal carcinoma resection were collected in Department of Pathology, Nanjing Drum Tower Hospital between June 2014 and June 2017, all samples were used IHC and PCR to detect microsatellite status, the consistency of results between the two methods was compared.

Results: We found that 48 cases of microsatellite instability (MSI) were detected by PCR, including 37 cases of microsatellite instability high (MSI-H), 11 cases of microsatellite instability low (MSI-L) and 521 cases of MSS. MSI accounted for 8.44% of all cases, of which the MSI-H accounted for 6.50%.The IHC results of 569 patients showed that 69 cases were deficient mismatch repair (dMMR), 500 cases were proficient mismatch repair (pMMR), dMMR accounted for 12.13% of all cases. The loss expression of PMS2 protein was the most common while the MSH6 was rare. The coincidence rate of the two methods for detecting microsatellite states was 91.92%.

Conclusions: IHC and PCR method had high consistency in microsatellite status. Compared with PCR, IHC method is more economical, convenient for clinical operations. When the 4 repair proteins were without missing detected by IHC, it can be diagnosed as MSS / MSI-L, further PCR was not necessary, and when any repair protein is found to be deficient, PCR detection was needed to determine whether there existed MSI. Our conclusion will save a lot of time and cost for clinical work.

Legal entity responsible for the study: The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University& Clinical Cancer Institute of Nanjing University.

Funding: National Natural Science Foundation of China; Nanjing Medical Science and Technique Development Foundation.

Disclosure: All authors have declared no conflicts of interest.

537P Assessment of local clinical practice for testing of mismatch repair deficiency in metastatic colorectal cancer: The need for new diagnostic guidelines prior to immunotherapy

R. Cohen[1], E. Hain[2], O. Buhard[2], A. Guilloux[3], A. Bardier[4], R. Kaci[5], P. Bertheau[6], F. Renaud[7], F. Bibeau[8], J-F. Fléjou[9], T. André[1], M. Svrcek[9], A. Duval[2]

[1]Medical Oncology, Sorbonne Université, AP-HP, Hôpital Saint-Antoine, Paris, France, [2]Centre de Recherche Saint-Antoine, Equipe Instabilité des Microsatellites et Cancer, Equipe Labellisée par la Ligue Nationale Contre le Cancer, Sorbonne Université, INSERM, Unité Mixte de Recherche Scientifique 938 and SIRIC CURAMUS, Paris, France, [3]UMR 8071, Évry University, Évry, France, [4]Pathology, AP-HP, Hôpital Pitié Salpétrière, Paris, France, [5]Pathology, AP-HP, Hôpital Lariboisière, Paris, France, [6]Pathology, AP-HP, Hôpital Saint-Louis, Paris, France, [7]Pathology, CHU Lille, Lille, France, [8]Service d'Anatomie Pathologique, CHU de Caen, Caen, France, [9]Pathology, Sorbonne Université, AP-HP, Hôpital Saint-Antoine, Paris, France

Background: Immune checkpoint inhibitors (ICKi) have been approved for patients with metastatic colorectal cancer (mCRC) displaying MSI/dMMR (microsatellite instability, defective mismatch repair). We aimed to evaluate the accuracy of standard immunohistochemistry and PCR methods for the detection of MSI/dMMR in mCRC in routine clinical practice.

Methods: The study was performed on a multicenter retrospective cohort of mCRCs previously determined as MSI and/or dMMR by local assessment and on a prospective, single center cohort of patients included in ICKi trials based on positive MSI and/or dMMR status previously determined by the originating institutes. We re-assessed dMMR and MSI status in our specialized diagnostic center using immunohistochemistry (antibodies directed against MLH1, MSH2, MSH6 and PMS2), and pentaplex PCR (BAT-25, BAT-26, NR-21, NR-24 and NR-27). The positive predictive value (PPV) of local assessment was the primary objective of the study. Detection rate (i.e. conclusive result) and sensitivity of immunohistochemistry and PCR by central review were evaluated.

Results: Nine false-positives (9.8%) were found in the retrospective cohort (N = 92). These were initially diagnosed as MSI and/or dMMR by the originating institute but were reclassified as MMR proficient /microsatellite stable in our laboratory (PPV=90.2%; 95%CI, 82.2-95.0). The PPV in the prospective cohort (N = 39) was 92.3% (95%CI, 79.0-98.1), with the 3 false-positive patients experiencing progressive disease with ICKi treatment. Amongst the 119 true-positive mCRCs, the detection rate and sensitivity were respectively 100% and 95.8% for immunohistochemistry, while for pentaplex PCR these were 81.5% and 95.9%. Only the combination of immunohistochemistry and pentaplex PCR methods resulted in 100% detection rate and 100% sensitivity.

Conclusions: Local assessment of MSI/dMMR status in mCRC resulted in misdiagnosis of 9.1% of cases as false positive and subsequently incorrect treatment with ICKi. We recommend new guidelines that mandate dual testing of mCRC samples in experienced diagnostic centers using both PCR and immunohistochemistry.

Legal entity responsible for the study: INSERM.

Funding: ARCAD Foundation, Institut National du Cancer, Ligue Contre Le Cancer.

Disclosure: T. André: Consultancy: Bristol-Myers Squibb, Fees: Merck. All other authors have declared no conflicts of interest.

538P The prognostic role of PD L1 expression according to MSI status in stage III colon cancer after curative resection

S-H. Cho[1], H-J. Shim[1], J.E. Hwang[1], W-K. Bae[1], I.J. Chung[2]

[1]Hemato-Oncology, Chonnam National University Medical School & Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea, [2]Hemato-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea

Background: Tumors expressing programmed death ligand 1 (PD-L1) can render immune inactivated via triggering of PD-1 receptor on T cells with various pathways. Based on this mechanism, the blockade PD-1/PD-L1 pathway has been used as a therapeutic target for metastatic CRC. In the present study, we evaluated the prognostic role of PD-L1 expression associated with microsatellite status in surgically resected stage III colon cancer patients.

Methods: PD-L1 expression was performed by immunohistochemistry from 182 stage III colon cancer patients after curative resection. The percentage of PD-L1 positive tumor cells and staining intensity were evaluated and categorized as 'strong' or 'weak' positive group. Clinical and histopathologic parameters including of MSI status and survival outcomes were analyzed with IDO expression which stands for the suppressive immune environment.

Results: Strong PD-L1 expression was observed in 29% of all patients. Perineural invasion and lymphocyte response were more frequently shown in strong expression of PD-L1 grop. Among resected patients, MSI was shown in 23 patients (12%). Although there was no significant difference between microsatellite status and PD-L1 expression, strong PD-L1 tended to better overall survival in microsatellite stable (MSS) colon cancer ($P = 0.056$). In contrast, strong PD-L1 expression was significantly correlated with worse DFS ($P = 0.001$) and OS ($P < 0.001$) than weak PD-L1 expression group in microsatellite instability (MSI) patients, regardless of adjuvant chemotherapy. Also, the strong IDO expression was tended to be more frequently shown in strong PD-L1 expression (36.4%) group than weak PD-L1 expression (14.3%) group in MSI patients.

Conclusions: The expression of PD-L1 is differently affected on the survival outcomes according to the status of microsatellite. There is no significant relationship between the expression of PD-L1 and prognosis in MSS stage III colon cancer patients. However, in MSI colon cancer which has been well known as a highly immunogenic property, strong PD-L1 expression is significantly associated with poor prognosis on survival outcomes reflecting the immunosuppressive microenvironment in curative resected stage III colon cancer patient.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

539P Pre-diagnostic anthropometry, sex, and risk of colorectal cancer according to tumor-infiltrating immune cell composition

J. Berntsson, J. Eberhard, B. Nodin, A.H. Larsson, K. Jirstrom

Department of Clinical Sciences, Division of Oncology and Pathology, Lund University, Lund, Sweden

Background: Obesity is a well-established risk factor for colorectal cancer (CRC), but whether this risk differs according to CRC subtype defined by the tumor immune microenvironment has been sparsely described. Herein, we examined the relationship between pre-diagnostic anthropometry and CRC risk according to tumor-infiltrating immune cell composition, with particular reference to potential sex differences.

Methods: The density of immune cells expressing PD1, PD-L1 (PD-L1/IC), CD3, CD8, FoxP3, CD20, CD68, CD163, and tumor cells expressing PD-L1 (PD-L1/TC) was assessed by immunohistochemistry in tissue microarrays with tumors from 584 incident CRC cases in the Malmö Diet and Cancer Study (n = 28098). Multivariable Cox regression models, adjusted for age, smoking and alcohol intake, were applied to calculate hazard ratios (HR) for CRC risk according to height, weight, bodyfat %, waist- and hip circumference, waist-hip ratio (WHR), body mass index (BMI), and different immune cell subsets.

Results: Obesity, measured as several anthropometric factors, was significantly associated with PD-L1$^+$/TC low, CD8$^+$ high, FoxP3$^+$ low, CD20$^+$ low, and CD163$^+$ low tumors in both sexes, and with PD1$^+$ low tumors in women. A contrasting risk between sexes was seen for PD-L1/IC$^+$ tumors, in that obesity was significantly associated with risk of PD-L1/IC$^+$ high tumors in women (p_{trend} for weight = 0.008, p_{trend} for BMI = 0.039), but with risk of PD-L1/IC$^+$ low tumors in men (p_{trend} for weight = 0.005, p_{trend} for bodyfat % = 0.003, p_{trend} for waist <0.001, p_{trend} for hip = 0.012, p_{trend} for BMI = 0.001, p_{trend} for WHR <0.001). Furthermore, obesity was associated with risk of any CD3$^+$ high or low and any CD68$^+$ high or low tumors in both sexes, and with any PD1$^+$ high or low tumors in men. In age and BMI-adjusted survival analysis, PD1$^+$, CD8$^+$, CD20$^+$, and CD68$^+$ high were favorable prognostic factors only in women, and FoxP3$^+$ high only in men. High PD-L1$^+$ and CD3$^+$ expression was prognostic in both sexes.

Conclusions: Anthropometric factors may influence the immune landscape of colorectal cancer, possibly in a sex-dependent manner. Thus, obesity and sex may be important factors to take into account when stratifying patients for immunotherapy.

Legal entity responsible for the study: Lund University.

Funding: Swedish Cancer Society, Swedish Research Council, the Swedish Government Grant for Clinical Research, the Mrs Berta Kamprad Foundation, Lund University Faculty of Medicine, University Hospital Research Grants.

Disclosure: All authors have declared no conflicts of interest.

540P Monocyte-to-lymphocyte ratio in metastatic colorectal cancer: Prognostic role evaluation and cut-off definition

D. Basile[1], S.K. Garattini[1], G. Pelizzari[1], F. Cortiula[1], L. Gerratana[1], M. Cattaneo[1], C. Corvaja[1], A. Parnofiello[1], V.J. Andreotti[1], E. Bertoli[1], C. Lisanti[1], D. Iacono[2], M. Casagrande[2], G.G. Cardellino[2], G. Miolo[3], N. Pella[2], G. Aprile[4], A. Buonadonna[3], G. Fasola[2], F. Puglisi[5]

[1]Department of Medicine (DAME), University of Udine, Udine, Italy, [2]Oncology, ASUIUD Azienda Ospedaliero-Universitaria di Udine, Udine, Italy, [3]Department of Medical Oncology and Cancer Prevention, CRO National Cancer Institute, Aviano, Italy, [4]Medical Oncology, ULSS 8 Berica, Vicenza, Italy, [5]University of Udine, Udine, Department of Medical Oncology and Cancer Prevention, CRO National Cancer Institute, Aviano, Italy

Background: Changes in peripheral blood cells composition may reflect tumor immune microenvironment and its role in cancer growth control. High monocyte-to-lymphocyte ratio (MLR) could be a sign of tumor's recruitment of suppressive cells, showing a prognostic role in many cancer types. This study aimed to evaluate the prognostic role of MLR in metastatic colorectal cancer (MCRC).

Methods: This retrospective study analyzed a consecutive cohort of 392 patients (pts) with MCRC treated in 2004-2017 at the Oncology Departments of Aviano and Udine (Italy). The prognostic impact of MLR on overall survival (OS) was evaluated with uni and multivariate Cox regression analyses. The best cut-off value to predict survival was defined through ROC analysis.

Results: Before first line therapy, 269 pts (69%) were aged <70, 120 pts (31%) had a right tumor, 150 pts (38%) a left tumor and 117 pts (30%) a rectal one. Of note, 105 pts (27%) received metastasectomy and 142 pts had >1 metastasis. Metastasis were more frequent in liver (40%), lung (20%) and peritoneum (20%) Overall, 57% had a KRAS mutation (m) and 11% had a BRAFm. At median follow-up of 60 months, median OS was 26 months. At univariate analysis, older age (HR 1.61, $p < 0.001$), nodes (pN2 HR 1.48, $p = 0.036$; pN3 HR 2.52, $p = 0.001$), KRASm (HR 1.36, $p = 0.020$) and MLR (HR 3.32, $p < 0.001$) were associated with worse OS. Conversely, sidedness (left HR 0.65, $p = 0.003$; rectum HR 0.73, $p = 0.042$), metastasectomy (HR 0.36, $p < 0.001$) and adjuvant chemotherapy (HR 0.66, $p = 0.008$) were associated with better OS. By multivariate analysis, sidedness and metastasectomy confirmed a better OS, while MLR (HR 3.20, $p < 0.001$), nodes (pN2 HR 1.89, $p = 0.006$; pN3 HR 2.25, $p = 0.014$), and KRASm (HR 1.50, $p < 0.001$) were associated with worse OS. The adoption of the cut-off value for MLR (i.e. 0.44) predicted worse OS both in univariate (HR 2.23, $p < 0.001$) and multivariate (HR 2.41; $p < 0.001$) analyses. Moreover, MLR was associated with number of metastatic sites ($p < 0.001$), type of sites ($p < 0.001$), sidedness ($p = 0.001$) and LDH level ($p < 0.001$).

Conclusions: High MLR is an independent prognostic factor associated with worse OS and pathological features of MCRC. Further studies are needed to confirm these data.

Legal entity responsible for the study: University of Udine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

541P Clinical relevance of circulating tumor DNA using amplicon-based deep sequencing panel in colorectal cancer patients with liver metastasis

H. Osumi[1], E. Shinozaki[1], H. Zembutsu[2], Y. Takeda[3], T. Wakatsuki[1], T. Ichimura[1], Y. Ota[1], I. Nakayama[1], M. Ogura[1], M. Suenaga[1], D. Takahari[1], K. Chin[1], A. Saiura[3], S. Takahashi[4], T. Noda[2], K. Yamaguchi[1]

[1]Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan, [2]Cancer Precision Medicine Center, Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan, [3]Department of Surgery, Cancer Institute Hospital of JFCR, Tokyo, Japan, [4]Department of Medical Oncology, Cancer Institute Hospital of JFCR, Tokyo, Japan

Background: Liquid biopsy system using the detection of circulating tumor DNA (ctDNA) is expected to provide the utility as a novel diagnostic tool for cancers.

Methods: We prospectively enrolled a total of 101 metastatic colorectal cancer(mCRC) patients with liver metastasis. We investigated frequency of detectable mutations in cell-free DNA (cfDNA), concordance rate of RAS mutation between tissue and cfDNA, and relationship between the mutant allele frequencies (MAFs) and clinicopathological factors. We further investigated the relationship between time course of ctDNA and chemoresponse. Amplicon-based deep sequencing with molecular barcode (including hotspots of 14 genes) was performed to detect the ctDNA.

Results: Mutation(s) in plasma cfDNA were detected in 87.1% (88/101) of patients. The frequencies of plasma cfDNA mutation at TP53, KRAS, APC, and PIK3CA were 68.3%, 38.6%, 23.7%, and 14.8%, respectively. RAS mutational concordance rate between tissues and cfDNA was 76.2% (77/101). MAFs were significantly associated with CEA ($P < 0.0001$), CA19-9 ($P = 0.006$), LDH ($P < 0.0001$) levels and the number of metastatic organs ($P < 0.0001$). Patients with liver or lymph node metastasis had significantly higher MAF compared with those without metastases ($P < 0.0001$, $P = 0.008$, respectively). The patients with lower MAF at 8 weeks after initiation of chemotherapy showed significantly longer survival than those with higher MAF (>median vs $\leq$ median, PFS, $P = 0.001$, OS, $P = 0.049$). Increase of MAF had been observed earlier than tumor markers before disease progression were confirmed by computed tomography ($P = 0.01$).

Conclusions: Our results suggested that this cfDNA assay could detect mutations at a high rate of mCRC patients, and could be a useful tool for early detection of chemoresistance as well as a prognostic marker in the clinic.

Editorial acknowledgement: Cancer Precision Medicine Center, JFCR: Ms.Aya Imai, Dr. Hiroshi Ohnishi, Mr. Yuki Sano Clinical Examination Center, JFCR: Ms. Kazumi Kaihara and Dr. Konosuke Nakayama University of Chicago: Dr. Yusuke Nakamura.

Legal entity responsible for the study: The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Institutional Review Board.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

542P Droplet digital PCR of circulating tumour DNA for the detection of RAS/BRAF mutation in metastatic colorectal cancer

E. Van Cutsem[1], K. Lesniewski-Kmak[2], M.P. Saunders[3], H. Wasan[4], G. Argiles[5], C. Borg[6], G-J.M. Creemers[7], M. Fedyanin[8], R. Glynne-Jones[9], P. Pfeiffer[10], C.J.A. Punt[11], D. Stroyakovskiy[12], A.J. Ten Tije[13], A. van de Wouw[14], V. Cattan[15], G. Desachy[16], N. Amellal[15], V.M. Moiseyenko[17]

[1]Digestive Oncology, University Hospitals Leuven, Leuven, Belgium, [2]Oncology, Szpital Morski, Gdynia, Poland, [3]Oncology, The Christie NHS Foundation Trust, Manchester, UK, [4]Oncology, Imperial College London - Hammersmith Hospital, London, UK, [5]Gastrointestinal and Endocrine Tumors Group, Vall d'Hebron Institute of Oncology, VHIO, Barcelona, Spain, [6]Oncology, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [7]Oncology, Catharina Hospital Eindhoven, Eindhoven, Netherlands, [8]Clinical Pharmacology and Chemotherapy, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [9]Radiotherapy, Mount Vernon Cancer Centre, Northwood, Middlesex, UK, [10]Experimental Research in Medical Cancer Therapy, Odense University Hospital, Odense, Denmark, [11]Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [12]Oncology, Moscow City Oncology Hospital No. 62, Moscow, Russian Federation, [13]Oncology, Amphia Ziekenhuis-location Molengracht, Breda, Netherlands, [14]Oncology, VieCuri MC, Venlo, Netherlands, [15]Oncology, Servier, Suresnes, France, [16]Methodology and Data Valorisation, Instut de Recherches Internationales Servier, Suresnes, France, [17]St. Petersburg Scientific Practical Center for Specialized Medical Care (Oncological), Petrov Research Institute of Oncology, St. Petersburg, Russian Federation

Background: Circulating tumour DNA (ctDNA) provides a non-invasive approach for gene mutation detection. The aim of this study is to evaluate the concordance of RAS/BRAF mutational status in tumour tissue and plasma in metastatic colorectal cancer (mCRC) patients.

Methods: Plasma samples were collected prospectively from previously untreated mCRC patients (TASCO1 NCT02743221) and analysed centrally by droplet digital PCR (ddPCR) with sensitivity down to 0.2% for KRAS exon 2, 0.5% for NRAS exon 2 and BRAF. Tumour RAS/BRAF status was determined locally from primary or metastatic tumours according to routine practice.

Results: Out of the 153 patients included, 121 had tissue and plasma mutation status available for KRAS exon 2, 129 patients for NRAS exon 2 and 70 patients for BRAF V600E. In these subgroups, the prevalence of KRAS exon 2, NRAS exon 2 and BRAF mutations detected in plasma was 30.6%, 0.8% and 11.4%, respectively vs. 47.1%, 1.6% and 12.9%, respectively in tumours. For KRAS, the concordance was 81.8% with a Kappa coefficient of 0.63. KRAS mutation was detected in tumour tissue and not in plasma for 21 patients (17.4%), potentially explained by low tumour burden or low tumour DNA shedding. KRAS mutation was detected in plasma but not in tumour tissue for just one patient. For NRAS, a concordance of 99.2% (kappa = 0.66) was observed between plasma and tumour tissue. One discordant case (0.8%) was observed for which NRAS was detected only in tissue. This case also presented KRAS mutation both in plasma and tumour tissue excluding an explanation related to tumour DNA shedding. For BRAF, a concordance of 95.7% (kappa = 0.80) was observed between plasma and tumour tissue: BRAF mutation was detected only in plasma in one case (1.4%) and only in tumour tissue in 2 cases (2.9%). One of the two cases displaying BRAF V600E in tumour but not in plasma also had an NRAS mutation in plasma and unknown NRAS status in tumours.

Conclusions: This study showed that RAS/BRAF mutations can be detected in plasma samples from mCRC patients by ddPCR. However, in the context of the study, analysis of the ctDNA did not allow detection of RAS/BRAF mutations in all patients where these mutations were present in the tumour.

Clinical trial identification: TASCO1 NCT02743221.

Legal entity responsible for the study: Servier Oncology.

Funding: Servier.

Disclosure: E. Van Cutsem: Research funding: Amgen, Bayer, Boehringer, Celgene, Ipsen, Lilly, Merck, Merck KgA, Novartis, Roche, Sanofi, Servier. M.P. Saunders: Honoraria: Roche, Merck, Amgen, Servier, Eisai. G. Argiles: Advisor: Hoffman la Roche, BMS, Bayer. C. Borg: Advisory boards: Roche, Servier, Sanofi; Research grant: Roche. P. Pfeiffer: Research funding: Amgen, Celgene, Lilly, Merck KgA, Roche, Taiho, Servier. V. Cattan, G. Desachy, N. Amellal: Employee: Servier. All other authors have declared no conflicts of interest.

543P Gene mutation status in circulating tumor DNA (ctDNA) and first-line FOLFOXIRI plus bevacizumab (bev) in metastatic colorectal cancer (mCRC) harboring RAS mutation

Y. Sunakawa[1], J. Usher[2], H. Satake[3], Y. Jaimes[2], Y. Miyamoto[4], M. Nakamura[5], M. Kataoka[6], M. Shiozawa[7], A. Takagane[8], T. Terazawa[9], T. Watanabe[10], K. Ishigure[11], C. Tanaka[12], T. Sekikawa[13], M. Takeuchi[14], M. Fujii[15], K. Danenberg[2], P.V. Danenberg[16], H-J. Lenz[17], W. Ichikawa[13]

[1]Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan, [2]Liquid Genomics, NantHealth, Inc., Culver City, CA, USA, [3]Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan, [4]Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan, [5]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan, [6]Surgery, National Hospital Organization Nagoya Medical Center, Nagoya, Japan, [7]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, [8]Surgery, Hakodate Goryoukaku Hospital, Hakodate, Japan, [9]Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki, Japan, [10]Surgery, Himeji Red Cross Hospital, Himeji, Japan, [11]Surgery, Konan Kosei Hospital, Konan, Japan, [12]Surgery, Gifu Prefectural General Medical Center, Gifu, Japan, [13]Medical Oncology, Showa University Fujigaoka Hospital, Yokohama, Japan, [14]Clinical Medicine (Biostatistics), Kitasato University, Tokyo, Japan, [15]Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan, [16]Biochemistry and Molecular Medicine, University of Southern California, Los Angeles, CA, USA, [17]Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Background: We have conducted a phase II trial of 1st-line modified (m)-FOLFOXIRI plus bev for RAS mutant mCRC, which included a biomarker study using liquid biopsies [Oncotarget 2018]. There are few reports on monitoring changes in gene mutation (mt) status in mCRC harboring RAS mt. Therefore, the pre-planned analysis was performed to investigate a number of genes in ctDNA during therapy that might be determinants of therapeutic efficacy.

Methods: Sixty-two patients (pts) with unresectable/measurable tumors received protocol treatment with m-FOLFOXIRI (irinotecan 150 mg/m^2, oxaliplatin 85 mg/m^2, levofolinate [LV] 200 mg/m^2, and fluorouracil 2400 mg/m^2 repeated biweekly) plus bev. The phase II trial included objective response rate (ORR) for primary endpoint and progression-free survival (PFS), overall survival, early tumor shrinkage, depth of response (DpR), and safety for secondary endpoints. In 53 pts who enrolled in the biomarker study, plasma samples for extraction of ctDNA were collected at 3 points (pre-, 8wks, and progression) and analyzed for specific KRAS and NRAS variants with real-time PCR assays.

Results: Fifty-three pts had the following clinical data: median age of 61yrs, 57% male, 91% PS0, 28% right-sided tumors, ORR of 72%, median DpR of 49%, and median PFS of 10.8 months. RAS mt was detected in pre-treatment plasma in 79% (42/53) of pts. Among pts with mt in ctDNA at pre-treatment, 76% changed to mt-negative 8wks after treatment. ORR and DpR were higher in pts of mt-negative at 8wks compared to pts of mt-positive (81% vs. 50% and 55% vs. 34%, respectively). Median PFS was 11.9 and 8.8 months in pts who were mt-negative and mt-positive, respectively (HR 0.58, 95%CI 0.25-1.33, $P = 0.20$). Interestingly, in 26 pts who experienced progressive disease (PD)

and were evaluable for ctDNA analysis, 52% (11/21) of pts with mt at pre-treatment still had no mt in plasma at PD. Pts of mt-negative at PD had longer survival time from PD compared to pts of mt-positive (9.3 vs. 7.0 months).

Conclusions: Gene mt status in ctDNA during therapy may predict clinical outcome of triplet plus bev treatment in RAS mutant mCRC. Our study suggests that pts with no mt in plasma at PD may have more favorable post-treatment.

Clinical trial identification: UMIN000015152.

Editorial acknowledgement: We acknowledge Sachika Koyama and Yasushi Ohtake (JACCRO) for editorial assistance.

Legal entity responsible for the study: Wataru Ichikawa.

Funding: Japan Clinical Cancer Research Organization (JACCRO).

Disclosure: Y. Sunakawa: Honoraria for talks: Taiho Pharmaceutical, Chugai Pharma, Yakult Honsha, Takeda, Merck Serono, Bayer Yakuhin, Sanofi. H. Satake: Honoraria: Bayer, Chugai Pharma, Eli Lilly Japan, Merck Serono, Takeda, Taiho Pharmaceutical, Yakult Honsha. M. Nakamura: Honoraria: Chugai Pharma, Taiho Pharmaceutical, Yakult Honsha. M. Takeuchi: Consulting fees: Hisamitsu Pharmaceutical, Kowa, Shionogi Pharma, Abbvie, Astellas. H-J. Lenz: Consulting or advisory role, travel expenses, honoraria: Roche. W. Ichikawa: Consulting fees: Ono Pharmaceutical; Research funding: Takeda, Taiho Pharmaceutical, Eisai, Chugai Pharma, Merck Serono, Shionogi Pharma, Daiichi Sankyo; Honoraria: Merck Serono, Taiho Pharmaceutical, Chugai Pharma, Takeda, Ono Pharmaceutical, Lilly. All other authors have declared no conflicts of interest.

544P ctDNA assays identify alterations in RAS, EGFR, and cMET that are unique to RAS-WT patients progressing on anti-EGFR therapy

R. Gupta, D. Chevalier, J. Saluja, C. Lau, C. Wang, M. Fakih

Department of Medical Oncology and Therapeutics, City of Hope, Duarte, CA, USA

Background: Circulating tumor DNA (ctDNA) assays and tumor sequencing provide insight to tumor heterogeneity and mechanism of resistance in patients with MCRC. Direct comparisons between Guardant360® (G360) ctDNA panel and the comprehensive Foundation One® NGS (FO) panel in MCRC patients (pts) are limited.

Methods: We identified MCRC pts with FO at diagnosis and subsequent G360 ctDNA assays. Pts were divided into 3 categories based on ctDNA collection date: 1) ctDNA testing prior to any treatment, 2) ctDNA following non-anti-EGFR therapy and 3) ctDNA following anti-EGFR progression (PD). We compared genomic alterations by FO and G360 within the same pts to characterize clonal evolution and its impact on outcome.

Results: 43 pts with MCRC with FO had at least one ctDNA assay. High concordance between ctDNA and FO was noted in untreated pts ($n = 11$) for common oncogenic drivers, including RAS and BRAF. In 2/11 cases, 2 RAS mutations were identified on G360 only: NRAS E31D (unknown significance), and a low frequency G12D (0.3%) which may have been below the reporting limits for FO. Concordance was also noted in pts pre-treated with non-anti-EGFR therapy ($n = 11$). In contrast, ctDNA assays of RAS-wild type pts with PD following anti-EGFR ($n = 19$) showed a high rate of emergent activating KRAS [Q61H (3/19 cfDNA 0.08% -9.8%) and L19F (1/19 cfDNA 1.1%)], EGFR V441G (3/19 cfDNA 0.4%-7.9%), and FGFR2 mutations (2/19 cfDNA 1.8%-2.1%), suggesting that these are common mechanisms of resistance[VR1] . 1 pt had emergence of EGFR V441G mutation without any KRAS or NRAS mutations. Only 3 pts had serial ctDNA assays. 1 pt with BRAF V600E mutation developed cMET amplification after progressing following 6 months of response on BRAF + MEK + EGFR inhibitors. Upon withdrawal of targeted therapy, his cMET amplification resolved and he responded again to BRAF + EGFR inhibitors (5 months and ongoing), confirming clonal evolution in response to BRAF inhibitors and their withdrawal.

Conclusions: In untreated and progressing anti-EGFR naïve pts, ctDNA provides an accurate assessment of oncogenic RAS and BRAF status. Clonal evolution is captured on ctDNA in response to anti-EGFR therapy and extends beyond emerging RAS mutations to EGFR mutations and cMET amplification.

Legal entity responsible for the study: Marwan Fakih.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

545P Clinical impact of circulating tumor RAS and BRAF mutation dynamics in metastatic colorectal cancer patients treated with first-line chemotherapy plus anti-EGFR therapy: Combined analysis of two prospective clinical trials

C. Montagut[1], V. Alonso[2], P. Escudero[3], C. Fernández-Martos[4], A. Salud Salvia[5], M. Méndez[6], J. Gallego Plazas[7], J.R. Rodriguez[8], M. Martín-Richard[9], J. Fernández-Plana[10], J. Aparicio[11], J. Feliu Batlle[12], X. García de Albéniz[13], F. Rojo[14], V. Fernández[15], B. Claes[16], G.G. Maertens[16], E. Sablon[16], B.A.W. Jacobs[17], J. Maurel[18]

[1]Medical Oncology, Hospital del Mar, Barcelona, Spain, [2]Medical Oncology Service, Hospital Miguel Servet, Zaragoza, Spain, [3]Medical Oncology Service, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain, [4]Medical Oncology Service, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [5]Medical Oncology Service, Hospital Arnau de Vilanova, Lleida, Spain, [6]Medical Oncology Service, Hospital de Móstoles, Móstoles, Spain, [7]Medical Oncology Service, Hospital General Universitario de Elche, Elche, Spain, [8]Medical Oncology Service, Hospital Infanta Cristina, Madrid, Spain, [9]Medical Oncology Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [10]Medical Oncology Service, Hospital Mútua de Terrasa, Terrassa, Barcelona, Spain, [11]Medical Oncology Service, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [12]Medical Oncology Service, Hospital Universitario La Paz, Madrid, Spain, [13]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston (MA), US, Boston, MA, USA, [14]Pathology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [15]DNA & Fluis Biobank, Idibaps, Barcelona, Spain, [16]Division of Clinical Pharmacology, Department of Medical Oncology, Biocartis, Mechelen, Belgium, [17]Division of Clinical Pharmacology, Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [18]Medical Oncology, Hospital Clínic of Barcelona, Barcelona, Spain

Background: To evaluate RAS and BRAF mutation testing in circulating tumor (ct) DNA for prediction of chemotherapy plus anti-EGFR benefit and acquisition of resistance in metastatic colorectal cancer (mCRC) patients (pts).

Methods: RAS and BRAF mutational status, were assessed by Idylla™ system (Biocartis) ctDNA methodology in a baseline plasma sample and a serum sample collected at the time of the last available determination from KRAS exon 2 wild-type (WT) mCRC patients treated with first-line antiEGFR therapy within two first-line prospective biomarker-designed clinical trials (PULSE; NCT01288339 and POSIBA; NCT01276379).

Results: Analysis of extended RAS and BRAF in tissue and plasma from 178 KRAS exon 2 wild-type mCRC pts showed a sensitivity of 59% and a specificity of 90%. Patients with baseline RAS and BRAF ($n = 36$) mutant ctDNA had a median Progression Free Survival (mPFS) of 8.2 months (CI 95% 6.3-10 months) and 6.7 months (CI 95% 4.3-9.1 months) respectively, whereas double wild-type (2WT) pts had a mPFS of 13.6 months (CI 95% 11.7-15.4 months; $p < 0.0001$). Analogously the median overall survival (mOS) of baseline RAS and BRAF ctDNA mutant pts was 22.3 months (CI 95% 15.6-29 months) and 8.9 months (CI 95% 6.3-11.4 months) respectively, which were significantly inferior to the mOS of 40.4 months (CI 95% 35.9-44.9 months) in 2WT pts ($p < 0.0001$). Acquisition of RAS/BRAF mutations was 9/63 (14%) in pts with progressive disease (PD) (i.e, blood draw within 1 month before PD or after PD) (median 24.8 days (-29 to 484 days)) compared to 6/73 (8%) in pts with no PD or blood extraction for ctDNA analysis before 1 month of PD (median -265.6 days (-31 to -1126 days) ($p = 0.47$). Median OS in patients with RAS/BRAF acquisition was 23.9 months (CI 95% 19.7-27.9 months) compared to 40.6 months (CI 95% NR-NR months) in pts who remained free of mutations ($p = 0.016$).

Conclusions: Our results confirm that baseline RAS and BRAF testing in ctDNA discriminates PFS and OS. The emergence of RAS/BRAF mutations has limited impact on the time to progression to antiEGFR therapy and confers poor prognosis.

Legal entity responsible for the study: Grupo Español Multidisciplinar de Cáncer Digestivo.

Funding: Biocartis.

Disclosure: All authors have declared no conflicts of interest.

546P First-line treatment outcomes according to cfDNA analysis of RAS mutation status in metastatic colorectal cancer (mCRC) patients (pts): PERSEIDA study

P. García Alfonso[1], M. Valladares-Ayerbes[2], J. Muñoz Luengo[3], P. Pimentel[4], J.M. Viéitez[5], J.J. Cruz Hernandez[6], M. Llanos[7], C. Garcia Girón[8], A. Salud Salvia[9], A. Lloansí Vila[10]

[1]Medical Oncology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain, [2]Medical Oncology Department, University Hospital Reina Sofia. CIBERONC Instituto de Salud Carlos III, Córdoba, Spain, [3]Medical Oncology Department, Hospital San Pedro de Alcántara, Cáceres, Spain, [4]Medical Oncology Department, Hospital General Universitario Santa Lucia, Cartagena, Spain, [5]Medical Oncology Department, Hospital Central de Asturias, Oviedo, Spain, [6]Medical Oncology Department, Hospital Universitario de Salamanca, Salamanca, Spain, [7]Medical Oncology, Hospital Universitario de Canarias, Santa Cruz De Tenerife, Spain, [8]Medical Oncology Department, Hospital Universitario de Burgos, Burgos, Spain, [9]Medical Oncology Department, Hospital Arnau de Vilanova, Lleida, Spain, [10]Medical Oncology Department, Amgen S.A., Barcelona, Spain

Background: Tumour-tissue biopsy testing is the standard of care (SOC) to assess RAS mutation in mCRC pts. However, the analysis of circulating cell-free DNA (cfDNA) has the added advantage of being able to evidence genetic tumour heterogeneity. We explored the correlation of the RAS mutational status assessed in plasma samples with first-line (1L) treatment outcomes in SOC RAS wild type (wt) mCRC pts.

Methods: Prospective, observational, multi-centre study in mCRC pts with RASwt according to tumour-tissue biopsy and treated following standard clinical practice. Plasma samples were collected before starting 1L treatment and sent to Sysmex Inostics GmbH for BEAMing analysis. The lower threshold limit was a mutant allele fraction (MAF) $\geq$ 0.02%. Tumour response (TR) was evaluated approximately every 3 months based on RECIST criteria.

Results: 119 pts were included (61% male; median age: 65 y). 113 received chemotherapy (CT) + anti-EGFR, 4 CT + anti-VEGF and 2 CT alone. Overall response rate (ORR) was 68.1% (95%CI: 58.9-76.3) for all pts and 75% (95%CI: 65.8-82.8) in the108 pts with TR data. In pts treated with panitumumab (n = 92), the most homogeneous group, 76.1% (n = 70) presented left-sided tumours and 19.6% (n = 18) right-sided; overall ORR was 78.3% (95%CI: 68.4-86.2); 81.4% (95%CI: 70.3-89.7) for left and 72.2% (95%CI: 46.5-90.3) for right-sided pts. ORR in the panitumumab subgroup according to RAS mutational status analysed in cfDNA for the three MAF (cut-offs) considered is presented in the table.

Table: 546P

	ORR (not confirmed) % (95% CI)	ORR (not confirmed) % (95% CI)	Odds Ratio (95% CI); P-value*
Mutant allele fraction, cut-off (n)	RASwt	RASmt	
≥1% (90 wt/2 mt)	78.9 (69.0 – 86.8)	50.0 (1.3 - 98.7)	3.7 (0.2 – 62.6) 0.389
≥0.1% (87 wt/5 mt)	79.3 (69.3 – 87.3)	60.0 (14.7 - 94.7)	2.6 (0.4 – 16.5) 0.297
≥0.02% (80 wt/12 mt)	80.0 (69.6- 88.1)	66.7 (34.9-90.1)	2.0 (0.5 – 7.5) 0.285

*Fisher Test; CI=confidence interval; ORR: Overall Response Rate.

Conclusions: A high ORR was observed in pts treated with panitumumab independently of the localization. ORR in panitumumab treated patients tends to be higher in plasma RASwt. ORR in pts with plasma RASmt increases when a lower MAF cut-off is used. Further investigation is needed to find the optimal clinical cut-off. Study supported by Amgen.

Legal entity responsible for the study: Amgen.

Funding: Amgen.

Disclosure: P. García Alfonso: Consulting fees: Amgen, Bristol, Merck, Sanofi, Roche, Bayer, Servier. M. Valladares-Ayerbes: Research grants: Roche; Consulting fees: Amgen, Roche, Merck, Sanofi, Servier. J.M. Viéitez: Research grants: Amgen, Roche; Consulting fees: Amgen, Roche, Servier, Shire, Bayer. J.J. Cruz Hernandez: Consulting fees: Amgen, Merck, Roche, BMS. A. Lloansí Vila: Full time employee, stocks: Amgen. All other authors have declared no conflicts of interest.

547P Serial monitoring of circulating tumor DNA in patients with metastatic colorectal cancer to predict the therapeutic response

J. Zhou[1], C. Bai[2], Z. Sun[2], Y. Cheng[2], N. JIA[3], Y. Zhou[2]

[1]Department of Medical Oncology, PUMCH, Beijing, China, [2]Medical Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [3]Medical Oncology, PUMCH, Beijing, China

Background: Early biomarkers of therapeutic responses could help optimize the treatment of metastatic colorectal cancer (mCRC). This prospective exploratory study was designed to explore the serial changes in plasma-circulating tumor DNA (ctDNA) as an early marker of therapeutic response to systemic treatment in mCRC.

Methods: Forty-seven mCRC patients receiving standard first-line therapy every two weeks were enrolled. Somatic mutations in plasma ctDNA were detected serially before each of the first four cycles via next-generation sequencing, and the mutation of maximal frequency in pretreatment ctDNA was selected as the candidate mutation for analysis. Radiologic responses were assessed after the fourth cycle.

Results: The results indicated that mutations in pretreatment ctDNA could be detected in 45 (95.7%) patients. Among the 41 patients monitored serially, imaging after four cycles of treatment showed 17 PR, 18 SD, and 6 PD cases. Changes in ctDNA could differentiate patients with progressive disease two cycles (approximately four weeks) earlier than the changes in CEA and CA19-9 levels could, and changes in ctDNA levels as early as prior to cycle 2 predicted the radiologic responses after cycle 4. A log2 value of fold-change in ctDNA after cycle 1 (log2 (C1/C0)) > -0.832 predicted progressive disease, with a sensitivity and specificity of 100.0% (95%CI: 54.1-100.0%) cand 85.7% (95%CI: 69.7-95.2%), respectively, and an accuracy of 87.8% (95%CI: 73.8-95.9%). Patients with ctDNA log2 (C1/C0) > -0.832 showed significantly worse progression-free survival than did those with log2 (C1/C0) $\leq$ -0.832 (median 2.5 versus 9.0 months; P = 0.016).

Conclusions: The present exploratory study suggests that early changes in ctDNA that are detected via targeted sequencing might potentially predict later radiologic responses in mCRC.

Legal entity responsible for the study: Peking Union Medical College Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

548P Cross-platform comparison of NGS and MALDI-TOF for detecting RAS/RAF/PIK3CA mutations in circulating tumor DNA from metastatic colorectal cancer patient plasma

L. Liang[1], B-L. Wang[2], Q. Yu[2], T-S. Liu[1], W. Guo[2]

[1]Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China, [2]Laboratory Medicine, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Evaluating tumor RAS/RAF status is essential for treatment selection and prognosis evaluation in metastatic colorectal cancer (mCRC) patients. Analyzing ctDNA in mCRC patients has many advantages because of its non-invasive nature. However, since the signal of ctDNA is generally low, detection of ctDNA from different platforms need to be carefully interpreted before adapting new technology into routine clinical application.

Methods: 60 mCRC patients under different treatment status were recruited. A cross-platform comparison between MALDI-TOF (UltraSEEK) and next-generation sequencing (NGS) was done by examining KRAS/NRAS/BRAF/PIK3CA mutations frequency in plasma from patients. Inconsistent results between two platforms were examined by droplet digital polymerase chain reaction (ddPCR). All results were compared to the mutation status in tissue retrospectively.

Results: In the comparison between NGS and MALDI-TOF, we focused on 65 hotspots, 53.57% and 60.71% of the samples were reported to be positive by NGS and MALDI-TOF respectively. Concordance rate between two platforms was 73.21%. Discrepancy between two platforms was examined by ddPCR, and a reproducible result was then treated as a true positive. The PPA of NGS and MALDI-TOF was 93.94%, 90.91 %; NPA of NGS and MALDI-TOF was 99.97%, 99.63 %, respectively. After establishing a ground truth for plasma result, 56 patients were found to have comparable ARMS result from tissue. Apart from 10 patients undertaking chemotherapy or Cetuximab, 95.6% (44/46) patients have their plasma result consistent with that from tissue. For 10 patients undergoing treatment at the time of plasma acquisition, ctDNA status detected by NGS was showed to be an effective biomarker to monitor the response to treatment: 90% (9/10) of patients had a ctDNA status that were consistent with their progression status.

Conclusions: ctDNA detected by NGS was showed to be a reliable signal that reflects tumor burden and informs treatment response. Even challenge exists in detecting variants in low frequency in plasma, appropriate selection of technology allows reliable examination of clinical utility in upcoming clinical studies.

Legal entity responsible for the study: Zhongshan Hospital, Fudan University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

549P Second line EGFR-inhibitors in RAS mutant metastatic colorectal cancer: The plasma RAS wild type "window of opportunity"

P. Gazzaniga[1], C. Raimondi[2], F. Urbano[3], E. Cortesi[3]

[1]Molecular Medicine, Sapienza University of Rome, Rome, Italy, [2]Radiology, Oncology and Pathology, Sapienza Univeristy of Rome, Rome, Italy, [3]Radiology, Oncology and Pathology, Policlinico Umberto I, Rome, Italy

Background: RAS mutations are found in 30-50% of metastatic colorectal cancer (mCRC) and determine the ineligibility for EGFR-targeted therapies. Recent studies have demonstrated that the analysis of circulating tumor DNA (ctDNA) is a surrogate of tumor biopsy for mutations detection. To date, studies have been focused on the appearance of RAS-mutant clones in patients with RAS-wild type mCRC, as biomarkers of anti-EGFR therapy resistance. We here describe a population of RAS mutant

mCRC who converted to wt -RAS status in blood over the course of first-line treatments. As proof of concept, the absence of any clinically relevant mutation of RAS genes in blood has been used as a therapeutically exploitable window. To this purpose five patients received second-line treatment with anti-EGFR, achieving a durable clinical benefit.

Methods: Blood samples from 20 patients with mutant RAS status were prospectively collected before initiating first- line therapies. RAS mutational status was assessed on tumor tissue and plasma samples at baseline. In all cases with plasma-tissue concordance at baseline (n. 15), RAS mutations were serially monitored every 3 months. Idylla™(Biocartis) was used to investigate RAS mutational profile from plasma. Specifically, Idylla™ ctKRAS Mutation Assay and Idylla™ ctNRAS/BRAF/EGFR Mutation Assay were used.

Results: 15 mCRC patients harboring any RAS mutation in tumor tissue and plasma at the time of diagnosis were serially monitored through plasma ctDNA analysis. Eleven patients (73%) switched to a wild- type RAS status in blood during the course of first line treatments. At disease progression in the first-line setting, 5 of them have received EGFR inhibitors as a second-line treatment, achieving a durable clinical benefit.

Conclusions: ctDNA analysis might reveal a therapeutically exploitable window of opportunity, characterized by the prevalence of wt -RAS clones, which can be converted in a clinically meaningful benefit for patients. Our planned KAIROS trial might determine whether the response to EGFR inhibition, in patients with RAS mutant cancers converted to RAS wild-type in course of treatments, might become the rule rather than the exception.

Legal entity responsible for the study: Angela Santoni.

Funding: Has not received any funding.

Disclosure: E. Cortesi: Consulting or advisory role: Bristol-Myers Squibb Italy, Sirtex Medical. All other authors have declared no conflicts of interest.

550P Evaluation of the sensitivity of RAS mutation detection of the Idylla platform in comparison to the OncoBEAM RAS CRC assay

A. Vivancos[1], E. Aranda Aguilar[2], M. Benavides[3], E. Elez Fernandez[4], M. Toledano[2], M. Alvarez[5], E. Diaz Rubio[6], A. Gómez-España[2], V. Garcia-Barberan[6], M.R. Chica-Parrao[7]

[1]Genomics, Vall d'Hebron University Hospital, Barcelona, Spain, [2]Oncology, University Hospital Reina Sofia, Cordoba, Spain, [3]Oncology, Hospital Regional Universitario Carlos Haya, Malaga, Spain, [4]Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Pathology, Hospital Regional Universitario Carlos Haya, Malaga, Spain, [6]Oncology, Hospital Clinico Universitario San Carlos, Madrid, Spain, [7]Oncology, Hospital Universitario Virgen de la Victoria, Malaga, Spain

Background: Accurate detection of RAS mutations in metastatic colorectal cancer (mCRC) patients is of high clinical importance for therapy selection as RAS detection methods lacking sensitivity may lead to poor patient outcomes. Liquid biopsy has emerged as a viable alternative to individualize the management and treatment of mCRC patients. The objective of this study was to provide a head-to-head comparison of the sensitivity of two tests for KRAS mutation detection in plasma from mCRC patients: dPCR-based OncoBEAM and qPCR Idylla.

Methods: Plasma samples from mCRC patients determined to be KRAS-positive using OncoBEAM were re-tested using Idylla. 116 samples with mutant allelic fractions (MAF) below 5% were selected for analysis. The positive percent agreement (PPA) of KRAS mutation results was compared for replicate samples analyzed by OncoBEAM and Idylla.

Results: Idylla detected KRAS mutations in 81 out of 116 (69.8%, $p < 0.0001$) OncoBEAM KRAS-positive plasma samples. Categorization of results based on MAF% revealed distinct differences in sensitivity between the two technologies.

Table: 550P

MAF% Range	PPA Idylla vs OncoBEAM
1-5%	89.1% (33/37) ($p = 0.1336$)
0.1-1%	65.1% (41/63) ($p < 0.0001$)
0.02%-0.1%	43.8% (7/16) ($p = 0.0077$)

Significant differences have been observed in patients with liver and other metastases, except lung, 41/51 (80.4%, $p = 0.0044$) and patients with lung and other metastases, except liver, 16/24 (66.7%, $p = 0.0133$).

Conclusions: OncoBEAM demonstrated significantly greater sensitivity for plasma detection of RAS mutations than Idylla. Moreover, these data identify a "gray zone" below 1% MAF where Idylla fails to identify RAS-positivity in patient plasma samples. These findings show that liquid biopsy assays with diminished sensitivity may lack the dynamic range to provide accurate and timely RAS mutational status information to properly guide highly individualized anti-EGFR therapy and chemotherapy treatment decisions that may benefit patient outcomes.

Legal entity responsible for the study: Ana Vivancos.

Funding: Sysmex Inostics.

Disclosure: A. Vivancos: Consultant: Sysmex Inostics. All other authors have declared no conflicts of interest.

551P Non-invasive genotyping and monitoring of tumor evolution in locally advanced rectal cancer (LARC) patients using circulating tumor DNA (ctDNA)

S. Toomey[1], A. Sartori[2], D. Irwin[3], S. Hummel[4], A. Carr[1], C.L. Lee[5], P. Armstrong[1], A. Farrelly[6], S. El-Masry[7], D. McNamara[8], P.G. Morris[9], L. Grogan[9], O.S. Breathnach[9], L. O'Sullivan[10], S. Bradshaw[11], A.N.A.M. Rashed[12], R. Smyth[1], J. Workman[1], B. O'Neill[13], B. Hennessy[9]

[1]Molecular Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland, [2]Scientific Affairs, Agena Biosciences, Hamburg, Germany, [3]Agena Bioscience, Brisbane, Australia, [4]Agena Bioscience, San Diego, CA, USA, [5]Medical Oncology, St Vincents University Hospital, Dublin, Ireland, [6]Oncology Molecular Medicine, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland, [7]Surgery, Our Lady of Lourdes Hospital, Drogheda, Ireland, [8]Surgery, Beaumont Hospital, Dublin, Ireland, [9]Medical Oncology, Beaumont Hospital, Dublin, Ireland, [10]Cancer Trials Ireland, Dublin, Ireland, [11]Radiation Oncology, St Luke's Radiation Oncology Network, Dublin, Ireland, [12]Oncology, Our Lady of Lourdes Hospital, Drogheda, Co. Louth, Ireland, [13]Radiation Oncology, St. Luke's Radiation Oncology Network, Dublin, Ireland

Background: There is limited information on the feasibility and clinical potential of ctDNA analysis in non-metastatic rectal cancer. We assessed whether detection and analysis of plasma ctDNA could help monitor tumor evolution during neoadjuvant chemoradiotherapy (NACRT) treatment for LARC.

Methods: 27 LARC patients who were enrolled on the CTRIAL-IE (ICORG) 12-38 TRI-LARC clinical trial (NCT02151019) and received NACRT prior to surgery, had samples for ctDNA analysis taken at baseline pre-NACRT, during week 3 of radiotherapy (RT), during the final week of RT, prior to surgery, and 3-12 months post-surgery. DNA from baseline biopsy samples was genotyped for 86 hotspot mutations in BRAF, EGFR, KRAS, NRAS and PIK3CA using the iPLEX™ HS Colon Panel on the MassARRAY® System (Agena Bioscience). The UltraSEEK™ Colon Panel (Agena Bioscience) was used to track 107 hotspot mutations in serial ctDNA samples.

Results: At least one mutation was identified in 67% (18/27) of baseline biopsy samples. 15 patients (56%) had a KRAS mutation. Identical mutations were found in baseline ctDNA of 11/15 patients (73%). The median KRAS mutant allele frequency (MAF) in baseline ctDNA samples was 0.9% (range 0.1-2%). This significantly decreased over treatment (0.15% week 3 RT, 0.35% final week RT, 0.1% prior to surgery) ($p < 0.05$). 10 patients had a KRAS mutation in their baseline ctDNA that was not detected in their biopsy, with a median MAF of 0.3% (range 0.1-1.3%). Mutations in NRAS and PIK3CA were identified in 3/27 (11%) and 2/27 (7%) of patients, respectively. NRAS and PIK3CA mutations were identified in the ctDNA of 2/3 (67%) and 1/2 (50%) patients. Post-operative ctDNA samples were available for 13 patients and residual mutations were detected in 10 patients (77%), 3 of whom (30%) had recurrence at median follow up of 20.1 months. There was no recurrence in any patient with negative ctDNA post-surgery.

Conclusions: ctDNA can identify clinically relevant biomarkers and could be used as a minimally invasive alternative to repeated tumor biopsies to monitor tumor evolution. ctDNA detection after resection may provide evidence of residual disease and could identify patients at high risk of recurrence.

Clinical trial identification: NCT02151019.

Legal entity responsible for the study: Cancer Trials Ireland.

Funding: St. Luke's Institute of Cancer Research.

Disclosure: A. Sartori, D. Irwin: Employee, stock owner: Agena Biosciences. S. Hummel: Employee: Agena Biosciences. All other authors have declared no conflicts of interest.

552P Circulating tumor DNA by next generation sequencing as a prognostic and predictive biomarker in metastatic colorectal cancer

N. Jia[1], L. Chang[2], X. Dou[1], M. Guan[1], Y. Shao[1], N. Li[1], Y. Cheng[1], H. Ying[1], Z. Sun[1], Y. Zhou[1], L. Zhao[1], J. Zhou[1], C. Bai[1]

[1]Medical Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [2]Medical Science, Geneplus-Beijing, Beijing, China

Background: Biomarkers of prognosis and efficacy in patients with metastatic colorectal cancer (mCRC) are crucial for optimizing therapeutic strategies. The aim of our study was to explore the applicability of circulating tumor DNA (ctDNA) as a prognostic and predictive marker in mCRC.

Methods: Sequential Patients with mCRC were included. Both plasma ctDNA and serum CEA were assessed in samples obtained before treatment and after 4 cycles of chemotherapy (C4). Target-capture deep sequencing with a panel covering 1021 genes was performed to detected somatic mutations in ctDNA. Clonal population structures were identified based on variations from ctDNA using Bayesian cluster with Pyclone. Molecular tumor burden index (mTBI) was calculated with the mean variant allele frequency of mutations in trunk clonal population. Cox regression analysis, Spearman's

rank correlation, Receiver operating characteristic (ROC) curves and Kaplan-Meier plots were used for statistical analyses.

Results: A total of 20 patients were prospectively included and treated with FOLFOX (15/20) or FOLFIRI (5/20) from Sep 2015 to Aug 2016. Median follow-up was 6.9 months (range 1.6-26.6). Somatic mutations for baseline ctDNA analysis were identified in 17/20 (85%) of the patients. In a multivariable analysis, a high baseline mTBI was associated with the risk of disease progression (HR, 1.091; 95% CI, 1.032–1.153; P = 0.002). The optimal baseline mTBI for predicting progression-free survival (PFS), as determined by the ROC curves (ROC area = 0.83, P = 0.0126), was 6.81%. Patients with baseline mTBI below 6.81% had longer PFS compared to those above (median 9.9 versus 4.35 months; HR, 2.966; 95% CI: 1.075-8.184; P = 0.0115). Fold reductions of mTBI from baseline to post-C4 were obtained in 16/20 (80%) of the patients. In a bivariate correlations analysis, fold reduction of mTBI was related to tumor response (r = -0.661, P = 0.005). In contrast, serum CEA level and its variation did not correlate with PFS and tumor response, respectively.

Conclusions: High baseline mTBI and inferior PFS were correlated in mCRC, so were fold reduction of mTBI and tumor response. Therefore, ctDNA could be potentially a biomarker for prognosis and efficacy.

Legal entity responsible for the study: Department of Medical Oncology, Peking Union Medical College Hospital.

Funding: National Natural Science Foundation of China (81472785, 61435001), CAMS Innovation Fund for Medical Sciences (No. 2016-I2M-1-001).

Disclosure: All authors have declared no conflicts of interest.

553P Dynamic monitoring of KRAS, NRAS, BRAF and PIK3CA mutations in circulating cell-free DNA for metastatic colorectal cancer patients treated with cetuximab

L.L. Liu, Z. Tong, C. Yan, H. Zhang, W. Jiang, Y. Zheng, P. Zhao, W. Fang

Medical Oncology, First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: Genomic heterogeneity affects response to targeted agents. Liquid biopsy is a promising approach to detect genetic mutations in circulating cellfree DNA (cfDNA) and allows the tracking of treatment-induced genetic evolution in metastatic colorectal cancer (mCRC) patients.

Methods: Longitudinal plasma samples (n = 92) were collected from 15 mCRC patients receiving cetuximab contained regimen therapy. KRAS, NRAS, BRAF and PIK3CA mutational status relevant to cetuximab resistance were monitored by next-generation sequencing in plasma, which could be reflected by variant allele frequency (VAF). We also included 11 healthy controls to differentiate total cfDNA levels from mCRC patients.

Results: Of these 15 mCRC patients, baseline plasmas were collected in 8 patients. The average cfDNA level in treatment naive patients was significantly higher than healthy cohort (p = 0.0004). Moreover, cfDNA levels correlate with the tumor burden before systemic therapy (R^2=0.544). Dynamics of KRAS/NRAS/BRAF/PIK3CA VAF mirrored disease evolution, showing the same trend with partial response, disease progression and relapse. In addition, KRAS/NRAS/BRAF/PIK3CA VAF gradually declined upon cetuximab withdrawal for more than 2 months, and partial response was again achieved when cetuximab was re-used on 1 patient. This provided a molecular explanation for the efficacy of rechallenge therapies based on EGFR blockade.

Conclusions: Dynamic monitoring of KRAS/NRAS/BRAF/PIK3CA mutations in cfDNA is feasible and appears to be useful in early detection of drug resistance to cetuximab in mCRC patients.

Legal entity responsible for the study: Weijia Fang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

554P KRAS-dependent and independent mechanisms of progressive disease (PD) in colorectal cancer (CRC) patients (pts) with liver metastases (LM) while monitoring on circulating cell free DNA (cfDNA)

A. Kirov[1], Z. Mihaylova[2], V. Petrova[2], T. Todorov[3], D. Petkova[2], A. Garev[2], A. Todorova-Georgieva[4]

[1]Human Genetics, Independent Medico-Diagnostic Laboratory Genome Centre Bulgaria, Sofia, Bulgaria, [2]Department of Medical Oncology, Military Medical Academy, Sofia, Bulgaria, [3]Human Genetics, Genetic Medico-Diagnostic Laboratory Genica, Sofia, Bulgaria, [4]Medical Chemistry and Biochemistry, Medical University Sofia, Sofia, Bulgaria

Background: KRAS mutational analysis (MA) in plasma (P) cfDNA is an alternative to tissue (T) analysis with concordance rate (ConR) from 30 to 90%. The emergence of KRAS mutation (M) during the course of anti-EGFR therapy is responsible for acquired resistance (AR). We aimed to evaluate the RAS ConR between T and cfDNA in mCRC pts, and to monitor changes in RAS M status.

Methods: All blood samples were collected in cfDNA Preservative Tubes (Norgen Biotek Corp., Canada). ctDNA was extracted within 3 days after sampling, the extraction was performed by commercial kit (P/Serum cfDNA Purification Mini Kit, Norgen Biotek). KRAS (ex 2) M on P cfDNA and tumor T were detected by real-time PCR kits TheraScreen: K-RAS Mutation Kit. The other M were detected by Sanger sequencing (BigDye Terminator v3.1 Cycle Sequencing Kit - Thermo Fisher Scientific).

Results: In the ConR evaluation were enrolled prospectively 63 mCRC pts. Only LM had 52,4% (33) pts, from whom - 27,3% (9) pts had primary resectable LM. The median time from T biopsy (primary -97%) to P collection was 275, 7 days (range 26 - 1560). TMA revealed 58,7% (37) M pts from whom 78,4% (29) pts had KRAS ex.2 M. cfDNA evaluation showed the distribution of M to wild (W) - 81%/19% with KRAS ConR of 58,7%. To reduce time between T and P samples MA in the monitoring analysis were included only 31 pts who had primary unresectable LM, with baseline (b) P collection. In 5 pts with KRAS M after converting treatment, LM resection resulted in W type on consecutive cfDNAs. In responding pts (10) with W disease on bcfDNA, there was no change in MA consequently. In non-responders with W type the appearance of KRAS M was noted in 6 pts, while in the rest 3 pts PD was not correlated to KRAS M. In non-responders with KRAS M on bcfDNA (6 pts), monitoring of cfDNA revealed disappearance of KRAS M contemporary with mainly LM PD.

Conclusions: The estimated ConR between primary tumor and cfDNA KRAS MA was 58%. The emergence of KRAS M in W type pts reveled AR to anti-EGFR therapy. In pts with M KRAS on bcfDNA, liver resection in responders and LM PD in non-responders correlated with loss of KRAS M as a mechanism of AR to anti-angiogenesis treatment in the later.

Legal entity responsible for the study: Prof. Albena Parvanova Todorova-Georgieva.

Funding: Medical University Sofia.

Disclosure: All authors have declared no conflicts of interest.

555P Correlation between ctDNA methylation and CEA in colorectal cancer

W-W. Tang[1,2], H-X. An[3,1], D. Zhou[3], M-Q. Cai[1], R. Zeng[1], X-J. Lv[4,1], L-L. Chen[1], F. Ye[1], Y. Zhang[5]

[1]Department of Medical Oncology, Xiamen Cancer Hospital, The First Affiliated Hospital of Xiamen University, Xiamen, China, [2]Oncology, Fujian Medical University, Fuzhou, China, [3]Department of Medical Oncology, Xiang'an Hospital of Xiamen University, Xiamen, China, [4]Xiamen Cancer Hospital, The First Affiliated Hospital of Xiamen University; Xiamen Humanity Hospital, Xiamen, China, [5]Key Laboratory of Design and Assembly of Functional Nanostructures, Fujian Provincial Key Laboratory of Nanomaterials, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Xiamen, China

Background: Compared with the classical tumor markers, ctDNA has higher accuracy and specificity while being noninvasive. Based on the prophase work, we explore the role of ctDNA methylation in the detection of PCDH18 as a new tumor marker compared with CEA in the clinical diagnosis and progressive evaluation of colorectal cancer (CRC).

Methods: We collected peripheral blood from 60 patients with advanced primary CRC before and after two courses of treatment, as well as from 60 healthy individuals, and the clinicopathologic characteristics were analyzed. The changes of CEA levels before and after treatment were dynamically monitored by electrochemiluminescence (ECL). The methylation status of PCDH18 was detected by qMSP, the correlation between them was also statistically analyzed, and the value of different indexes in the diagnosis and monitoring of tumor progression of CRC were compared.

Results: We found that the percentage of methylation of PCDH18 in plasma of CRC before treatment was significantly higher than that of normal plasma samples. The difference ($p < 0.01$) suggests that PCDH18 methylation may be involved in the carcinogenesis of CRC. PCDH18 methylation was not significantly correlated with sex, tumor location, histological type, tumor differentiation, TNM or CEA($P > 0.05$). To further explore the relationship between the methylation of PCDH18 and the risk of CRC, the results showed that with the increase of methylation level of PCDH18, the risk of CRC and tumor progression increased significantly, while in CEA group, the OR > 1 only in the group with CEA elevation as the dividing point, but the P value was not statistically significant. The sensitivity and specificity of PCDH18 ctDNA methylation combined with CEA in the diagnosis of progression of CRC were 90.0% and 67.6%, respectively. The area under the curve (AUC) reached 0.861. Further analysis showed that PCDH18 ctDNA methylation was 67.86% while CEA was negative in CRC progression patients, indicating that PCDH18 ctDNA methylation could significantly increase the detection of progression in comparison with CEA.

Conclusions: The methylation of PCDH18 ctDNA may play an important role in the diagnosis and prediction of tumor progression in CRC as a new tumor marker and can significantly increase the detection of tumor progression in CEA-negative patients. W-W. Tang, H-X. An and D. Zhou contributed equally to this work.

Legal entity responsible for the study: Clinical Research Ethics Committee of the First Affiliated Hospital of Xiamen University.

Funding: This study was supported by the National Natural Science Foundation of China (No. 81702414), the Fujian Provincial Health and Family Planning Commission Foundation of Youth scientific research project (No. 2015-2-43) and Xiamen Science and Technology Bureau Foundation of science and technology project for the benefit of the people (No. 3502Z20164010).

Disclosure: All authors have declared no conflicts of interest.

556P Cell free DNA and hepatic arterial infusion of oxaliplatin plus systemic capecitabine for patients with colorectal cancer liver metastases

A.K. Boysen[1], J.V. Schou[2], B.V. Jensen[2], D.L. Nielsen[2], B.S. Sørensen[3], J.S. Johansen[2], K-L.G. Spindler[3]

[1]Oncology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [3]Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

Background: Hepatic Arterial Infusion (HAI) where the cytotoxic agents are administered intrahepatic is an experimental treatment option for patients with colorectal cancer liver metastases (CRCLM). We aimed to investigate the level of cell free DNA (cfDNA) in patients with CRCLM receiving HAI with oxaliplatin and systemic capecitabine.

Methods: Patients were treated according to a single arm phase II study including patients with liver limited mCRC from November 2004 to May 2010, who were not eligible for any other standard local treatment. Therapy comprised intrahepatic infusion of oxaliplatin 100 mg/m2 every second week with concomitant oral capecitabine 3500 mg/m2 every second week for up to 12 cycles. A pre-treatment plasma sample was used for quantification of cfDNA by a modified fluorescent assay. Survival was analyzed by the Kaplan-Meier method and Cox multiple regression analysis.

Results: Baseline plasma samples were available from 62 patients. The majority of patients were males (61%), the median age 61.3 years (range 40.8-74.8) and distribution of colonic/rectal cancers 68%/32%. The median level of cfDNA was 0.92 ng/µL (95% CI 0.84-1.00) with no significant differences according to pre-treatment patients characteristics apart from significantly higher cfDNA levels with poor PS ($p < 0.001$). Plasma cfDNA was significantly lower (0.91 ng/µL, 95% CI 0.76-0.98) in patients who achieved an objective response compared to non-responders (1.79 ng/µL, 95% CI 0.99-2.57, $p = 0.02$). Patients with a baseline value of cfDNA above the 75th quartile had a median overall survival of 2.4 years (95% CI 0.7-2.8), compared to 3.9 years (95% CI 2.8-5.9) for patients below the 75th quartile ($p = 0.02$). In multivariate analysis, only increasing baseline level of cfDNA, (HR 1.90, 95% CI 1.07-3.38, $p = 0.03$), and mutated KRAS status, (HR 3.17, 95%CI 1.67-6.03, $p < 0.001$), remained associated with short survival.

Conclusions: Patients with a low baseline level of plasma cfDNA had a favorable outcome from treatment with HAI and capecitabine for CRCLM. Consequently, cfDNA could hold clinically relevant predictive and prognostic information, which needs validation in this setting.

Legal entity responsible for the study: Karen-Lise Spinder.

Funding: Danish Cancer Society Novo Nordisk Foundation.

Disclosure: A.K. Boysen: Advisory board: Bayer A/S. All other authors have declared no conflicts of interest.

557P Metastatic colorectal signet-ring cell carcinoma: Clinical, histological and molecular description from an AGEO French multicenter retrospective cohort

M. Allart-Sava[1], F. Le Roy[2], S. Kim[3], D. Sefrioui[4], C. Mariette[5], A. Zaanan[6], B.J-C. Rousseau[7], M. Ben Abdelghani[8], C. De La Fouchardière[9], W. Cacheux[10], R. Legros[11], S. Louafi[12], D. Tougeron[13], N. Fares[14], G. Roquin[15], A.L. Bignon Bretagne[16], M. Maillet[17], B. Tchoundjeu[18], A. Pozet[19], V. Hautefeuille[20]

[1]Gastroenterology, Amiens University Hospital, Amiens, France, [2]Gastroenterology, Gustave Roussy Institute, Villejuif, France, [3]Medical Oncology, Besançon University Hospital, Jean Minjoz Hospital, Besançon, France, [4]Gastroenterology, Rouen University Hospital - Charles Nicolle, Rouen, France, [5]Dept of Digestive and Oncological Surgery, Lille University Hospital - Claude Huriez, Lille, France, [6]Gastroenterology, European George Pompidou Hospital, Paris, France, [7]Gastroenterology, Henri-Mondor University Hospital, Créteil, France, [8]Gastroenterology, Paul Strauss Center Hospital, Strasbourg, France, [9]Gastroenterology, Leon Berard Center Hospital, Lyon, France, [10]Gastroenterology, René Huguenin Hospital - Curie Institute, St. Cloud, France, [11]Gastroenterology, Limoges University Hospital, Limoges, France, [12]Gastroenterology, Longjumeau Center Hospital, Longjumeau, France, [13]Gastroenterology, Poitiers University Hospital - Jean Bernard Hospital, Poitiers, France, [14]Gastroenterology, Toulouse University Hospital, Toulouse, France, [15]Gastroenterology, Angers University Hospital, Angers, France, [16]Gastroenterology, Caen University Hospital, Caen, France, [17]Gastroenterology, Saint-Louis Hospital, Paris, France, [18]Gastroenterology, Orleans University Hospital, Orléans, France, [19]Biostatistics, Besançon University Hospital, Besançon, France, [20]Gastroenterology, Amiens University Hospital, Amiens, France

Background: Metastatic colorectal signet ring cell carcinoma (mSRCRC) is a rare entity and data are limited, concerning small number of patients. Chemosensitivity for metastatic disease has never been assessed. This study analyzes their chemosensitivity and investigates their clinicopathological, molecular and prognostic characteristics.

Methods: This nationwide retrospective study included patients with mSRCRC from 2003 to 2017 in 31 french centers. They were divided into three groups: curative care (group 1), palliative chemotherapy (group 2) and best supportive care (group 3).

Results: Data on 204 patients were collected. Median age was 63 years. Tumors were more frequent in proximal colon (46%) and rectum (29%), were T4 (71%) and poorly differenciated (86%). Sites for metastases were mainly peritoneum (69%), lymph nodes (28%) and liver (23%). Microsatellite instability (MSI) and BRAF V600E mutation were found in 19% (21/108) and 9% (9/103) of patients, and were mainly right sided (respectively 27% and 12% respectively). BRAF mutation was found in 19% of MSI tumors. RAS mutation was found in 23% (29/127) and did not vary with side. Median overall survival (mOS) was 10,1 months ($_{95\%}$CI = [7.9;12.8]). mOS for group 1 (n = 38), group 2 (n = 112) and group 3 (n = 54) were 45,1 months, 10,9 months and 1,8 months. No difference in mOS was found between tumor location, signet ring cell's percentage and MSI status ($p = 0,13$; $p = 0,40$ and $p = 0,82$). In group 2, first-line treatment (1L) was antiVEGF-based in 28,4% and antiEGFr-based in 22% of cases. Response and control rates were 13,2% and 50% respectively in 1L. Progression-free survival (PFS) was 5 months with biotherapy and 3,9 months with cytotoxics alone ($p = 0,016$). There was no difference in PFS between antiVEGF and antiEGFr ($p = 0,8$) in 1L, and between right-sided ($p = 0,275$) and left-sided ($p = 0,265$) tumors.

Conclusions: This large cohort of mSRCRC shows poor prognosis, specific location and molecular alterations which provides low chemosensitivity. Microsatellite analysis should be done regarding promising results of immunotherapy in MSI-high tumors.

Legal entity responsible for the study: AGEO (Association des Gastroentérologues Oncologues).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

558P The combination of trifluridine/tipiracil and oxaliplatin induces immunogenic cell death in microsatellite stable colorectal cancer

F. Ghiringhelli[1], E. Limagne[2], M. Thibaudin[2], L. Nuttin[2], A. Spill[2], V. Derangere[2], V. Cattan[3], E. Peranzoni[4], N. Amellal[3]

[1]Medical Oncology Unit, Centre Georges-François Leclerc, Dijon, France, [2]Plateform of Cancer Biology, Centre Georges-François Leclerc, Dijon, France, [3]Servier Oncology, Instut de Recherches Internationales Servier, Suresnes, France, [4]Servier Oncology, Instut de Recherches Servier, Croissy, France

Background: Patients with microsatellite-stable (MSS) colorectal cancer have limited clinical benefit with PD-1 blockade [1, 2]. These tumors are poorly immunogenic and highly infiltrated by immunosuppressive populations [3]. In this context, identification of drug combinations both inducing immunogenicity and modulating tolerogenicity is crucial for the sensitization of MSS colorectal cancer to immune-checkpoint inhibitors. The aim of this study was to evaluate the immunological properties of the trifluridine/tipiracil and oxaliplatin combination in the murine MSS colorectal cancer CT26 model.

Methods: Immunogenic cell death was evaluated both in vitro and in vivo (HMGB1/ATP release, calreticulin and EIF2α endoplasmic reticulum stress marker). Both antitumor CD8 (IFNγ, Granzyme B, PD-1) and tolerogenic (including Treg, polymorphonuclear-granulocytic/monocytic myeloid-derived suppressor cells and tumor-associated macrophages [TAM]) responses were analyzed by immunochemistry and flow cytometry.

Results: Combined therapy induced all immunogenic cell death markers in vitro. In tumor tissue, HMGB1 nuclear delocalization and EIF2α phosphorylation were significantly increased after trifluridine/tipiracil and oxaliplatin exposure as compared to each single agent; no effect was seen with the single agents. These immunogenic signals allow the recruitment of PD-1$^+$ CD8 cells with high capacity for production of IFNγ, TNFα and granzyme B production capacities. Furthermore, the trifluridine/tipiracil and oxaliplatin combination was seen to markedly deplete TAM, in particular TAM2.

Conclusions: The trifluridine/tipiracil and oxaliplatin combination induces immunogenic cell death and antitumor CD8 activation as well as depletion of immunosuppressive TAM2 in MSS colorectal cancer. This chemotherapy combination could therefore be considered as a potential new therapeutic option for immune checkpoint inhibitor sensitization in MSS colorectal cancer. 1. Le DT, Uram JN, Wang H, et al. N Engl J Med. 2015;372(26):2509-20. 2. Lochhead P, Kuchiba A, Imamura Y, et al. J Natl Cancer Inst. 2013;105(15):1151-6. 3. De Smedt L, Lemahieu J, Palmans S, et al. Br J Cancer. 2015;113(3):500-9.

Legal entity responsible for the study: Servier and CGFL.

Funding: Servier.

Disclosure: F. Ghiringhelli: Consultant: AstraZeneca, Servier, Roche, BMS, Enterome, Sanofi. V. Cattan, E. Peranzoni, N. Amellal: Employee of Servier. All other authors have declared no conflicts of interest.

559P Distribution of endocrine tumor marker-positive cells in adenocarcinoma tissue between right-sided and left-sided colon cancer

T. Ogimi[1], S. Sadahiro[1], H. Miyakita[1], G. Saito[1], K. Okada[1], A. Tanaka[1], T. Suzuki[1], H. Kajiwara[2]

[1]Surgery, Tokai University School of Medicine, Isehara, Japan, [2]Pathology, Tokai University School of Medicine, Isehara, Japan

Background: Neuroendocrine carcinoma (NEC) is a rare disease accounting for 0.03% to 0.2% of all colorectal cancers and has been reported to occur significantly more frequently in the right-sided colon. Tumors consisting of both adenocarcinoma and NEC components or mixtures of these components have been reported. Some cases of adenocarcinoma diagnosed on H-E staining include neuroendocrine tumor

components. We tested the hypothesis that distribution of endocrine tumor marker-positive cells in cancer tissue differ between right-sided and left-sided colon cancer.

Methods: The study group comprised 354 patients with stage II or III colon cancer who underwent curative resection from 2007 to 2012. Immunostaining was performed using chromogranin A (cgA), synaptophysin, and CD56 as gastrointestinal endocrine tumor markers. Cases in which positive cells were seen in some part of the cancer tissue were evaluated to be positive.

Results: Tumors were located in the right-sided colon in 181 patients (51.1%) and the left-sided colon in 173 patients (48.8%). Immunohistochemical staining was positive for cgA in 66 patients (18.6%), positive for synaptophysin in 102 patients (28.8%), and positive for CD56 in 55 patients (15.5%). Immunohistochemical staining was positive for at least one of these markers in 118 patients (33.3%) and for all of the markers in 27 patients (7.6%). The rate of positive staining for cgA was 23.7% (43/181) in right-sided colon cancer and 13.2% (23/173) in left-sided colon cancer. The rate of positive staining for synaptophysin was 35.3% (64/181) in right-sided colon cancer and 21.9% (38/173) in left-sided colon cancer. The rate of positive staining for CD56 was 22.6% (41/181) in right-sided colon cancer and 8.0% (14/173) in left-sided colon cancer. The rates of positive staining for cgA, synaptophysin, or CD56 were significantly higher in right-sided colon cancer ($p = 0.0115$, $p = 0.0054$, and $p = 0.0062$).

Conclusions: Overall, 33.3% of patients with adenocarcinoma of the colon had endocrine tumor components in cancer tissue. The rates of positive staining for endocrine tumor markers were significantly higher in right-sided colon cancer, which may be associated with the high incidence of NEC in the right side of the colon.

Legal entity responsible for the study: Sotaro Sadahiro, MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

560P Prospective DPYD testing in colorectal cancer patients in a realworld UK population

B.K. Eccles[1], A.S. Harle[1], S. Pullinger[2], C. Holling[1], A. Ingram[3], S. Stark[2], M. Bunce[2], G. Melville[1], J. Gibbins[3], N. Calcutt[3], T. Hickish[4], M. Flubacher[1], T. Marinaki[5]

[1]Oncology, Poole Hospital NHS Foundation Trust, Poole, UK, [2]Surgical Oncology, Royal Bournemouth Hospital, Bournemouth, UK, [3]Oncology, Dorchester County Hospital, Dorchester, UK, [4]Oncology, Royal Bournemouth Hospital and University, Bournemouth, UK, [5]Purine Research Laboratory, St. Thomas Hospital, London, UK

Background: Polymorphisms within the DPYD gene are present in 7% of Europeans but account for 23% of life-threatening toxicity from fluoropyrimidine (FP) chemotherapy. Four DPYD variants have an adjusted relative risk for toxicity of 1.59 - 4.4. Upfront genotyping is safe and cost effective but not mandated by ESMO guidelines. To reduce the risk of life-threatening toxicity we implemented prospective DPYD testing as standard practice.

Methods: Consecutive colorectal cancer (CRC) patients in a UK cancer centre due to receive FP chemotherapy were genotyped by real time PCR for known clinically relevant DPYD mutations: c.1905+G>A 2*, c.2846A>T, c.1679T>G and c.1605 G>A and from March 2017, c.1236G>A/HapB. We followed published recommendations for dose reduction or alternative drug. Demographics, dose, toxicity and survival data were collected.

Results: Between 1/1/16-31/12/2017, 230 patients were tested. 72% had capecitabine, 24% 5-fluorouracil, and 4% raltitrexed combinations. After dose reduction or alternative therapy, grade 3/4 diarrhoea was similar in wildtype and mutations (10 vs 13%) and any toxicity admissions were not significantly different ($p = 0.284$). There were no treatment deaths.

Conclusions: To our knowledge, we are the only UK centre to implement prospective DPYD testing in routine clinical practice for CRC patients. In published data of unselected CRC patients the G3/4 GI toxicity is 15%, but if 2* variant is present this increases to 73%. In the latter population, genotype guided dosing reduces the risk to 28%. Our rate for all variants was 10% but limited by small numbers. Pharmacokinetics in another study showed adequate 5FU exposure with a 50% dose reduction, alleviating underdosing concerns. The growing evidence supports prospective DPYD testing. We have shown it is practical and may mitigate serious toxicities.

Legal entity responsible for the study: Bryony Eccles.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 560P

DPYD Heterozygote mutations (No homozygote or compound heterozygote mutations)	Adjusted RR	No. (%)	Mean 1st dose %	Any grade 3/4 toxicity No. (%)	Grade 3/4 diarrhoea No. (%)
c.1905+G>A	1.59	3 (2%)	77%	1	0
c.2846A>T	3.02	2 (1%)	100%	1	1
c.1679T>G	4.4	0 (0%)			
c.1236G.A/ HapB3	1.59	7 (3%)	76%	1	0
c.1601G>A	1.52 (Non significant)	11(5)%	80%	4	2
Any heterozygote mutation		23 (10%)	80%	7 (30%)	3 (13%)
Wildtype	1	207 (90%)	93%	42 (20%)	20 (10%)
Total 58% adjuvant 27% neoadjuvant 24% palliative		230 (100%)	92%	49 (21%)	23 (10%)

561P Standard fluoropyrimidine dosages in chemoradiation therapy result in an increased risk of severe toxicity in DPYD variant allele carriers

C.A.T.C. Lunenburg[1], L.M. Henricks[2], E. Dreussi[3], F.P. Peters[4], M. Fiocco[5], D. Meulendijks[6], G. Toffoli[3], H-J. Guchelaar[7], J.J. Swen[7], E. Cecchin[3], J.H.M. Schellens[2], H. Gelderblom[1]

[1]Department of Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [2]Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [3]Experimental and Clinical Pharmacology Unit, National Cancer Institute, Aviano, Italy, [4]Department of Radiotherapy, Leiden University Medical Center (LUMC), Leiden, Netherlands, [5]Medical Statistics, Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, Netherlands, [6]Dutch Medicines Evaluation Board, CBG-MEB, Utrecht, Netherlands, [7]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, Netherlands

Background: Prospective DPYD genotyping prevents severe fluoropyrimidine-induced toxicity by decreasing initial dosages in DPYD variant allele carriers. However, fluoropyrimidine dosages in chemoradiation therapy are already lower compared to other fluoropyrimidine-containing regimens. It is unknown if recommended dose reductions of pharmacogenetic guidelines are valid for DPYD variant allele carriers receiving fluoropyrimidines in chemoradiation therapy. The aim of this study was to investigate severe toxicity in DPYD variant allele carriers receiving chemoradiation therapy.

Methods: Three databases were used, containing data on patients who received fluoropyrimidine-based chemoradiation therapy. Frequencies of severe (grade $\geq$3) toxicity in DPYD variant allele carriers (DPYD*2A, DPYD*13, c.2846A>T or c.1236G>A) receiving upfront fluoropyrimidine dose reductions according to current pharmacogenetic dosing guidelines (50 or 75% depending on the variant), and DPYD variant allele carriers receiving full-dose were compared to DPYD wild-type patients receiving standard dose fluoropyrimidines in chemoradiation therapy.

Results: DPYD variant allele carriers treated with standard dosages ($N = 34$) showed an increased risk of severe gastrointestinal (adjusted OR = 2.58, 95% CI = 1.02-6.53, $P = 0.045$) or severe haematological (adjusted OR = 4.19, 95% CI = 1.32-13.25, $P = 0.015$) toxicity compared to wild-type patients ($N = 771$). DPYD variant allele carriers who received dose reductions ($N = 22$) showed a comparable frequency of severe gastrointestinal toxicity, but a higher frequency of severe haematological toxicity, compared to wild-type patients. The mean duration of hospitalisation was significantly shorter in DPYD variant allele carriers who received dose reductions compared to DPYD variant allele carriers treated with standard dosages (4 versus 23 days, $P = 0.010$).

Conclusions: Standard fluoropyrimidine dosages in chemoradiation therapy resulted in an increased risk of severe toxicity in DPYD variant allele carriers. Fluoropyrimidine dose reductions for DPYD variant allele carriers should also be applied in patients receiving chemoradiation therapy.

Legal entity responsible for the study: Leiden University Medical Centre.

Funding: Has not received any funding.

Disclosure: C.A.T.C. Lunenburg: Previously supported by an unrestricted grant from Roche Pharmaceuticals. All other authors have declared no conflicts of interest.

562P Determination of DPYD polymorphisms before treatment with chemotherapy with a pyrimidine: Should we continue doing it?

C. Avila Andrade[1], A.J. Cunquero Tomas[1], A.B. Fernandez Diaz[1], M. Meri Abad[1], L.D. Condori Farfan[1], I. Shaheen[1], S. Cervantes Garcia[2], M.J. Safont Aguilera[1], V. Iranzo Gonzalez-Cruz[1], V. Sforza[3], C. Caballero[4], M.C. Godes de Bremond[1], M. Gil[1], F.D.A. Aparisi Aparisi[5], A. Blasco Cordellat[6], A. Berrocal Jaime[6], I. Ferrer Bolufer[2], M. Lobo de Mena[6], G. Marcaida Benito[2], C. Camps[7]

[1]*Medical Oncology Service, Hospital General Universitario Valencia, Valencia, Spain,* [2]*Clinical Analysis, Hospital General Universitario Valencia, Valencia, Spain,* [3]*Department of Medical Oncology, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy,* [4]*Medical Oncology, Hospital General, Valencia, Spain,* [5]*Oncology, Fundación de Investigación Hospital General Universitario de Valencia, Valencia, Spain,* [6]*Medical Oncology, Hospital General Universitario Valencia, Valencia, Spain,* [7]*Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain*

Background: The toxicity produced by chemotherapy worsens in the presence of mutations in certain enzymes of metabolism or degradation. Such is the case of dihydropyrimidine dehydrogenase (DPYD) in the treatment with fluoropyrimidines. Detection prior to the start of treatment could be beneficial to prevent this increase in toxicity.

Methods: A prospective study in which the DPYD polymorphisms are analyzed, after the first visit in Oncology of patients with a diagnosis of colorectal cancer (CRC), gastroesophageal cancer (CGE) or cancer in the head and neck, that can be treated with fluoropyrimidine-based chemotherapy. After DNA extraction from the peripheral blood sample the methodology used was: 1. Directed genotyping of variant * 2A, * 13 and rs67376798 of the DPYD gene, by analysis of allelic discrimination polymorphisms with TAQMAN probes, previous amplification in an ABI Prism 7900 (Applied Biosystems).

Results: We included 374 patients, with an average age of 67a, 62% men, with PS 0 or 1 in 97% of the cases. Localization of the primary tumor was: CRC 85%, GEC 12%, H&N (3%). 97% were adenocarcinomas and 3% squamous carcinoma. The intention of adjuvant treatment in 46%, neoadjuvant 17%, a first line of metastatic disease 33%, the second line of metastatic disease 3%. Schemes used: combinations of 5FU with oxaliplatin (58%), capecitabine in monotherapy or radiotherapy in neoadjuvant (33%). Toxicities G3-4: diarrhea 1.3%, neutropenia 0.8%, rash, 1.3% and mucositis 0.3% Four patients with DPYD deficit (1.1%) were found. two patients with a complete deficit that started capecitabine adjuvant at 50%, increasing to 75% in the 2nd cycle with G1 diarrhea as a relevant toxicity. Another two patients with DPYP heterozygous deficit decided to change treatment scheme to ralitrexed every 3 weeks.

Conclusions: In our study, we observed that the enzymatic deficit in the metabolic pathways related to 5FU are rare, and probably do not influence the initiation of chemotherapy treatment.

These results will not influence the usual clinical practice, but we think are very important to avoid toxicity to the patient if these are present.

Legal entity responsible for the study: Hospital General Valencia Deparment of Medical Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

563P Updated results of phase I study of trastuzumab deruxtecan (DS-8201a) in HER2-expressing advanced colorectal cancer

T. Yoshino[1], H. Iwata[2], K. Tamura[3], S. Takahashi[4], C. Redfern[5], S. Modi[6], T. Doi[1], H. Kawakami[7], H. Taniguchi[2], A. Takashima[8], K. Yamaguchi[9], J. Fisher[5], B. Li[6], K. Saito[10], Y. Fujisaki[10], M. Sugihara[11], J. Tsurutani[7]

[1]*Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan,* [2]*Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan,* [3]*Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan,* [4]*Department of Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan,* [5]*Clinical Oncology Research, Sharp HealthCare, San Diego, CA, USA,* [6]*Department of Medicine, Breast Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA,* [7]*Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan,* [8]*Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan,* [9]*Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan,* [10]*Clinical Development, Daiichi Sankyo Co., Ltd, Tokyo, Japan,* [11]*Biostatistics and Data Management, Daiichi Sankyo Co., Ltd, Tokyo, Japan*

Background: DS-8201a is a HER2-targeting antibody-drug conjugate with a novel peptide-based cleavable linker, a topoisomerase I inhibitor payload, and a high drug-to-antibody ratio (7 to 8). In preclinical studies, DS-8201a showed a broad antitumor activity in a wide range of tumors, including colorectal cancer (CRC) regardless of KRAS status. The ongoing phase 1 trial has a dose-escalation (part 1) and -expansion (part 2) and includes subjects (sbj) with advanced breast cancer, gastric cancer, and other HER2-expressing/mutated solid tumors. Here, we present updated results for HER2-expressing CRC.

Methods: Sbj with advanced HER2-expressing (defined as IHC $\geq$1+) CRC were eligible to enroll. HER2 expression was assessed using archival tissue. Objective response rate (ORR), disease control rate (DCR; CR + PR + SD), duration of response (DOR), and adverse events (AEs) were assessed.

Results: As of Apr 18, 2018, 19 HER2-expressing CRC sbj received $\geq$1 dose of DS-8201a at 6.4 mg/kg. Median age was 59 y with median of 4 prior regimens (range: 1 to 8). Sixteen of 19 sbj had prior treatment (tx) with irinotecan, another topoisomerase -I inhibitor. At the data cutoff, 7 of 19 (36.8%) sbj remain on treatment. Median duration of tx was 2.76 months (range 0.69, 15.44). Two sbj were known to have KRAS mutations. Overall, confirmed ORR and DCR in the efficacy evaluable sbj was 3 of 12 (25.0%) and 10 of 12 (83.3%), respectively. All responses were observed in KRAS wild-type sbj. One sbj with a KRAS mutation had SD with reduction in tumor markers. Median DOR has not been reached (NR, range 2.76, 5.52+ mo). Nine of 15 (60.0%) sbj with $\geq$1 post baseline scan experienced tumor shrinkage. Major reason for tx discontinuation was progressive disease (9/12; 75.0%). As for the safety outcomes, 12/19 (63.2%) experienced a grade $\geq$3 AE. Common AEs included nausea 57.9% (0.0% grade $\geq$3), platelet count decreased 52.6% (26.3% grade $\geq$3), anemia 47.4% (26.3% grade $\geq$3), vomiting 42.1% (0% grade $\geq$3), and diarrhea 42.1% (0% grade $\geq$3).

Conclusions: DS-8201a demonstrated antitumor activity with manageable safety profile in heavily pretreated subjects with HER2-expressing CRC and warrants further investigation in a phase 2 trial.

Clinical trial identification: NCT02564900.

Editorial acknowledgement: Editorial and submission support was provided by Stefan Kolata, PhD of AlphaBioCom, LLC (King of Prussia, PA USA).

Legal entity responsible for the study: Daiichi Sankyo Co,. Ltd.

Funding: Daiichi Sankyo Co,. Ltd.

Disclosure: T. Yoshino: Grants: MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co., Ltd; Grants and personal fees: Sanofi K.K., Chugai Pharmaceutical Co., Ltd.; Personal fees: Eli Lilly Japan K.K, Merck Serono Co., Ltd. H. Iwata: Dr. Iwata Grants and personal fees: Daiichi Sankyo, during the conduct of the study; Grants and personal fees: Chugai, AstraZeneca, Pfizer; Personal fees: Eisai; Grants from MSD, Kyowahakou Kirin, GSK, Lilly, Novartis, Bayer. S. Takahashi: Grants and personal fees: Daichi-Sankyo, during the conduct of the study; Grants and personal fees: Daiichi-Sankyo, outside the submitted work. T. Doi: Grants: Daiichi Sankyo during the conduct of the study; Grants and personal fees: Lilly, Chugai Pharma, Kyowa Hakko Kirin, MSD, Daiichi Sankyo; Personal fees: Amgen; Grants from Taiho, Novartis, Merck Serono, Astellas Pharma, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Sumitomo Group, Celegene, Bristol Myers Squibb, Abbvie, Quintiles. H. Kawakami: Grants: Diaiichi Sankyo; Personal fees: Eli Lilly, Ono Pharmaceutical, Co., Ltd., Chugai Pharmaceutical, Co., Ltd., Taiho Pharmaceutical, Co., Ltd., MSD Pharmaceutical, Co., Ltd., Merck Serono, Takeda Pharmaceutical, Co., Ltd., Astra Zeneca K.K., Yakult Pharmaceutical industry, Co., Ltd. H. Taniguchi: Grants and personal fees: Takeda; Personal fees: Taiho, Chugai. K. Yamaguchi: Research grants: MSD, Ono Pharmaceuticals, Dainppon-Sumitomo, Taiho Pharmaceuticals, Daiichi-Sankyo, Eli Lilly, Giriad, Yakurt Honsha; Consultation fees: Daiichi Sankyo Bristol-Myers Squibb; Speakers' bureau: Taiho Chugai, Merck, Tkeda, Yakurt Honsha, Bayer, Ono Pharmaceuticals, Sanofi, Eli Lilly. B. Li: Grants: Daiichi Sankyo, during the conduct of the study; Personal fees: Genentech. K. Saito, Y. Fujisaki, M. Sugihara: Full-time employee: Daiichi Sankyo Co., Ltd. J. Tsurutani: Grants: Daiichi-Sankyo, during the conduct of the study; Personal fees: Daiichi-Sankyo, outside the submitted work. All other authors have declared no conflicts of interest.

564P TRICC-C: Nintedanib vs. placebo in patients receiving mFOLFOX6 for metastatic, chemorefractory colorectal cancer: Final results from the randomized phase II trial of the AIO

T.J. Ettrich[1], A.W. Berger[1], T. Decker[2], R.D. Hofheinz[3], V. Heinemann[4], T. Hoffmann[5], H.F. Hebart[6], T. Herrmann[7], C-V. Hannig[8], P. Büchner-Steudel[9], H. Bartholomäus[1], M. Güthle[1], L. Perkhofer[1], T. Seufferlein[1]

[1]*Department of Internal Medicine I, Ulm University, Ulm, Germany,* [2]*Onkologie Ravensburg, Ravensburg, Germany,* [3]*Interdisciplinary Tumor Center, Universitätsklinikum Mannheim, Mannheim, Germany,* [4] *Department of Medical Oncology and Comprehensive Cancer Center, Ludwig Maximilians University - Grosshadern, Munich, Germany,* [5]*Internal Medicine II, Klinikum Weimar, Weimar, Germany,* [6]*Department of Internal Medicine, Stauferklinikum Schwäbisch Gmünd, Mutlangen, Germany,* [7]*Medizinische Klinik, Westküstenklinikum Heide, Heide, Germany,* [8]*Private Practice, Schwerpunktpraxis Haematologie/Onkologie, Bottrop, Germany,* [9]*Internal Medicine I, Martin-Luther-University Halle-Wittenberg, Halle, Germany*

Background: Anti-VEGF agents in combination with chemotherapy improve PFS of patients with mCRC in the 1st- and 2nd-line-setting. During anti-VEGF treatment tumour angiogenesis is driven by other factors but VEGF. Nintedanib is a triple angiokinase inhibitor of human VEGFR-1-3, FGFR-1/-3 and PDGFR-α/-β thereby additionally targets angiogenic escape mechanisms upon resistance to anti-VEGF treatment. The TRICC-C trial evaluates the combination of mFOLFOX6 plus Nintedanib. Final results of the randomized phase II trial are presented.

Methods: Patients with mCRC having received one line of non-oxaliplatin containing palliative chemotherapy, with an ECOG-PS of 0 or 1 were randomized 1:1 in a double-blind design to receive: mFOLFOX6 plus Nintedanib (2 x 200 mg p.o./d, d1-d14) or placebo, respectively, repeated every 14 days. Primary endpoint was PFS. Secondary endpoints were ORR, OS and safety. Patients who received at least one dose of trial medication were included in the efficacy and safety analyses.

Results: From 12/2012 to 5/2016 53 patients (scheduled n = 180) were randomized. The trial was terminated prematurely due to slow accrual. Compared to mFOLFOX6 plus

placebo (F+P), the combination of mFOLFOX6 plus Nintedanib (F+N) improved mPFS (F+P: 4.6 vs F+N: 8.1 mo.; HR 0.65; 95% CI 0.32-1.30; p = 0.2156), mOS (F+P: 9.9 vs. F+N: 17.1 mo.; HR 1.03, 95% CI 0.48-2.23; p = 0.9387) and DCR (F+P: 50 vs. F+N: 66,7%; p = 0.2709). ORR was comparable in both arms (F+N: 3.8 vs. F+P: 3.7%). Toxicity was low to moderate without major differences between both arms except G 3/4 neutropenia (F+N: 19%, F+P: 12%) and GI disorders (F+N: 23%, F+P: 15%).

Conclusions: Final results suggest a PFS, OS and DCR benefit for mFOLFOX6 + Nintedanib vs. mFOLFOX6 + placebo in the 2nd-line therapy of mCRC. Due to the premature termination of the trial there was no statistical significance demonstrable. Showing no clinically significant PFS-benefit in the 1st-line situation (mFOLFOX6 plus Nintedanib/Bevacizumab, Ann Oncol. 2015) or the last line as single agent, respectively (ESMO 2016) the TRICC-C results suggests that Nintedanib could be an interesting therapeutic option for the 2nd-line situation in combination with mFOLFOX6.

Clinical trial identification: NCT01362361.

Legal entity responsible for the study: Martin-Luther-Universität Halle-Wittenberg, Germany.

Funding: Boeringer Ingelheim.

Disclosure: T.J. Ettrich: Research grants: Baxalta/Shire; Consulting fees or other remuneration: Merck-Serono, Sanofi, Sirtex, Medical, Novartis, Bayer, Bristol-Myers Squibb, Pfizer. A.W. Berger: Consulting fees: Sanofi. R.D. Hofheinz: Consulting or advisory role: Boehringer Ingelheim. T. Seufferlein: Research Funding: Celgene, Sanofi Consulting or Advisory role: Celgene, Lilly Pharma, Boehringer Ingelheim, Merck Serono, Amgen. All other authors have declared no conflicts of interest.

565P Dose finding and safety study of reovirus (Reo) with irinotecan/ fluorouracil/ leucovorin/ bevacizumab (FOLFIRI/B) in patients with KRAS mutant metastatic colorectal cancer (mCRC): Final results

S. Goel[1], A. Ocean[2], R. Parakrama[1], M.H. Ghalib[1], I. Chaudhary[1], U. Shah[1], M. Coffey[3], E. Kaledzi[1], R. Maitra[1]

[1]Medical Oncology, Montefiore Medical Center (East campus) - Medical Park at Eastchester Albert Einstein Cancer Center, Bronx, NY, USA, [2]Solid Tumor Division, New York Presbyterian-Weill Cornell Medical College, New York, NY, USA, [3]Oncology, Oncolytics, Calgary, AB, Canada

Background: KRAS mutation is a biomarker of exclusion of anti-EGFR agents in patients with mCRC, who have limited options once they progress on oxaliplatin and irinotecan-based regimens. Reo is a naturally occurring, ubiquitous, non-enveloped double stranded RNA virus that selectively replicates in tumor cells harboring KRAS mutations. Reo is synergistic with irinotecan (IRI) in in vitro and in vivo models.

Methods: This was a phase I dose escalation study of FOLFIRI/B and Reo to determine maximum tolerated dose (MTD) and recommended phase two dose (RPTD). Eligible pts were adults with oxaliplatin refractory KRAS-mutant mCRC. Both, IRI (150-180 mg/m^2) and Reo (1x10^{10} $TCID_{50}$ to 3x10^{10} $TCID_{50}$) were escalated. Reo was given intravenously over 1 hour on days 1-5 every 4 weeks (wk). FOLFIRI/B was delivered every 2 wk as per standard protocol. Pharmacokinetics (PK), on study tumor biopsies, and immune response was studied.

Results: 36 pts enrolled; 23 females (64%), median age 63 years, FOLFIRI naïve (24) and pre-treated (12). At the highest dose of 180 mg/m^2 of IRI, among FOLFIRI pre-treated pts, 2 had dose-limiting toxicity (DLT) in cycle 1; one suffered from grade 4 thrombocytopenia, and another developed febrile neutropenia and urosepsis. However, in FOLFIRI naïve patients, none/6 had a DLT. Common (>10%) toxicities included neutropenia, anemia, thrombocytopenia, fatigue, and diarrhea. One patient died of acute renal failure. The MTD was the highest individual dose of FOLFIRI/B (180 mg/m^2 IRI) and reovirus (3x10^{10} $TCID_{50}$), and is the RPTD. At this dose, 3 of 6 patients (50%) had a PR and the median progression free survival (PFS) and overall survival (OS) were 65.6 wk and > 98.3 wk (as of May 9, 2018), respectively. There was no PK interaction noted. Immunogold staining against viral capsid protein σ demonstrated viral "homing" in the tumor cells. Flow cytometry revealed rapid dendritic cell maturation with subsequent activation of cytotoxic T cells.

Conclusions: The combination of reovirus with FOLFIRI/B is safe, and well tolerated. The PFS and OS is superior to historic data and this combination deserves further exploration.

Clinical trial identification: NCT01274624.

Legal entity responsible for the study: Sanjay Goel.

Funding: Conquer Cancer Foundation and Oncolytics Inc.

Disclosure: S. Goel, A. Ocean: Oncolytics funding to conduct clinical investigations with reovirus. M. Coffey: Employee, Stock owner: Oncolytics Inc. All other authors have declared no conflicts of interest.

566P A first-in-human phase I study of GC1118, a novel monoclonal antibody inhibiting epidermal growth factor receptor (EGFR), in patients with colorectal cancer and gastric/GEJ cancer

D-Y. Oh[1], K-W. Lee[2], S-W. Han[3], J.W. Kim[4], J-W. Shin[5], S-J. Jo[6], N.H. Kim[7], A. Woo[8], J. Won[9], S. Hahn[10], H. Lee[11], W.H. Kim[12], Y-J. Bang[13]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [3]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [4]Oncology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [5]Department of Dermatology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [6]Dermatology, Seoul National University Hospital, Seoul, Republic of Korea, [7]Green Cross Corp., Yongin, Republic of Korea, [8]Clinical Development, Green Cross Corporation, Yongin, Republic of Korea, [9]Oncology Team, MOGAM Institude for Biomedical Research, Gyeonggi-do, Republic of Korea, [10]Division of Medical Statistics, Seoul National University Hospital, Seoul, Republic of Korea, [11]Clinical Pharmacology, Seoul National University Hospital, Seoul, Republic of Korea, [12]Pathology, Seoul National University Hospital, Seoul, Republic of Korea, [13]Internal Medicine (Medical Oncology), Seoul National University Hospital, Seoul, Republic of Korea

Background: GC1118 is a novel anti-EGFR monoclonal antibody and has unique binding epitopes and different ligand binding inhibitory activity compared to cetuximab and panitumumab. In dose escalation part of a first-in-human phase 1 study, RP2D were determined as 4 mg/kg, in weekly dosing schedule (NCT02352571). DLT was skin toxicity. Here we report efficacy and safety data of GC1118 in patients (pts) with colorectal cancer (CRC) and gastric cancer (GC) tested in dose expansion part.

Methods: Cohort 1 (C1) recruited pts with metastatic CRC with no prior EGFR antibody treatment who have failed to 5-FU, oxaliplatin and irinotecan. Cohort 2 (C2) enrolled pts with metastatic CRC with resistance to prior EGFR antibody. Cohort 3 (C3) enrolled pts with EGFR over-expressing (2+,3+) metastatic GC cancer who have failed to standard treatment. GC1118 was administrated on days 1, 8, 15 and 22 every 4 weeks.

Results: A total of 39 pts were enrolled (C1: 14, C2:12, C3:13). Evaluable pts were 12 in each cohort. In C1, SD was observed in 58.33% (7/12) and there was no CR/PR case. In C2, 2 patients (16.67%) obtained PR, 1 SD (8.33%), and 9 PD (75.0%). In C3, PR was 8.33% (1/12), SD 16.67% (2/12), and PD 75.0%. The progression-free survival (PFS) were 14 weeks (95% CI: 7.1-30.1), 6.93 weeks (95% CI: 4.2-14.8), and 6.7 weeks (95% CI: 5.0-11.0), respectively Adverse event (AE) was observed in 97.4% of patients and treatment-related AE (TRAE) occurred in 92.3% of patients. Skin toxicity (all grade) was observed in 89.7% of patients (35/39), stomatitis 20.51%(all grade 1/2), and diarrhea 17.95% (all grade 1/2). Dose reduction due to AE was required in 23.08% of patients (9/39), and dose interruption due to AE was needed in 58.9% of patients (23/39). TRAE higher than grade 3 was observed in 20.5% of patients (8/39). Among them, skin toxicity was most common (12.8%, 5/39 patients) There was no treatment-related death.

Conclusions: GC1118 showed promising anti-tumor activity, especially in CRC with resistance to prior EGFR antibody with 16.7% PR, even in heavily treated population. GC1118 was generally well tolerated, and skin toxicities were by far the most common AEs.

Legal entity responsible for the study: Green Cross Corp., Seoul National University Hospital.

Funding: Green Cross Corp.

Disclosure: N.H. Kim, A. Woo, J. Won: Employee: Pharmaceutical company. All other authors have declared no conflicts of interest.

567P Results of a phase I study of andecaliximab in combination with mFOLFOX6 and bevacizumab in patients with previously untreated metastatic colorectal cancer

H-J. Lenz[1], H. Park[2], M.A. Shah[3], J.D. Berlin[4], D. Bruetman[5], J. Chaves[6], M. Gordon[7], R. Patel[8], A. Starodub[9], J. Liu[10], C. Baker Brachmann[11], P. Bhargava[12], Z.A. Wainberg[13], J. Bendell[14]

[1]Medical Oncology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA, [2]Oncology, Washington University School of Medicine, St. Louis, MO, USA, [3]Department of Medicine, Weill Cornell Medicine/ New York Presbyterian Hospital, New York, NY, USA, [4]Medicine, Vanderbilt Ingram Cancer Center, Nashville, TN, USA, [5]Department of Medicine, Goshen Center for Cancer Care, Goshen, IN, USA, [6]Department of Medicine, Northwest Medical Specialties PLLC, Tacoma, WA, USA, [7]Medical Oncology, HonorHealth Research Institute, Scottsdale, AZ, USA, [8]Department of Medicine, Comprehensive Blood and Cancer Center, Bakersfield, CA, USA, [9]Department of Medicine, Indiana University Health Goshen Hospital, Goshen, IN, USA, [10]Department of Biostatistics, Gilead Sciences, Inc., Foster City, CA, USA, [11]Department of Biomarkers, Gilead Sciences, Inc., Foster City, CA, USA, [12]Department of Clinical Research, Gilead Sciences, Inc., Foster City, CA, USA, [13]Department of Medicine, UCLA Medical Center, Los Angeles, CA, USA, [14]Department of Medicine, Sarah Cannon Research Institute, Nashville, TN, USA

Background: Matrix metalloproteinase-9 (MMP-9) is highly expressed in metastatic colorectal cancer (mCRC) and other advanced cancers and confers an adverse prognosis. In a preclinical CRC model, inhibition of MMP-9 was associated with reduced tumor growth. Andecaliximab (ADX) is a chimeric antibody directed against MMP-9, engineered to remove T cell epitopes and reduce risk of human anti-mouse antibodies. In this phase I

multi-cohort study, we evaluated the combination of ADX with standard chemotherapy in patients with previously untreated mCRC. (Clinicaltrials.gov NCT# 01803282).

Methods: The study enrolled 45 eligible patients (19 female) with measurable disease and previously untreated mCRC. The median age was 62 years (range 34-78) and 18% (8/45) of patients had received prior adjuvant chemotherapy. Patients were treated with 800 mg ADX IV every two weeks plus standard doses mFOLFOX6 and bevacizumab. Safety and efficacy were assessed. Primary endpoints were safety and tolerability. Exploratory endpoints were investigator-assessed objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Molecular analysis of archival tumor samples was performed.

Results: As of March 5, 2018, the median duration of ADX treatment was 8.8 months. Median PFS follow up time was 13.5 months. The most common adverse events were fatigue (78%), nausea (71%), diarrhea (56%), peripheral sensory neuropathy (49%), decreased appetite (40%), and neutropenia (40%). 38% of patients reported serious adverse events (SAEs). Acute respiratory failure and sepsis (both 4%) were the most common SAEs. Median PFS was 10 months (90% CI 9.0-12.0 months), median duration of response was 8.1 months (90% CI 6.1, 10.4). Overall response rate was 62% (90% CI 49 – 74%) with 4% complete response rate. The response rate was 50% for mutated BRAF, 67% for mutated RAS, 67% for right-sided disease. The median OS was not reached. Study treatment continues in 7% of patients.

Conclusions: Combination of ADX with mFOLFOX6 and bevacizumab was safe and shows response and PFS similar to historical data with FOLFOX-bevacizumab in first-line treatment of patients with previously untreated mCRC.

Clinical trial identification: NCT 01803282.

Legal entity responsible for the study: Gilead Sciences, Inc.

Funding: Gilead Sciences, Inc.

Disclosure: H.J. Lenz: Consulting/Advisory Role: Bristol Myers Squibb, Roche, Merck Serono, Bayer; Travel/Expenses: Bayer, Merck Serono; Honoraria: Bristol Myers Squibb, Roche, Merck Serono, Bayer, and Takeda. M. Shah: Research funding: Lilly/ImClone, Gilead Science, Merck, Sanofi/Regeneron, Boston Biomedical. J. Berlin: Research funding: Genetech/Roche, OncoMed, Novartis, Immunomedics, Abbvie, Gilead Science, Merrimack, Taiho Pharmaceuticals, Five Prime Theraputics, Loxo, Vertex, Bayer, Symphogen, Incyte, Pharmacyclics, Karyopharm Theraputics; Consulting/Advisory Role: Celegene, Symphogen, Genetech/Roche, EMD Serono, Aduro Biotech, Cornerstone Pharmaceuticals, Five Prime Theraputics, Opsona Theraputics, Pierre Fabre, Exelixis, Gritstone Oncology, Erytech Pharma, BeiGene, Karyopharm Theraputics; Travel/Expenses: Genetech/Roche, Celgene, Nestle Health Science, End Serene; Honoraria: Genetech, Nestle Health Science; Other: Symphogen, AstraZeneca. J. Chaves: Stock Ownership: Abbott Laboratories, Johnson & Johnson, Merck; Research Funding: Calithera Biosciences, Celgene, EMD Serono, Halozyme, Immune Design, Novartis, Pfizer. A. Starodub: Consultant/Advisor: Sandoz, Bayer; Speakers' bureau: Bristol Myers Squibb; Travel/Expenses: Bayer, Bristol Myers Squibb, Sandoz. J. Liu, C. Brachmann, P. Bhargava: Employee and stock ownership: Gilead Science Inc. Z.A. Wainberg: Research funding: Novartis, Plexxikon, Pfizer, Merck; Consulting, Advisory role: Sirtex Medical, Amgen, Array BioPharma, Five Prime Therapeutics, Novartis, Lilly, Merck, Merck KGaA, Bristol-Myers Squibb, Aduro Biotech; Speakers' bureau: Genentech; Travel expenses: Genentech. J. Bendell: Research funding: Lilly, Genetech/Roche, Incyte, Gilead Science, Bristol-Myers Squibb, Leap Theraputics, AstraZeneca/MedImmune, Boston Biomedical, GlaxoSmithKline, Novartis, Array BioPharma, Taiho Pharmaceutical, Celgene, Oncomed, Daiichi Sankyo, Bayer, Apexigen, Kolltan Pharmaceuticals, SynDevRX, Merck, Macrogenics, Five Prime Theraputics, EMD Serono, TG Theraputics, Boehringer Ingelheim, Forty Seven, Stem CentRx, Onyx, Sanofi, Takeda, Abbott/AbbVie, Eisai, Celldex, Agios, ARMO BioScience, CytomX Theraputics, Nektar, Ipsen, Merrimack, Tarveda Theraputics, Tyrogenex, Oncogenex, Marshall Edwars, Pieris Pharmaceuticals, Mersana, Calithera BioScience, Blueprint Medicines, Gritstone Oncology, Evelo Therapeutics, Forma Therapeutics, Forty Seven, EMD Serono, Merus. All other authors have declared no conflicts of interest.

568P A phase II study of pemetrexed and erlotinib for metastatic colorectal cancer refractory to standard chemotherapy

S-H. Beom[1], K-W. Lee[2], S-H. Cho[3], Y.S. Park[4], T.W. Kim[5], K.H. Lee[6], M. Jung[1], S.J. Shin[1], J.B. Ahn[1]

[1]Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea, [3]Hemato-Oncology, Chonnam National University Medical School & Chonnam National University Hwasun Hospital, Hwasun, Jeollanam-do, Republic of Korea, [4]Hematology-Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [5]Asan Medical Center, University of Ulsan, Seoul, Republic of Korea, [6]Yeungnam University College of Medicine, Department of Internal Medicine, Daegu, Republic of Korea

Background: There are very limited treatment options in metastatic colorectal cancer (mCRC) after progression on chemotherapy including fluoropyrimidine, oxaliplatin and irinotecan. This open label, multi-center, phase II study was conducted to investigate the combination of pemetrexed and erlotinib in patients who were refractory to previous chemotherapy for mCRC.

Methods: Patients were eligible if they had metastatic colorectal cancer that progressed to standard chemotherapy including fluoropyrimidine, oxaliplatin, and irinotecan. Each 21-day cycle consisted of intravenous pemetrexed at 500 mg/m^2 on day 1 and daily oral erlotinib at 150 mg (reduced to 100 mg after the first 29 patients).

Results: Fifty patients were enrolled onto this phase II study. Twenty-seven patients (54%) had KRAS wild type tumors and 23 patients (46%) did KRAS mutant tumors. Forty-six patients were evaluable for response; twenty-seven patients (59%) had stable disease (SD) and 4 patients (9%) achieved prolonged SD for >6 months. No complete or partial responses were seen. The median progression-free survival was 2.5 months and the median overall survival was 7.3 months. Clinically significant grade 3 to 4 toxicities included diarrhea (6%), fatigue (6%), ileus (4%), skin rash (2%), and myalgia (2%); grade 3 or 4 toxicities were reduced with a lower starting dose of erlotinib.

Conclusions: The combination of pemetrexed and erlotinib seems to have limited activity in refractory mCRC patients. Further research for the regimen is not warranted without understanding predictive biomarkers.

Clinical trial identification: NCT02723578.

Legal entity responsible for the study: Joong Bae Ahn.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

569P ISO-CC-005; A phase I/II study of arfolitixorin (MTHF) in combination with 5-FU, irinotecan, and oxaliplatin ± bevacizumab in patients with metastasizing colorectal cancer

G.U. Carlsson[1], T.K. Guren[2], J. Haux[3], P. Pfeiffer[4], H. Taflin[1], D. Mavroudis[5], V. Georgoulias[6], C. Papadimitriou[7], N. Kentepozidis[8], D. Boumpas[9], L. Skintemo[10], K.M.E. Ganlöv[11], B. Gustavsson[12]

[1]Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden, [2]The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway, [3]Department of Surgery, Skaraborg Hospital, Skövde, Sweden, [4]Experimental Research in Medical Cancer Therapy, Odense University Hospital, Odense, Denmark, [5]Medical Oncology, University General Hospital, Heraklion, Greece, [6]Oncology, IASO General Hospital, Cholargos Athens, Greece, [7]Oncology, Alexandra Hospital, Athens, Attiki, Greece, [8]Oncology, 251 Hellenic Airforce General Hospital, Athens, Greece, [9]Oncology, University Hospital Attikon, Chaidari Athens, Greece, [10]Clinical Reserach, Isofol Medical AB, Gothenburg, Sweden, [11]Medical, Isofol Medical AB, Gothenburg, Sweden, [12]Surgical Oncology Lab, University of Gothenburg, Goteborg, Sweden

Background: Chemotherapy treatment of Colorectal Cancer, often include 5-Fluorouracil (5- FU). 5-FU inhibits the enzyme thymidylate synthase (TS), stopping the supply of thymidine for DNA synthesis. 5-FU is always combined with a folate, which enhances the 5-FU effect. Marketed folates such as LV/L-LV are prodrugs needing enzymatic conversion. Arfolitixorin (formerly Modufolin®) is the natural, biologically active form of the folates and is expected to be efficacious in a larger proportion of patients with less inter- and intra-individual variability.

Methods: ISO-CC-005 is a multi-center, phase I/II study in mCRC patients eligible for 5-FU/folate therapy alone or in combination with irinotecan or oxaliplatin ± bevacizumab. The study investigates safety and tolerability of arfolitixorin at 4 dose levels by analysing the number and severity of AEs, SAEs and DLTs. Efficacy is evaluated as ORR after 4 cycles of chemotherapy. Gene expression, deoxyuridine levels as an indirect marker of TS inhibition and time to death is also investigated. 3-6 patients per cohort are included. All receives arfolitixorin twice every two weeks during at least 4 cycles of chemotherapy.

Results: Today, 67 patients have been enrolled and 59 have initiated treatment. 13 are 1st line patients, 16 are in 2nd line, 10 are in 3rd line and 1 is in 5th treatment line. 27 SAEs have been reported in 13 patients, 6 of these were judged as at least possibly related to arfolitixorin. No SAE were judged as solely related to arfolitixorin. 49 patients have today been evaluated for efficacy. ORR 1st line patients (n = 14) at 8 weeks All 43% (6 PR, 7 SD, 1PD) Patients with arfolitixorin dose ≥60 mg/m^2 56% (5 PR, 3 SD, 1 PD) Patients with arfolitixorin dose ≥60 mg/m^2 + oxaliplatin 60% (3 PR, 1 SD, 1 PD).

Conclusions: The lack of need for metabolic activation makes arfolitixorin a better candidate than LV/L-LV for improved outcome of 5-FU-based chemotherapy regimens in mCRC. The ISO-CC-005 study evaluates arfolitixorin in combination with 5-FU, irinotecan, oxaliplatin ± bevacizumab in mCRC patients in 4 countries in Europe. The results, so far, for both safety and efficacy seems promising.

Clinical trial identification: EudraCT: 2014-001862-84; NCT02244632.

Legal entity responsible for the study: Isofol Medical AB.

Funding: Isofol Medical AB.

Disclosure: P. Pfeiffer: Advisory board member: Isofol Medical AB. H. Taflin: Family member is the founder of, have a leadership role, owns shares, have an advisory role, have conducted funded research, hold patents and have received travel expenses: Isofol Medical AB. L. Skintemo, K.M.E. Ganlöv: Employee, stock ownership: Isofol Medical AB. B. Gustavsson: Founder of, have a leadership role, owns shares, advisory role, conducted funded research, hold patents, received travel expenses: Isofol Medical AB. All other authors have declared no conflicts of interest.

570P Detection of frailty in elderly colorectal càncer patients: Is G8 a good screening tool?

G. Soler, J.C. Ruffinelli Rodriguez, R. Legido, M. Martinez Villacampa, F.J. Perez, B. Pardo-Burdalo, J.A. Marín, I. Morilla Ruiz, L. Heras Lopez, S. Vazquez, S. Recalde, M. Plana Serrahima, C. Santos, N. Mulet Margalef, A. Teule, R. Salazar, M.C. Galan, J. Saldaña

Medical Oncology, Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain

Background: Colorectal cancer (CRC) is one of the most commonly diagnosed cancers. About one half of cases are diagnosed in patients over 70 years of age. A multidimensional geriatric assessment is recommended in older patients but requires considerable time and resources. The aim of this study was to explore whether the G8 questionnaire to identify frailty may be helpful in decision-making in older CCR patients.

Methods: From October 2015 to July 2017, 142 patients over 75 years old were included prospectively. All the patients were assessed on four scales: G8, Pfeiffer, Barthel and TIRS scale, in addition to assessing age, comorbidity and functional status. Positive screening was performed for those older than 85 years, and those younger than 85 with 2 criteria (G8 $\leq$14, Pfeiffer $>$ 2, Barthel $<$ 90 and TIRS +).

Results: The median age was 80.4 years (75.1 – 88.9). 45% had metastatic disease. 82% had G8 score$\leq$14; 38% decided not to be treated with chemotherapy. 62% were treated with chemotherapy (47% capecitabine, 11% FOLFOX6 and 4% in a clinical trial). 43 % of the patients with G8$\leq$14 started treatment with adapted doses and 39% at subsequent cycles. Of the G8$>$ 14, only 28% were reduced at the beginning and 14% at subsequent cycles. Grade 3/4 toxicities in the G8$\leq$14 versus G8$>$14. were: plantar palmar syndrome 14.3% vs 0%; hematological 15% vs 0%; gastrointestinal 18% vs 14%; mucositis 3.6% vs 0%; asthenia 11% vs 0%; and renal failure 4% vs 0%.

Conclusions: The G8 questionnaire helps to discriminate which patients are candidates for chemotherapy. If the G8 score is $\leq$ 14, it supports the decision to reduce the dose and it predicts toxicity. This suggests that G8 could be an instrument that detects frailty in older patients with CRC with the intention of undergoing systemic treatment. After analyzing these results, it is recommended to perform a complete geriatric assesment in these patients to validate our conclusions.

Legal entity responsible for the study: Gemma Soler.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

571P Interim results from a real world European survey on the unmet needs of patients living with metastatic colorectal cancer (mCRC)

Z. Maravic[1], J.M. Borras[2], E. Espin Basany[3], Á. Petrányi[4], Z. Kapitany[5], P. Rakonczai[6], A. Benedict[6], N. Muszbek[7]

[1]Group and Project Development, EuropaColon UK, Salisbury, UK, [2]Hospitalet de Llobregat, Hospital Duran i Reynals, Barcelona, Spain, [3]Unidad de Cirugía de Colon y Recto, Hospital Valle de Hebron, Universitat Autonoma de Barcelona, Barcelona, Spain, [4]Onkoradiológia, Egyesített Szent István és Szent László Kórház, Budapest, Hungary, [5]Department of Physiotherapy, Semmelweis University Faculty of Health Sciences, Budapest, Hungary, [6]Modeling and Simulation, Evidera, Budapest, Hungary, [7]Modelling and Simulations, Evidera, London, UK

Background: With increasing emphasis on patients' voices, EuropaColon, a European CRC patient organization, conducted a cross-sectional European survey on unmet needs in mCRC, in 12 countries. The aim was to better understand the challenges, needs and the health-related quality of life (HRQoL). The objective of this work is to report the preliminary results for Hungary (HU), Poland (PL), Serbia (RS) and Spain (ES).

Methods: IRB approval was obtained. Clinicians, and nurses with partner organizations of EuropaColon recruited patients. The survey had two sections: treatment-related information and HRQoL. The former comprised questions on timing of diagnosis/treatment, multidisciplinary team discussion (MDT), type of treatments received, and information on treatments and side-effects. Both paper-based and online completion were available. Single data entry was done by EuropaColon. Descriptive analyses were carried out in Excel. No imputation of missing data was done.

Results: 548 surveys were analyzed. Completion rates were high. Most responders were treated in public hospitals and 85-92% in HU, ES and PL and 57% in RS were undergoing treatment at the time. Most patients (82%) received treatments within 3 months after diagnosis with CRC, 16% within first 2 weeks. 60% underwent MDT discussion and were informed about the outcome. Proportions however varied between countries, with lowest for PL (46%) and highest for RS (74%). Proportion of patients feeling their views were considered prior starting treatment varied (from 30% in RS to 83% in HU). Most patients had surgery and chemotherapy (83% and 91%), 21% radio- and 9% targeted therapy. Specific therapies however were not given in 13-23% of cases. Patients were relatively informed about side effects (73%). A fifth of patients received molecular test, from a low 6% in RS up to 34% in PL.

Conclusions: Among mCRC patients in HU, ES, RS and PL the degree of information varies. Patients know about MDT and are informed about potential side effects. However, the specific treatment is not well known, and molecular testing is rare. Variations across countries need to be investigated further. Study limitations include cross-sectional design and single data entry.

Legal entity responsible for the study: EuropaColon.

Funding: Merck, BMS, Sandoz, Sirtex.

Disclosure: All authors have declared no conflicts of interest.

572P Socioeconomic discrepancies in survival of stage IV colorectal cancer

H.S. Kim[1], J. Uhlig[2], S. Stein[3], L. Jill[3], C.S. Fuchs[4]

[1]Section of Interventional Radiology, Yale School of Medicine - Interventional Radiology Yale Cancer Center, New Haven, CT, USA, [2]Section of Interventional Radiology, Yale School of Medicine, New Haven, CT, USA, [3]Medical Oncology, Yale School of Medicine, New Haven, CT, USA, [4]Yale Cancer Center, Yale University, New Haven, CT, USA

Background: To evaluate the impact of socioeconomic factors on survival in stage IV colorectal cancer (CRC).

Methods: The United States National Cancer Database was searched for stage IV colorectal adenocarcinomas diagnosed between 2010 and 2015. Overall survival (OS) was assessed via multivariable Cox proportional Hazards models, adjusting socioeconomic factors for potential confounders.

Results: A total of 73,685 patients with median age of 64 years were included. 54.5% of patients were male. After adjustment for potential confounders, improved OS was seen for female patients (vs. male HR = 0.95, $p < 0.001$), Caucasians (vs. African Americans HR = 0.95, $p < 0.001$) and those with higher income (63.000 vs. $<$ 38.000 USD HR = 0.92, $p < 0.001$). Independently, insurance status impacted survival with higher OS seen for patients with private insurance (vs. Medicaid HR = 0.89, $p < 0.001$; vs. Medicare HR = 0.85, $p < 0.001$). Further, OS correlated with type and location of the treating center: improved OS was evident for patients treated at academic/research centers (vs. other centers HR = 0.84, $p < 0.001$). Highest survival rates were observed in the Middle Atlantic and West South Central US state regions compared to other regions (HR = 1.18 to HR = 1.35, $p < 0.001$). The table summarizes adjusted 2-year and 5-year overall survival rates by US state region.

Table: 572P Adjusted survival rates for stage IV CRC by US state region

location	Adjusted Two-year OS	Adjusted Five-year OS
Middle Atlantic	43%	13%
West South Central	43%	15%
Mountain	38%	8%
South Atlantic	36%	8%
New England	35%	5%
Pacific	35%	8%
East North Central	34%	6%
East South Central	32%	7%
West North Central	32%	5%

Conclusions: Socioeconomic factors independently impacted survival in stage IV CRC. Improved outcomes were observed for female Caucasians with high socioeconomic status and access to academic treatment centers in certain US state regions.

Legal entity responsible for the study: Hyun S. Kim, MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

573P Influence of not having children on mortality in patients with metastatic (mCRC) colorectal cancer

S. Ahmed[1], T. Baig[2], A. Zaidi[1], H. Chalchal[3], K. Haider[1], T. Asif[1], N. Iqbal[1]

[1]Oncology, Saskatoon Cancer Centre University of Saskatchewan, Saskatoon, SK, Canada, [2]Microbiology, University of Saskatchewan, Saskatoon, SK, Canada, [3]Oncology, Allan Blair Cancer Center, Regina, SK, Canada

Background: Although there is evidence that parents live longer than non-parents, prognostic effect of parenthood in cancer patients is not well established. We previously noted that palliative use of chemotherapy in patients with mCRC significantly varied in those with and without children and use of chemotherapy was 3-fold lower in patients with no children (2018 GI Cancers Symposium). In this study we examined if childless individual with mCRC have higher mortality than patients with children.

Methods: Patients with mCRC diagnosed in 2006-2010 in Saskatchewan were assessed. Cox proportional hazard multivariate analyses were performed to determine correlation between not having children and mortality.

Results: 569 patients with median age 69 yrs (IQR 59-77) and M:F was 59:41 were identified. Of 569 patients, 461 (81%) had children. Significant differences were noted between the group with children and the group with no children with respect to being married/partnered (74 vs. 32%, $p < 0.001$), performance status $\geq$2 (33 vs. 45%, $p = 0.02$), distance to travel to cancer center $>$ 100 km (45 vs. 60%, $p = 0.007$), low

albumin (70 vs. 85%, p = 0.001), anemia (68 vs. 87%, p < 0.001), and use of chemotherapy (64 vs. 31, p < 0.001 respectively. On Cox proportional multivariate analysis after adjustment for other variables, not having children (HR 1.4; 95%CI: 1.10-1.90), not having chemotherapy (3.6, 2.8-4.6), no metastasectomy (2.15, 1.60-2.91), intact primary tumor (1.91, 1.56-2.33), leukocytosis (1.35, 1.07-1.70), elevated alkaline phosphatase (1.32, 1.07-1.62), performance status ≥2 (1.30, 1.10-1.60), right colon cancer (1.28, 1.04-1.57), grade III cancer (1.28, 1.05-1.56) and stage IVb disease (1.25, 1.04-1.50) were correlated with poor survival.

Conclusions: The present study demonstrated that not having children was independently associated with an increased risk of mortality in patients with metastatic colorectal cancer. Future studies are warranted to confirm the finding and to determine underlying etiology.

Legal entity responsible for the study: Shahid Ahmed.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

574P Interim quality of life results from a real world European survey on the unmet needs of patients living with metastatic colorectal cancer (mCRC)

Z. Maravic[1], L. Wyrwicz[2], B. Karczmarek-Borowska[3], A. Horvath[4], A. Ruiz Casado[5], A. Carrato Mena[6], N. Muszbek[7], P. Rakonczai[8]

[1]Group and Project Development, EuropaColon UK, Salisbury, UK, [2]Medical Oncology, Centrum Onkologii-Instytut im. M. Sklodowskiej Curie, Warszawa, Poland, [3]Medical Oncology, Provincial Specialized Hospital in Rzeszów, Rzeszow, Poland, [4]Medical Oncology, Semmelweis University Kutvolgyi Clinical Center, Budapest, Hungary, [5]Medical Oncology, Hospital Puerta de Hierro, Majadahonda, Spain, [6]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [7]Modelling and Simulations, Evidera (European Headquarter), London, UK, [8]Modeling and Simulation, Evidera, Budapest, Hungary

Background: With increasing emphasis on health-related quality of life (HRQoL), EuropaColon, a European CRC patient organization, conducted a European survey on experience and HRQoL in mCRC in 12 countries. The aim is to report the interim results with the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) for Hungary (HU), Poland (PL), Serbia (RS) and Spain (ES).

Methods: After IRB approval, clinicians, nurses with partner organizations of EuropaColon recruited patients. In addition to demographics, diagnosis and treatment (reported elsewhere), the survey assessed HRQoL using EORTC QLQ-C30. Single data entry was done by EuropaColon. The QLQ-C30 global score, function- and symptom-specific scores, and the financial difficulties item were summarized by country using the "QoLR" package in R .

Results: 548 surveys were analyzed. Completion rates were high in RS, PL and HU (>95%), and lower in ES (77-79%). Place in treatment pathway varied (e.g. in HU 92.2% were undergoing, while in RS 25.6% completed treatment). Scores were consistently higher in HU and ES, with emotional function affected the most.

Table: 574P

Country	Mean score (SD)					
	Global Quality of Life	Functions				
		Physical	Role	Emotional	Cognitive	Social
HU	69.4 (20.7)	82.9 (16.3)	81.4 (23.7)	73.9 (22.5)	87.9 (19.1)	80.9 (24.6)
PL	56.1 (18.1)	70.1 (20.5)	71.9 (28.2)	67.1 (22.7)	76.7 (22.3)	67.2 (27.5)
RS	55.9 (21.1)	69.7 (19.5)	63.6 (25.7)	53.5 (28.4)	71.3 (24.6)	53.9 (26)
ES	68.1 (21.6)	84.3 (17.9)	81.8 (25.4)	76.4 (24.1)	85.4 (19.4)	77.7 (24.1)

Mean fatigue and pain symptom scores were lower in HU/ES and higher in RS/PL. This was maintained in nausea, insomnia, appetite loss, constipation, but not in dyspnea, diarrhea. Differences could be affected by the patients' place in the treatment pathway. Global health scores for RS and PL were lower, and symptom scores were higher than reported in mCRC trials.

Conclusions: mCRC has an important effect on HRQoL, which can differ among real-world mCRC patients and those in clinical trials. Variations across countries and comparisons to HRQoL in trials require further analysis.

Legal entity responsible for the study: EuropaColon.

Funding: Merck, BMS, Sandoz, Sirtex.

Disclosure: All authors have declared no conflicts of interest.

575P Interim analysis of the non-interventional study QoLiTrap (AIO-LQ-0113) in patients with metastatic colorectal cancer (mCRC) treated with aflibercept (AFL) + FOLFIRI: Efficacy according to age group ≤65 and >65 years

R.D. Hofheinz[1], H-G. Derigs[2], G. Piringer[3], R. von Moos[4]

[1]Interdisciplinary Tumor Center, Universitätsklinikum Mannheim, Mannheim, Germany, [2]Clinic of Internal Medicine, Klinikum Frankfurt Höchst, Frankfurt A. M., Germany, [3]Palliative Medicine, Klinikum Wels-Grieskirchen GmbH, Wels, Austria, [4]Department of Oncology/Hematology, Kantonsspital Graubünden, Chur, Switzerland

Background: AFL targets VEGF-A, VEGF-B and PlGF. It is approved in combination with FOLFIRI for treatment of mCRC that is resistant to or has progressed after oxaliplatin-containing therapy.

Methods: QoLiTrap is an ongoing non-interventional study conducted in DACH region to evaluate Quality-of-life (QoL) in 1500 mCRC patients treated with AFL+FOLFIRI using the EORTC-QLQ C30 questionnaire at baseline and before every cycle.

Results: For this interim analysis according to age groups (≤ 65 and > 65 years / cut-off: 05 Dec 2017) 702 patients (mean age: 64.8 ± 9.9 yrs; 65.0% male, 50.9% with RAS mutation) who completed the baseline and at least 2 additional questionnaires were evaluated. 50% of patients each were ≤65 and >65 yrs old at therapy start. 86.3% and 85.8% of younger and older patients, respectively, had an ECOG of ≤ 1. A median of 7 cycles (range 1 – 65) was given to patients aged ≤65, patients >65 yrs received a median of 6 cycles (range 1 - 54). Mean global health scores at baseline was 55.6 for patients aged ≤65 yrs and 59.1 for patients aged >65 yrs. Mean score decreased slightly in both age groups. 48.4% of younger and 46.7% of older patients received study treatment as second line. More than 75% of patients in both age groups received prior anti-EGFR and / or bevacizumab (BEV) treatment. 89.5% of younger and 92.3% of older patients received prior palliative therapies or prior therapies during metastatic stage. Median PFS of patients pretreated with anti-EGFR or BEV only was 7.6 months (95% CI 3.7-) and 7.0 months (95% CI 5.6- 8.5), respectively, for younger patients, and 9.4 months (95% CI 5.9-) and 7.6 months (95% CI 5.8- 9.0), respectively, for older patients. Regarding evaluable patients pretreated with anti-EGFR and/or BEV 11.2% and 10.4% of age group ≤65 and >65 yrs, respectively, exhibited CR+PR.

Conclusions: This interim analysis showed that there are no obvious differences between age groups regarding previous treatment and efficacy in mCRC patients treated with AFL+FOLFIRI under routine conditions. Toxicity was in line with the known safety profile of the study medication. Supported by Sanofi-Aventis Deutschland GmbH.

Clinical trial identification: AIO-LQ-0113.

Editorial acknowledgement: Medical writing assistence was provided by Claudia Lorenz-Schlüter (Alcedis GmbH Gießen, Germany), funded by Sanofi-Aventis Deutschland GmbH.

Legal entity responsible for the study: Sanofi-Aventis Deutschland GmbH.

Funding: Sanofi-Aventis Deutschland GmbH.

Disclosure: R.D. Hofheinz: Consulting fees, honorarium: Sanofi, Merck, Amgen, Roche, Servier; Grant received/grants pending: Sanofi, Merck, Amgen, Roche. H-G. Derigs: Sponsoring congresses: Roche, Jannsen, Celgene, BMS. R. von Moos: Advisory board: Amgen Roche, Merck und Sanofi; Speaker Honoraria: Roche, Bayer. All other authors have declared no conflicts of interest.

576P Inhibitory effect of a synthetic bioresorbable adhesion membrane on small bowel obstruction (SBO) in patients undergoing elective surgery for colon cancer: A randomized controlled trial

G. Saito, S. Sadahiro, H. Miyakita, K. Okada, A. Tanaka, T. Suzuki

Surgery, Tokai University School of Medicine, Isehara, Japan

Background: Intraabdominal adhesion may occur in about 70% to 100% after abdominal surgery and is one of the most common causes of SBO. Seprafilm®, a synthetic bioresorbable adhesion membrane, has been reported not to decrease the incidence of SBO, but to significantly decrease the reoperation in patients with inflammatory bowel disease. However, the inhibitory effect of Seprafilm® on SBO in colon cancer remains unclear. We therefore conducted a randomized study to investigate the inhibitory effect of Seprafilm® on SBO in patients with colon cancer.

Methods: The study group comprised 345 patients (pts) with colon cancer who underwent curative surgery electively from 2006 through 2013. Seprafilm® were placed under the midline incision before closing the abdomen in 166 pts (Seprafilm® group), and no sheet of Seprafilm® was placed in the remaining 179 pts (control group). We compared the incidence of SBO and adhesive findings at the time of reoperation. SBO was defined as bowel obstruction which need decompression after readmission. The median follow-up period in the surviving patients was 66.3 months.

Results: Patient characteristics did not differ between the groups. SBO developed in 13 pts (7.8%) in the Seprafilm® group and 19 pts (10.6%) in the control group. SBO occurred within 30 days after surgery in 3 pts (23.1%) in the Seprafilm® group and 8 pts (42.1%) in the control group. The incidences tended to be higher in the control group, but the difference was not significant. Reoperation was required by 5 pts (38.5%) in the Seprafilm® group and 7 pts (36.8%) in the control group, with no

significant difference. Among the pts who required surgery, SBO was caused by adhesion to the midline incision in 1 patient (7.7%) in the Seprafilm® group and in 2 pts (10.5%) in the control group. This difference was also not significant. Multivariate analysis showed that a history of laparotomy was only an independent risk factor for SBO and the use of Seprafilm® was unrelated to the incidence of SBO.

Conclusions: A midline incision was an infrequent cause of SBO in pts who underwent surgery for colon cancer. It was unclear whether the placement of Seprafilm® under the midline incision can decrease SBO.

Legal entity responsible for the study: Sotaro Sadahiro, MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

577P Short- and long-term outcomes of high tie versus low tie with lymph node dissection around the inferior mesenteric artery in sigmoid colon or rectal cancer surgery

X. Li

Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Controversy is ongoing on the level of inferior mesenteric artery (IMA) ligation in sigmoid colon or rectal cancer surgery. In the present study, we aimed to reevaluate the mortality and morbidity especially for anastomotic leakage of low tie combined with lymph node dissection (LT+LND) around the inferior mesenteric artery compared with high tie (HT) in sigmoid colon or rectal cancer surgery using propensity score matching (PSM) analyses.

Methods: A total of 1895 patients with sigmoid colon or rectal cancer who underwent curative surgery from 2012 to 2017 in Fudan University Shanghai Cancer Center were recruited into this study. After PSM, LT+LND-and HT-matched patients were comparable. Ultimately, 277 patients were ligated at the origin of IMA and 277 patients experienced the preservation of left colic artery plus lymph node dissection around IMA. The survival outcomes and clinicopathological characteristics were reviewed from the database retrospectively.

Results: The median follow-up period was 13.7 months (range from 1 to 69 months). There were no differences in terms of postoperative complication rate and overall survival (OS) as well as disease-free survival (DFS). In the HT group and LT+LND group, the 3-year OS rates were 90.8% and 90.0%, respectively, whereas the 3-year DFS rates were 78.7% and 73.9%, respectively. Further, LT+LND was associated with prolonged operation time and less blood loss.

Conclusions: LT+LND seems to be less invasive and is not inferior to HT from the point of oncological safety. Further prospective studies and long-term follow-up data are needed.

Legal entity responsible for the study: Xinxiang Li.

Funding: This work was supported by the National Natural Science Foundation of China (Grant NO. 81772599).

Disclosure: The author has declared no conflicts of interest.

578P Mesenteric vs. antimesenteric colorectal cancer: A single center study

K.H. Lee[1], W.R. Kim[2], J.W. Kim[3]

[1]Department of Surgery, Bundang Cha Medical Center, Seongnam, Republic of Korea, [2]Surgery, CHA Bundang Medical Center, Seongnam, Republic of Korea, [3]Surgery, Cha University, Gyunggi, Republic of Korea

Background: We investigated the possible correlation between the prognosis and circumferential location of the tumor according to the cancer involvement on the mesenteric side. This study is based on the hypothesis that mesenteric tumors, which are closer to blood and lymphatic vessels, could spread more aggressively and rapidly compared to the antimesenteric tumors.

Methods: We reviewed the retrospectively collected data of 251 patients treated during the period of October 2008 to May 2012. 162 patients with mesenteric side involving tumors were included in the mesenteric group, and 89 patients with antimesenteric tumors were included in the antimesenteric group. The analyzed information included age, gender, location, size of the main lesion, extent of lymph node metastasis, pathologic features, metastasis, complication, TNM stage, recurrence and 5-year survival. We retrospectively studied the survival of patients by examining of our 5-year follow-up archive. Data were analyzed using Pearson-Chi square test and Kaplan-Meier curve analysis.

Results: There was no statistical difference between the two groups regarding age, gender, location, extent of lymph node metastasis, pathologic features, complication, and TNM stage. The size of the main tumor was statistically larger in the mesenteric group compared to the antimesenteric group. (P value = 0.03) The mesenteric group showed statistically higher rate of distant metastasis and carcinomatosis than the antimesenteric group. (P value = 0.02) In addition, the mesenteric group showed lower 5-year survival rate than the antimesenteric group.

Conclusions: In conclusion, mesenteric tumors have significantly larger size of main tumor, higher rate of distant metastasis and worse 5-year survival than antimesenteric tumors. This difference implies that colorectal cancers should be regarded differently according to the circumferential location and more careful follow up is necessary with mesenteric side involving colorectal cancer patients.

Legal entity responsible for the study: Jong Woo Kim.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

579P The SLICE study: The prognostic role of visceral fat in metastatic colorectal cancer

D. Basile[1], C. Lisanti[1], M. Borghi[2], M. Bartoletti[1], L. Gerratana[1], L. Bortot[1], G. Pelizzari[1], C. Corvaja[1], E. Ongaro[1], S.K. Garattini[1], V. Fanotto[1], A. Parnofiello[1], F. Cortiula[1], M. Cattaneo[1], V.J. Andreotti[1], E. Bertoli[1], M. Guardascione[3], G. Miolo[4], F. Puglisi[5], A. Buonadonna[4]

[1]Department of Medicine (DAME), University of Udine, Udine, Italy, [2]Intensive Care Unit, CRO National Cancer Institute, Aviano, Italy, [3]Clinical and Experimental Pharmacology, CRO National Cancer Institute, Aviano, Italy, [4]Department of Medical Oncology and Cancer Prevention, CRO National Cancer Institute, Aviano, Italy, [5]University of Udine, Udine, Department of Medical Oncology and Cancer Prevention, CRO National Cancer Institute, Aviano, Italy

Background: Body composition, more specially the excess of body weight, was established as a risk factor of the colorectal cancer initiation and progression. Aim of this study was to investigate the prognostic role of adiposity, especially visceral fat (VAT), in metastatic colorectal cancer (MCRC).

Methods: This retrospective study analyzed a consecutive cohort of 71 patients (pts) with MCRC treated between 2013 and 2017 at the Oncology Department of Aviano National Cancer Institute (Italy). VAT area was measured as cross-sectional (cm^2) area at the L3 level divided by the square of the height (m^2). A ROC analysis was performed to define a threshold capable to identify distinct prognostic categories of patients according to VAT. Subsequently, the value of VAT in predicting overall survival (OS) and progression free survival (PFS) was evaluated with uni- and multivariate Cox regression analyses. Survival outcomes were estimated with Kaplan-Meier curves.

Results: Before first line therapy, 19 pts (27%) were aged>70, 14 pts (20%) had a right tumor, 21 pts (30%) a left tumor and 35 pts (50%) a rectal one. Of note, 59 pts (83%) underwent primitive tumor resection and 24 pts (33%) received metastasectomy. Interestingly, 40 pts (56%) had a body mass index (BMI)>25 and 42 (59%) had median VAT of 51.94. LDH level > =480 UI/L was recorded in 12 pts (27%) reflecting the inflammatory response. The obtained cut-off for VAT was 44. Median OS was 30.97 months. At univariate analysis, older age (HR 2.46, p = 0.013), primary tumor resection (HR 0.40, p = 0.029), VAT>44 (HR 2.85, p = 0.011), metastasectomy (HR 0.22, p = 0.005), were significantly associated with OS. By multivariate analysis, only VAT>44 (HR2.64; p = 0.030) was significantly associated with OS. Conversely, VAT showed no prognostic impact in terms of PFS.

Conclusions: This exploratory study supported the prognostic role of adiposity evaluation in patients with MCRC. In particular, high values of VAT were predictors of worse outcome. These encouraging preliminary data merit to be validated through prospective investigations.

Legal entity responsible for the study: University of Udine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

580P Safety and outcomes of self-expandable metal stents (SEMS) versus emergency surgery for acute colonic obstruction in metastatic colon cancer patients treated with bevacizumab (BV)

V.E. Pacheco-Barcia[1], R. Mondéjar Solís[2], O. Martínez-Sáez[3], F. Longo[4], E. Bermejo[5], J.A. Moreno[6], C. Marin[5], A. Correa[5], R. Maqueda[5], J. Rogado[1], A. García de Paredes[7], E. Rodriguez de Santiago[7], V. Pachón Olmos[3], R. Ferreiro Monteagudo[3], M. Rodriguez Garrote[3], A. Carrato Mena[4], O. Donnay[1], E. Martin Perez[5], C. Santander[6], R. Colomer Bosch[1]

[1]Medical Oncology- Instituto de Investigación Sanitaria La Princesa, Hospital Universitario de La Princesa, Madrid, Spain, [2]Medical Oncology, Hospital Universitario de La Princesa, Madrid, Spain, [3]Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, [4]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [5]Surgical Oncology, Hospital Universitario La Princesa, Madrid, Spain, [6]Gastroenterology, Hospital Universitario de La Princesa, Madrid, Spain, [7]Gastroenterology, Hospital Universitario Ramon y Cajal, Madrid, Spain

Background: Colorectal cancer presents with malignant bowel obstruction in about 10% of cases. SEMS can be an alternative for immediate surgery but long-term data is limited regarding clinical outcomes and safety of BV in this subset of patients.

Methods: We performed a retrospective review of 2850 cases of colon cancer from January 2012 to October 2017, and identified metastatic patients with malignant bowel obstruction initially treated with SEMS or emergency surgery. Differences in procedure-related morbidity and overall survival (OS) were assessed.

Results: We selected 119 cases, 79 treated with SEMS and 40 with surgery. Median age: 76. Median follow-up time: 11 months. No differences in sidedness or RAS status between

cohorts. SEMS and surgery had a similar rate of complications (35.5% vs 32.5%, p = 0.45) and showed longer time to complications (18m vs 1m, p = 0.004). In patients treated with BV, complications were similar in SEMS and surgery (40% vs 31%, RR 1.28, p = 0.5) and perforation was also similar (13% vs 19%, RR 1.46, p = 0.4). The incidence of perforation in the SEMS group was similar between BV and chemotherapy alone (13% vs 9%, p = 0.2). In patients without systemic therapy, complications were higher in the surgery group compared to SEMS (50% vs 25%, RR 1.34, p = 0.1), also the incidence of perforation (20% vs 6%, RR 1.57, p = 0.2), but not statistically significant. SEMS and surgery showed similar OS (14m vs 15m, p = 0.5). Treatment with BV increased OS in SEMS group (18 months vs 7 months, p = 0.001) and surgery group (20 months vs 4 months, p = 0.001) compared to patients without subsequent medical treatment. In the multivariate analysis, patients treated with subsequent medical treatment showed a statistically significant longer OS [HR 0.43, CI95% 0.19-0.94, p = 0.02] and patients who had complications, showed a shorter OS (HR 2.45, CI95% 1.17-5.12, p = 0.01).

Conclusions: Bevacizumab-based therapy increased survival in metastatic colon cancer and, was not associated with a higher risk of perforation in patients with SEMS. Emergency surgery and SEMS showed a similar incidence of complications and perforations, with no differences between both strategies in patients treated with BV.

Legal entity responsible for the study: Hospital Universitario La Princesa, Instituto de Investigación Sanitaria La Princesa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

581P Metronomic capecitabine plus cyclophosphamide in unresectable or relapsed pseudomyxoma peritonei

A. Raimondi[1], S. Corallo[1], M. Niger[1], M. Antista[1], G. Randon[1], F. Morano[1], C. Cremolini[2], M. Di Bartolomeo[1], F.G.M. de Braud[1], F. Pietrantonio[1]

[1]Medical Oncology Department, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [2]Polo Oncologico, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy

Background: The standard treatment of Pseudomyxoma Peritonei (PMP) is cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). No consensus was reached on treatment of unresectable or recurrent disease. PMP is considered chemoresistant for its low mitotic index but non-randomized series showed promising results with regimens for gastrointestinal tumors. Metronomic schedules may be preferred for their antiangiogenic and immunomodulatory activity.

Methods: We conducted a single center prospective single arm trial. Inclusion criteria were histologically confirmed PMP, unresectable or relapsed after CRS/HIPEC, in progression to surgery or previous treatments. Patients received continuous metronomic capecitabine (625 mg/sqm b.i.d.) plus cyclophosphamide (50 mg/day) until progressive disease, unacceptable toxicity or consent withdrawal. The primary endpoint was progression free survival (PFS); secondary endpoints were disease control rate (DCR), overall survival (OS) and safety profile. Ion Torrent® next generation sequencing technology (Hot-spot Cancer Panel) was used to characterize molecular profile.

Results: 23 consecutive patients were enrolled from April 2015 to October 2017. At a median follow up of 13.5 months, median PFS was 9.5 months and 1-year OS rate 73.7% (95% CI 47.3% - 88.3%). No partial or complete responses were observed but DCR was 74% and 22% patients achieved a prolonged disease stability (>13 months). A significant tumor markers reduction (>20%) was seen in 43% patients for CA19.9, 22% for CA125 and 39% for CEA. The safety profile was manageable: 78% patients reported G1/2 drug related adverse events, only 17% G3 and none G4/5. As expected, the main toxicities were anemia, neutropenia, nausea, diarrhea, fatigue and hand foot syndrome. Only 17% patients required capecitabine dose reduction. Molecular profile was available in 15/23 cases: KRAS mutations were found in all cases and GNAS mutations in 47%.

Conclusions: Metronomic capecitabine plus cyclophosphamide is an active and well tolerated regimen in unresectable or recurrent PMP, with a safety profile comparing favorably with historical data. Further studies are needed to identify predictive biomarkers for novel treatment strategies.

Legal entity responsible for the study: Istituto Nazionale dei Tumori di Milano, Fondazione IRCCS.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

582P Utility of carcinoembryonic antigen (CEA) in appendiceal carcinoma

A. Karippot[1], S. Groover[2], J. Ai[3], S. Nambiar[4]

[1]Hematology/Oncology, Cancer Treatment Centers of America, Tulsa, OK, USA, [2]Biochemistry & Microbiology, Oklahoma State University Center for Health Sciences, Tulsa, OK, USA, [3]Oncology, Cancer Treatment Centers of America, Tulsa, OK, USA, [4]Hematology/Oncology, Cancer Treatment Centers of America, Tulsa, OK, USA

Background: Primary cancers of the appendix are rare and are frequently diagnosed after surgery for appendicitis. There is no designated staging system or evidence-based guideline for treatment. The staging and treatment of appendiceal adenocarcinoma mirror that of colon cancer. Elevated serum carcinoembryonic antigen (CEA) has been strongly associated with poor prognosis in colorectal cancer, so our study aims to first compare appendiceal cancers with tumors of the ascending colon, and then evaluate the prognostic value of CEA in appendiceal cancers.

Methods: We performed a retrospective analysis of all patients (n = 2,614) diagnosed with appendiceal adenocarcinoma from 2004 to 2014 in the National Cancer Institute's Surveillance, Epidemiology and End Results database. All appendiceal cancer patients were designated as either elevated (C1) or normal (C0) based on the pretreatment serum CEA level. We performed univariate and multivariate analyses to compare appendiceal cancer characteristics to tumors of the ascending colon (n = 73,057), then identified independent factors associated with CEA elevation in appendiceal cancers.

Results: Upon multivariate analysis, compared to tumors of the ascending colon, appendiceal cancers are significantly more likely (P < 0.05) to have higher stage at diagnosis (OR 2.95, 1.19, 6.56 for stage 2, 3, and 4). They are less likely to have the CEA test ordered (OR 0.31). Appendiceal cancers are being diagnosed more in recent years (OR 1.90, 2.11, 1.86 for years 2012, 2013, and 2014) while colon cancer incidence is remaining the same. Compared to C0 appendiceal cancers, C1 cancers are more likely to have higher tumor grade (OR 6.56 and 5.50 for grade 2 and 3) and higher overall stage (OR 1.96, 2.44, 9.60 for stage 2, 3, and 4).

Conclusions: Though appendiceal cancers are rare, they are increasing in incidence. They are less likely than colorectal cancers to have the CEA test ordered despite CEA elevation odds ratio having no significant difference between the two cancers. Elevated CEA in appendiceal cancers is associated with later stage and higher grade. CEA levels should be checked in all appendiceal cancer patients to assist in the development of treatment strategies.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

583P Thromboembolic risk and survival with Khorana score in resected colorectal cancer patients: Subgroup analysis from the adjuvant TOSCA trial

S. Barni[1], G. Rosati[2], V. Zagonel[3], N. Pella[4], M. Banzi[5], M.G. Zampino[6], M. Di Bartolomeo[7], L. Rimassa[8], P. Marchetti[9], E. Maiello[10], F. Artioli[11], D. Ferrari[12], R. Labianca[13], P. Bidoli[14], A. Zaniboni[15], A. Sobrero[16], V. Iaffaioli[17], S. de Placido[18], L.G. Frassineti[19], F. Galli[20], F. Petrelli[1]

[1]Oncology, ASST Bergamo Ovest, Treviglio, Italy, [2]Oncology, Ospedale San Carlo, Potenza, Italy, [3]Oncology, Istituto Oncologico Veneto-IRCCS, Padua, Italy, [4]Oncology, Azienda Ospedaliero Universitaria Santa Maria della Misericordia, Udine, Italy, [5]Oncology, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy, [6]Oncology, Istituto Europeo di Oncologia, Milan, Italy, [7]Istituto Nazionale dei Tumori, Fondazione IRCCS, Milan, Italy, [8]Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy, [9]Oncology, Azienda Ospedaliera St. Andrea, Rome, Italy, [10]Oncology, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy, [11]Oncology, Ospedale Ramazzini, Carpi, Italy, [12]Oncology, Azienda ospedaliera San Paolo, Milan, Italy, [13]Oncology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy, [14]Oncology, San Gerardo dei Tintori Hospital, Monza, Italy, [15]Oncology, Casa di Cura Poliambulanza, Brescia, Italy, [16]Medical Oncology, IRCCS Ospedale San Martino IST, Genoa, Italy, [17]Oncology, National Cancer Institute, IRCCS Foundation Pascale, Naples, Italy, [18]Oncology, AOU Policlinico Federico II, Naples, Italy, [19]Oncology, Istituto Tumori della Romagna I.R.S.T., Meldola, Italy, [20]Laboratory of Clinical Research Methodology, IRCCS Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy

Background: The risk of venous thromboembolic events (VTE) during adjuvant chemotherapy for colorectal cancer (CRC) is unknown. We aim to evaluate if the Khorana score (KS) can predict this risk of VTEs and overall survival (OS) in a randomised phase III, noninferiority, open-label trial of different durations of adjuvant chemotherapy in resected stage II-III CRC.

Methods: Data were obtained using a TOSCA ['Randomised trial investigating the role of FOLFOX-4 or XELOX (three versus six months) regimen duration as adjuvant therapy for patients with stage II/III colon cancer'] study. A logistic regression model was used to test the associations between the risk of VTEs and the KS. The results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). To assess the effect of the KS on OS, multivariate analyses using Cox regression models was performed. The results are expressed as hazard ratios (HR) with 95% CI.

Results: Among n = 1,380 CRC patients with available data, the VTE risk (n = 72 events: 5.2%) was similar in the three- and six-month duration arms (5.5% vs. 4.9%) with 0.2% of patients belonging to the high-risk KS group. Rates of VTE were similar in the low- and intermediate-risk groups (4.8% vs. 6.4%). KS did not represent an independent predictive factor for VTE risk, with a low positive predictive value and accuracy (6.4% and 74.1%). Chemotherapy duration was not associated with VTE risk. Also, KS was not associated with OS in multivariate analysis (HR = 0.92, 95% CI, 0.63–1.36; P = 0.68).

Conclusions: The use of the KS was not a predictor of VTEs in a low–moderate thromboembolic risk population as CRC. These data did not support the use of KS to estimate the occurrence of VTE during adjuvant chemotherapy and suggest that other assessment risk tools must be evaluated.

Legal entity responsible for the study: GISCAD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

584P The clinical utility of early follow-up computed tomography in patients with stage II-III colorectal cancer receiving oxaliplatin-based chemotherapy

Y. Lee, S.Y. Kim, J.E. Kim, Y.S. Hong, T.W. Kim

Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Surveillance after curative resection for colorectal cancer with computed tomography (CT) of abdomen, pelvis and chest is a standard practice, but the optimal interval of surveillance CT is unclear. Usually recommended interval is 6 to 12 months, but in South Korea, earlier follow-up CT during adjuvant chemotherapy for stage II or III disease is a common practice. This study aimed to show clinical utility of early follow-up CT (EFCT) within 6 months after surgery.

Methods: The medical records of patients with stage II or III colorectal cancer who received oxaliplatin-based adjuvant chemotherapy between January 2011 and December 2014 in Asan Medical Center were retrospectively reviewed. Those who started adjuvant chemotherapy beyond 3 months after surgery and who were dead or lost to follow-up before 6 months after surgery were excluded. Information on the results of EFCT and subsequent treatment was obtained.

Results: In a total of 678 patients, 597 (88%) underwent EFCT. EFCT was associated with advanced stage: 78% (74/95) of stage II, 88% (317/359) of low-risk stage III (pT1-3 and N1), and 92% (206/224) of high-risk stage III (pT4 or N2) checked EFCT ($p = 0.002$). EFCT revealed recurrence in 6 (1%); 0 of stage II, 1 (0.3%) of low-risk stage III, and 5 (2.4%) of high-risk stage III ($p = 0.132$). Only 1 of 6 patients with recurrence underwent surgical resection of curative intent. There were no differences in overall survival (OS), disease-free survival (DFS), and cumulative occurrence of local treatment for DFS events according to undergoing EFCT with adjustment to age, gender, and stage.

Conclusions: Early recurrence within 6 months after surgery occurred in 1% of patients who were treated with oxaliplatin-based adjuvant chemotherapy, mostly in high-risk stage III disease. The practice of EFCT was associated with advanced stage but did not affect OS, DFS, or cumulative occurrence of local treatment. Clinical utility of EFCT seems to be low and should be discouraged especially in stage II or low-risk stage III disease.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

585P Clinical benefit of whole genome and transcriptome analysis (WGTA) in metastatic colorectal cancer (MCRC): Results from the personalized oncogenomics program (POG)

S.L. Liu[1], J. Loree[1], D. Renouf[1], M. Jones[2], S. Yip[2], M. Marra[3], S. Jones[3], J. Nelson[3], J. Laskin[1], H. Lim[1], S. Gill[1]

[1]Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, [2]Genomics, BC Genome Science Centre, Vancouver, BC, Canada, [3]Genome Science Centre, BC Cancer Agency, Vancouver, BC, Canada

Background: Standard guidelines recommend mutation testing for KRAS, NRAS and BRAF in MCRC. POG at BC Cancer is an investigational project that performs WGTA to identify potential hypothetical actionable biomarkers. We aimed to determine its clinical significance compared to standard sequencing panels by analyzing the prevalence of actionable variants and their impact on treatment decisions.

Methods: We analyzed 69 POG MCRC patients (pts) and summarized their WGTA results to identify germline and somatic coding variants, copy number alterations, structural alterations and gene expression outliers. Actionable items were defined as variants that could direct therapy with an investigational or approved agent, and were classified as either standard (found in local sequencing panel- BC Oncopanel) or expanded (not in Oncopanel).

Results: 74% of pts received 2 or more prior lines of chemotherapy. 1 pt died before biopsy was made available and 1 pt had an unsuccessful biopsy. Remaining analysis of 67 pts revealed 49 (73%) pts with actionable alterations, of which 43% consisted of mutation changes, 40% expression changes, 14% copy number variants, and 3% high mutational burden or HRD. Most common standard alterations (54%) were mutations in TP53, KRAS, BRAF, PIK3CA and most common expanded items (46%) were high expression of FGFR1/3, FLT1/3, and VEGFA/B. Among these, 13 (27%) pts had alterations that led to standard chemotherapy or anti-EGFR based treatment, and 7 (14%) pts had a variant that resulted in non-standard therapies. Of those, only irbesartan, targeting the FOS-JUN pathway, resulted in a meaningful response duration of 28 months, while the remaining had an average PFS of 1.7 month. 29 (59%) pts did not receive therapy outlined in POG analysis due to lack of access for the target drug ($n = 15$), poor performance status ($n = 7$), and patient or physician preference ($n = 7$).

Conclusions: WGTA in MCRC provided additional understanding of tumor biology, with high rates of expression changes not otherwise captured in standard sequencing panel. However, at the present time, there is limited additional clinical therapeutic benefit in comparison. Future development is needed and ongoing.

Legal entity responsible for the study: BC Cancer.

Funding: BC Cancer Foundation.

Disclosure: All authors have declared no conflicts of interest.

586P Sequencing of KRAS and NRAS in 1501 colorectal carcinomas reveals significant share of mutations, which are not included in common diagnostic kits

E.N. Imyanitov[1], N.V. Mitiushkina[1], E.S. Kuligina[1], M. Holmatov[1], G.A. Yanus[1], I. Demidova[2], T. Kekeeva[3], M. Gordiev[4], E. Kharitonova[5], I. Tsimafeyeu[5], S. Tjulandin[6]

[1]Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, St. Petersburg, Russian Federation, [2]Laboratory of Molecular Genetics, Moscow City Oncology Hospital No. 62, Moscow, Russian Federation, [3]Laboratory of Epigenetics, Research Centre for Medical Genetics, Moscow, Russian Federation, [4]Laboratory of Molecular Genetics, Tatarstan Cancer Center, Kazan, Russian Federation, [5]Head Office, Russian Society of Clinical Oncology, Moscow, Russian Federation, [6]Department of Clinical Pharmacology and Chemotherapy, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation

Background: KRAS and NRAS mutations render resistance to EGFR therapeutic antibodies. Some data indicate that erroneous administration of cetuximab or panitumumab to patients with RAS-mutated colorectal cancer (CRC) may even accelerate tumour growth.

Methods: 1501 CRC patients were included in the analysis. High-resolution melting (HRM) was performed for the initial screening of KRAS and NRAS mutations in exons 2, 3 and 4. Common RAS mutations were detected by allele-specific PCR, then the remaining samples were analysed by pyrosequencing.

Results: RAS mutations were identified in 756 (50.4%) CRCs. KRAS and NRAS alterations were generally mutually exclusive, with the exception of 2 CRCs carrying lesions in both oncogenes. Distribution or RAS mutations did not show correlation with age or gender. Significant number of the revealed mutations are not included in the spectrum of substitutions covered by commercial kits. For 681 identified KRAS mutations, the following coverage is expected according to manufacturer's brochures: Therascreen (Qiagen): 592 (86.9%); cobas® (Roche, US version): 615 (90.3%); AmoyDx: 665 (97.7%); KRAS StripAssay® (ViennaLab): 600 (88.1%); KRAS XL StripAssay® (ViennaLab): 671 (98.5%). For 77 detected NRAS mutations, these estimates would be 73 (94.8%) for AmoyDx and 75 (97.4%) for NRAS XL StripAssay® (ViennaLab).

Conclusions: Clinically significant share of KRAS and NRAS mutations is likely to be missed by conventional mutation-specific diagnostic kits. This limitation has to be considered while defining diagnostic standards for CRC therapy.

Legal entity responsible for the study: Evgeny Imyanitov.

Funding: Russian Society of Clinical Oncology.

Disclosure: All authors have declared no conflicts of interest.

587P Patterns of care and of biomolecular characterization of right, transverse, and left colorectal cancer from real-life evidence in Asia Pacific and European countries

E. Mari[1], S. Mpima[2], F. Guglielmetti[1], P. Nasuti[2]

[1]Oncology Medical Strategy and Science, IQVIA Milan, Italy, [2]Real World and Analytics Solutions, IQVIA, London, UK

Background: Colorectal cancer (CRC) is biologically heterogeneous with 4 distinct consensus molecular subtypes (CMSs) leading to different prognosis and different response to anti-VEGF and anti-EGFR agents, and different CMSs profiles in Right, Transverse (Trv), and Left location of primary CRC. We aim at describing the patterns of care by the location of primary CRC to provide the baseline reference for future research.

Methods: Anonymized CRC patients-level data collected through a large web-based survey between 9217 patients in EU5 (France, Germany, Italy, Spain & UK) and APAC (China, Japan & S. Korea) collected between January – December 2017.

Results: Data from overall 9217 (5041 advanced) pts from EU5 and APAC was analyzed. Left, Right, and Trv CRC location proportion was similar across regions (Left: 52% all pts, 53% EU5, 50% APAC; Right: 39% all pts, 39% EU5, 40% APAC; Trv: 9% all pts, 8% EU5, 10% APAC). Slightly more pts with liver metastases was reported for Left location of CRC (42% all pts, 44% EU5, 38% APAC) than Right (40% all pts, 43% EU5, 31% APAC) or Trv (37% all pts, 40% EU5, 31% APAC). The incidence of biomolecular alterations was: KRAS mutant: Left 38%, Right 45%, Trv 43%; NRAS mutant: Left 27%, Right 32%, Trv 32%; BRAF mutant: Left 7%, Right 12%, Trv 12%; High MSI: Left 16%, Right 22%, Trv 25%; PD-1/PDL-1/2 positive: Left 17%, Right 13%, Trv 25% (PD-1/PDL-1/2 testing on 225/9217 pts, 2,4%). More Bevacizumab based treatments are used for primary Right location, and more anti-EGFR based therapy for

primary Left location. The use of Immunotherapy was minimal, with these pts tested for either MSI or PD-1/L1 expressed.

Table: 587P

Treatments	LEFT			RIGHT			TRANSVERSE		
	Total %	EU5 %	APAC %	Total %	EU5 %	APAC %	Total %	EU5 %	APAC %
Bevacizumab based	17	17	18	22	22	20	16	16	19
Anti EGFR based	14	16	7	8	9	6	11	12	5
Immunotherapy based	0,04	0,03	0,10	0,03	0,04	–	0,12	0,17	–

Conclusions: This real-world data currently highlights slight but not marked differences in the management of disease in the Left, Right, and Transverse primary location of CRC. Over time we anticipate that differences will arise with primary location of CRC being increasingly considered for the clinical management of CRC.

Legal entity responsible for the study: IQVIA United Kingdom.

Funding: IQVIA United Kingdom.

Disclosure: All authors have declared no conflicts of interest.

588P The role of primary tumour location in the recurrence rate of metachronous metastasis of colon cancer

M. Rimini[1], C. Bardasi[2], F. Gelsomino[3], K. Andrikou[3], C. Santini[2], G. Orsi[4], M. Salati[5], M.L. Riggi[4], S. Pipitone[6], S. Cascinu[7], A. Spallanzani[3]

[1]Modena Cancer Center, Department of Oncology/Hematology, University of Modena, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [2]Modena Cancer Center, Department of Oncology/Hematology, University of Modena and Reggio Emilia, Modena, Italy, [3]Medical Oncology, University Hospital of Modena, Modena, Italy, [4]Department of Oncology/Hematology, University of Modena and Reggio Emilia, Modena Cancer Center, Modena, Italy, [5]Modena Cancer Center, Department of Oncology/Hematology, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [6]Dipartimento di Oncologia ed Ematologia, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [7]Oncology, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy

Background: Recent studies suggest that primary tumour location (PTL) has a prognostic value in patients (pts) with metastatic colorectal cancer (CRC), while its role in early stage disease remains unclear. The aim of this analysis is to investigate the relationship between PTL and the development of metachronous metastasis.

Methods: We performed a population-based study from Modena Cancer Registry collecting data of patients (pts) with early stage disease (stage I, II, III) who underwent surgery from 1995 to 2010. We hypothesized a potential impact of PTL on the postoperative recurrence rate. Fisher's exact test, univariate and multivariate Cox regression analysis were performed.

Results: During the study period, 1570 pts with left-sided colon cancer (LCC) and 841 pts with right-sided colon cancer (RCC) were registered. In the entire cohort, 268 of 1576 pts (17%) with LCC and 100 of 841 pts (11.2 %) with RCC developed metachronous metastasis, for a total of 368 of 2411 pts (15%). Comparing LCC and RCC clinical and pathological status we found no statistically difference in lymph-node status ($p = 0.737$) but an increasing rate of G3 cancers in RCC vs LCC ($p = 0.010$). Median overall survival (OS) from early stage disease diagnosis for LCC patients was 45 months versus 35 months for RCC patients, with no significant difference in relapse free survival between the two groups (23.8 Vs 23.0 months). When relapsed, time to death resulted to be significantly longer in LCC group than in RCC group (14.7 vs 6.3 months; HR 1.46, 95% C.I. 1,16-1,86; p 0,001). In the multivariate Cox regression analysis adjusted for grading and stage at diagnosis, we confirmed a statistically significant impact of the primary tumour sidedness on OS in the relapsed setting (HR 1.48, 95% C.I: 1.15-1.89, $p = 0.001$).

Conclusions: In accordance to literature, our registry data confirm the prognostic role of PTL in advanced colorectal cancers: in particular, right-sided tumours have low recurrence rate but poor prognosis once relapsed. Other investigations are necessary to better understand the substantial heterogeneity within the molecular biology of RCC and LCC in order to provide a better post-operative surveillance and to select the most effective treatment strategies after relapse.

Legal entity responsible for the study: Modena University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

589P The prognostic value of KRAS, NRAS, BRAF and DNA mismatch repair (MMR) status in left- and right-sided metastatic colorectal cancer (mCRC): A Belgian population-based study

K. Janssens[1], G. van Camp[2], K. Op de Beeck[3], E. Fransen[4], F. Calay[5], N. van Damme[5], M. Peeters[6]

[1]Internal Medicine, University of Antwerp, Antwerp, Belgium, [2]Medical Genetics, U.Z.A. University Hospital Antwerp, Edegem, Belgium, [3]Center of Oncological Research (CORE), University of Antwerp, Edegem, Belgium, [4]StatUa, University of Antwerp, Edegem, Belgium, [5]Belgian Cancer Registry, Sint-Joost-ten-Node, Belgium, [6]Medical Oncology, U.Z.A. University Hospital Antwerp, Edegem, Belgium

Background: In recent years, various studies have convincingly shown that mCRC patients with left-sided primaries have a significantly better prognosis than those with right-sided tumors. More research is required to identify the biomarkers that cause this difference in survival. Furthermore, these conclusions are mostly based on data of clinical trials and therefore selected patients. Confirmation in population-based studies is necessary. Therefore, the aim of current study is to compare the impact of biomarkers on survival rates in left- and right-sided mCRC in the (non-selected) Belgian population.

Methods: In Belgium, data on patient and tumor characteristics of all new diagnosed cancers are collected in the Belgian Cancer Registry. A random sample of 1035 patients diagnosed with mCRC in 2014 was included in our analysis. We obtained information on age, sex, primary tumor location, biomarker data (MMR status and BRAF, KRAS and NRAS mutational status) and survival. We constructed a logistic regression model, using location, age, gender and biomarkers as independent variables and survival as dependent variable.

Results: After exclusion of 177 patients with a second tumor, the study included 858 mCRC patients: 268 (31.24%) with right-sided mCRC, 352 (41.03%) with left-sided mCRC, 212 (24.71%) with rectal cancer and 26 (2.03%) with an overlapping lesion or unknown localization. KRAS and BRAF mutations were more frequently observed in right-sided tumors compared to left-sided tumors, whereas NRAS mutations were more frequently observed in left-sided CRC compared to right-sided CRC. Microsatellite instability (MSI)-high tumors were more frequently observed on the right side of the colon. Detailed overall survival data according to tumor location and biomarker status will be available at the congress.

Conclusions: We present the survival data of 1035 Belgian mCRC patients according to age, sex, tumor location and biomarker status. Currently, we can conclude that in Belgian patients left-sided mCRC has a better prognosis than right-sided mCRC, regardless of biomarkers status.

Legal entity responsible for the study: University of Antwerp.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

590P Increase in tumor-infiltrating FoxP3-positive regulatory T cells in left-sided colorectal cancer tissues after preoperative oral uracil and tegafur/leucovorin chemotherapy

S. Sadahiro[1], T. Suzuki[1], A. Tanaka[1], K. Okada[1], G. Saito[1], H. Miyakita[1], H. Kajiwara[2], H. Nagase[3]

[1]Surgery, Tokai University School of Medicine, Isehara, Japan, [2]Pathology, Tokai University School of Medicine, Isehara, Japan, [3]Applied Pharmacology Lab., Taiho Pharmaceutical Co., Ltd, Tokushima, Japan

Background: Oral uracil and tegafur (UFT)/leucovorin (LV) are widely used as a standard adjuvant chemotherapy (CT) for colorectal cancer (CRC). Immunotherapy (IT) such as pembrolizumab are being approved and developed for the treatment of CRC with high microsatellite instability which is specific to right-sided CRC. We previously showed that the increases in the gene expressions of the IT targets, CTLA4 and LAG3, after UFT/LV CT were specific to left-sided CRC (ESMO2017). In this study, we examined the amount of tumor infiltrating lymphocytes (TILs) and the subtype of TILs in tumor tissues after and without UFT/LV CT.

Methods: In 90 patients with CRC, UFT (300 mg/m^2/day) and LV (75 mg/day) were administered for 2 weeks before surgery (UFT/LV group), and in the other 170 patients with CRC, no CT was treated before surgery (control group). The amounts of TILs were quantitatively evaluated using HE-stained tumor tissue. The subtypes of TILs were evaluated by immunohistochemical analyses (IHA) of the surface markers of lymphocytes (CD3, CD4, CD8 and FoxP3). The patients were divided into low and high groups of the expressions of the markers using the appropriate cutoff values.

Results: The rate of TIL-high patients in UFT/LV group was significantly higher than in control group (34.4% vs. 15.3%, $p = 0.0008$). In IHA of TILs, the rate of FoxP3-high patients in UFT/LV group was significantly higher than in control group (41.1% vs. 22.4%, $p = 0.0024$). No differences were observed in other lymphocytic markers, CD3, CD4, and CD8. In left-sided tumors, the rates of TIL- and FoxP3-high patients in UFT/LV group were significantly higher than in control group (45.8% vs. 14.3%, $p < 0.0001$ and 43.8% vs. 20.9%, $p = 0.0060$, respectively). In right-sided tumors, there were no differences in both groups.

Conclusions: The increases in TILs, especially FoxP3-positive regulatory T cells, after UFT/LV CT may be specific to left-sided CRC, suggesting that the combination therapy of UFT/LV and immune checkpoint inhibitors or the sequential therapy of immune

checkpoint inhibitors followed by UFT/LV can be useful for patients with left-sided CRC.

Legal entity responsible for the study: Sotaro Sadahiro, MD.

Funding: Has not received any funding.

Disclosure: H. Nagase: Employee: Taiho Pharmaceutical Co. Ltd. All other authors have declared no conflicts of interest.

591P Comparing metastatic (M) young onset (YO) colorectal cancer (CRC) with average onset (AO): Do they differ clinically and genetically?

G. Dos Santos Fernandes[1], W. Chatila[1], R. Yaeger[1], R. Mendelsohn[1], Z. Stadler[1], N.H. Segal[2], A. Varghese[3], D. Reidy[3], L. Diaz[3], J. Shia[4], E. Vakiani[4], J. Hechtman[4], N. Schultz[5], M. Berger[4], D. Hyman[3], D. Solit[3], L. Saltz[2], J. Garcia Aguilar[6], A. Cercek[3]

[1]GI Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3]Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [4]Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [5]The Nikolaus Schultz Lab, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [6]Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background: The incidence of colorectal cancer in patients(pts) under the age of 50 has been steadily on rising over the last two decades. This is in sharp contrast to average onset CRC where there has been a decline. Little is known about clinical behavior and biology of metastatic CRC in the growing YO population.

Methods: We defined YO as < 45 yo and AO as > 50 yo. To better understand the differences in biology of early onset rectal tumors, we tabulated the clinical characteristics, genomics using next generation sequencing(MSK-IMPACT), treatments and outcomes in 175 metastatic pts with EO CRC, treated at Memorial Sloan Kettering Cancer Center between 2014 and 2017 and compared these cases to a cohort of AO M CRC cases ($n = 413$) with CRC related hereditary syndromes such as Lynch Syndrome and inflammatory bowel disease were excluded.

Results: We analyzed 175 in the YO cohort. Age at diagnosis was between 17-35yo in 46 and between 36-45 in 129 pts. Among YO patients, there were 50.2% males, 27.7% smokers and the median BMI was 25.5. Comparing to AO, YO pts have significantly less right sided tumors (22.8% vs 33%; $p = 0.01$). Treatment choices did not differ among YO vs AO groups; systemic chemotherapy (46.7% vs 42.6%; $p = 0.40$) and metastasectomy (54.6 vs 49.4; $p = 0.33$). Overall survival was 59months in the YO vs 63.9 for the AO ($p = 0.194$). Among genetic characteristics mutational burden and copy number comparison showed no significant differences between the groups.

Conclusions: Our series describes a comprehensive clinical and genomic profile of EO mCRC. In contrast to prior reports YO does not appear to be associated with more aggressive disease and there was no difference in treatment modalities. Detailed genomic and clinical characteristics will be presented.

Legal entity responsible for the study: Andrea Cercek.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

592P Impact of Charlson comorbidity index on survival of octogenarian patients with colorectal cancer

E.D. Inga Saavedra[1], J.R. Rodriguez[1], E. Casaut Lora[2], A. Gonzalez-Haba[1], V. Serrano Pecos[1], M.F. Martinez Barragan[1], E. Blanco[1], J. Gomez-Ulla[1]

[1]Medical Oncology Service, Hospital Infanta Cristina, Badajoz, Spain, [2]Oncology, Hospital Perpetuo Socorro, Badajoz, Spain

Background: Octogenarians have higher rates of comorbidity that are associated with a poor prognosis. Few studies have identified prognostic factors of elderly patients (pts) with colorectal cancer (CRC), so their optimized care strategies remain controversial. Charlson comorbidity index (CCI) is the most widely used clinical scoring system to predict the survival of patients with malignancies. The aim of this study was to investigate the prevalence of comorbidity and the prognostic impact of the CCI score for survival among octogenarian pts with CRC in our center.

Methods: We reviewed 151 pts referred to Medical Oncology between January 2012 and March 2017. Data on demographics, staging, treatment and survival were collected and analysed. CCI score was independent variable. OS rates was estimated by the Kaplan–Meier method, with differences in survival between groups compared by the log-rank test.

Results: We reviewed 151 pts with CRC referred to Medical Oncology between January 2012 and March 2017. Data on demographics, staging, treatment and survival was collected and analysed. CCI score was the independent variable. OS rates was estimated by the Kaplan–Meier method, with differences in survival between groups compared by the log-rank test. Results Octogenarians were a 19% of all pts, 82 (54%) men and 69 (46%) women. The median age was 84 years. There was no difference in performance status (PS) between genders with PS 0-1 in 76%, PS 2 in 26% and PS 3-4 in 10%. Pts were divided into high CCI score (CCI ≥ 3; $n = 52$) and low CCI score (CCI < 3; $n = 99$) groups for comparative analyses of differences in their short- and long-term outcomes. The overall survival (OS) in pts with a Low CCI Score was longer than that in high CCI score (46 versus 25 months; $p < 0.01$). High CCI score significantly relates to poorer survival outcome for all stages ($p < 0.001$).

Table: 592P

Characteristics	Low CCI group (n = 99)	High CCI group (n = 52)	p value
Sex (male/female)	46/53	23/29	0.74
Stage at diagnosis I II III IV	10 21 39 29	6 7 16 23	0.003
Primary tumor location Right Left Rectum	38 44 17	24 17 11	0.24

Conclusions: In our study CCI score (low or high) showed be independent factor in prognosis and survival in octogenarian patients with colorectal cancer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

593P The SENECA study: Prognostic role of serum biomarkers in elderly metastatic colorectal cancer patients

C. Lisanti[1], D. Basile[1], S.K. Garattini[1], G. Pelizzari[1], A. Parnofiello[1], F. Cortiula[1], E. Ongaro[1], M. Cattaneo[1], C. Corvaja[1], V.J. Andreotti[1], M. Bartoletti[1], M. Casagrande[2], D. Iacono[2], M. Bonotto[2], P. Ermacora[2], N. Pella[2], A. Buonadonna[3], F. Puglisi[4], G. Fasola[2], G. Miolo[3]

[1]Department of Medicine (DAME), University of Udine, Udine, Italy, [2]Department of Oncology, ASUIUD Santa Maria della Misericordia, Udine, Italy, [3]Department of Medical Oncology and Cancer Prevention, CRO National Cancer Institute, Aviano, Italy, [4]University of Udine, Department of Medical Oncology and Cancer Prevention, CRO National Cancer Institute, Aviano, Italy

Background: Aging induces meaningful changes in immune system and inflammation response with increase in monocyte-lymphocyte ratio (MLR) and serum lactate dehydrogenase (LDH) levels. Notably, high levels of these serum biomarkers are associated with poor prognosis in many tumors. We aim to explore the prognostic role of baseline (i.e. before first line chemotherapy) MLR and LDH levels in elderly patients (pts) with metastatic colorectal cancer (MCRC).

Methods: A retrospective analysis of a consecutive cohort of 120 elderly (>70 years) pts treated for MCRC between 2004 and 2017 at the Oncology Department of Aviano National Cancer Institute and University Hospital of Udine (Italy), was conducted. The prognostic role of MLR and LDH levels on overall survival (OS) was investigated through uni- and multivariate Cox regression analyses.

Results: At a median follow-up of 50.83 months, median OS was 19.96 months. Overall, 46 pts (38%) presented a right cancer, 43 pts (36%) a left cancer and 30 pts (25%) a rectal one. In 8 (8%) and 47 (50%) pts a mutation of BRAF or KRAS was detected, respectively. Liver (36%), lymph-nodes (22%), peritoneum (22%) and lung (17%) were the most frequent sites of metastasis. Noteworthy, 22 pts (18%) had undergone a metastasectomy. High levels of LDH (>480 U/L) and MLR (>0.45, obtained with ROC curve) were discovered in 23 (32%) and 51 (42%) patients respectively. By univariate analysis, high levels of LDH (HR 2.81, $p = 0.001$), MLR (HR 2.26, $p < 0.001$) or both (HR 6.42, $p < 0.001$) and node involvement at diagnosis (pN2 vs. pN0 HR 2.15, $p = 0.019$; pN3 vs. pN0 HR 2.69, $p = 0.052$) were associated with worse OS. Metastasectomy (HR 0.47, $p = 0.009$), tumor resection (HR 0.50, $p = 0.010$) and left sidedness (HR 0.53, $p = 0.01$) were associated with better OS. By multivariate analysis, high levels of LDH (HR 2.64, $p = 0.004$), MLR (HR 2.21, $p = 0.009$) or both (HR 4.19, $p = 0.019$) were independently associated with worse OS.

Conclusions: High baseline levels of LDH, MLR or both are unfavorable independent prognostic factors in elderly pts treated with first line chemotherapy for MCRC. These preliminary results emphasize the need of prospective studies to validate these cost-effectiveness biomarkers in this subgroup of pts.

Legal entity responsible for the study: University of Udine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

594P Determinants of oncologist's choice in offering drug holidays during first line therapy for patients with metastatic colorectal cancer

S.K.K. Garattini[1], M. Bonotto[1], L. Porcu[2], E. Ongaro[1], D. Basile[3], F. Cortiula[1], G. Pelizzari[3], M. Cattaneo[1], A. Parnofiello[1], V.J. Andreotti[1], C. Corvaja[3], G.G. Cardellino[1], P. Ermacora[1], M. Casagrande[1], D. Iacono[1], N. Pella[1], A. Buonadonna[3], A.M. Minisini[1], F. Puglisi[3], G. Fasola[1]

[1]Oncology, ASUIUD Azienda Ospedaliero-Universitaria di Udine, Udine, Italy, [2]Laboratory of Methodology for Clinical Research-Oncology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy, [3]Oncology, CRO di Aviano, Aviano, Italy

Background: Overall survival of patients (pts) with metastatic colorectal cancer (mCRC) has been increasing over the last decades. "Drug holiday" strategies were introduced by the oncologists to reduce toxicity. We aimed at studying what are the

clinico-pathological and treatment factors that drive the decision to propose a "drug holiday" in first line.

Methods: This is a retrospective series of consecutive pts affected by mCRC treated with first line chemotherapy. The pts included were treated from 1/1/2005 to 15/03/2017 at University Hospital of Udine and IRCCS CRO of Aviano, Italy. A "drug Holiday" was defined as 56 or more consecutive days without chemotherapy during first-line. Upfront metastasectomy were excluded. Logistic regression was used to find association between predictors and "holiday offer" in univariate and multivariate analysis.

Results: A total of 648 pts were included. In detail, 215 received a drug holiday (33.2%) while 433 (66.8%) received continuous treatment. In univariate analysis, the variables associated with holiday were: non-upfront metastasectomy (OR 11.8, IC 95% 6.62-22.6, $p < 0.001$), thermoablation (OR 6.08, IC 95% 3.19-11.58, $p < 0.001$), primary tumor (OR 2.79, IC 95% 1.79-4.34, $p < 0.001$), G3-G4 pathological grade (OR 1.49, IC 95% 1.01-2.19, $p = 0.046$), adjuvant CT (OR 1.54,IC 95% 1.06-2.33, $p = 0.023$). Adjuvant RT (OR 1.62, IC 95% 0.99-2.62, $p = 0.051$) showed a trend towards association. More than one metastatic site at diagnosis (OR 0.59, IC 95% 0.42-0.83, $p = 0.003$) and nodal involvement (OR 0.57, IC 95%, 0.34-0.95, $p = 0.032$) were associated to continuous treatment. In multivariate analysis, only first line non-upfront metastasectomy (OR 9.89, IC95% 4.38-22.33, $p < 0.001$), thermoablation (OR 4.48, IC95% 1.97-10.19, $p < 0.001$) and primary tumor resection (OR 2.43, IC95% 1.14-5.19, $p = 0.022$) were independently associated with drug-holiday.

Conclusions: In our cohort, clinicians were more prone to propose a drug holiday in pts who had received non-upfront metastasectomy or thermo-ablation or were treated on their primary tumor. Having more than one site of metastasis at the beginning of 1st line and nodal involvement favored continuous therapy.

Legal entity responsible for the study: ASUIUD- Azienda Ospedaliero-Universitaria di Udine, Dipertimento di Oncologia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

596P Combined inhibition of MEK and PI3KCA pathway induces synergic antitumor activity in HER2 amplified human colorectal cancer models

V. Belli[1], N. Matrone[1], S. Napolitano[1], E. Martinelli[1], M.D. Castellone[2], L. Trusolino[3], E.F. Giunta[1], V. De Falco[1], N. Zanaletti[1], P.P. Vitiello[1], D. Ciardiello[1], M. Terminiello[1], F. Ciardiello[4], T. Troiani[1]

[1]Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [2]Università degli Studi dell Istitute of Experimental Endocrinology and Oncology, CNR, Naples, Italy, [3]IRCCS, Istituto di Candiolo, Candiolo, Italy, [4]Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: Cetuximab and panitumumab, monoclonal antibodies direct against the epidermal growth factor receptor (EGFR) are a therapeutic option for mCRC patients wild type for KRAS and NRAS genes. However, only a subset of mCRC patients receives clinical benefit from these therapies due to the development of resistance mechanisms. HER2 gene amplification or HER2 activating mutations have been implicated as resistance mechanisms to anti-EGFR therapies. However, little is known about the role of HER2 in cancer resistance to anti-EGFR antibodies.

Methods: We transfected colon cancer cells sensitive to anti-EGFR antibodies (LIM1215 and SW48) with HER2 vector in order to obtain stable clones overexpressing HER2 protein. LIM1215-HER2 and SW48-HER2 cells were characterized by their morphological and molecular profile through cell migration and WB assays. Moreover, different drugs sensitivity was evaluated by MTT and colony formation. Furthermore, HER2 amplified cells were engrafted into nude mice and treated with different drugs.

Results: HER2 amplified cells show an overexpression and activation of the HER family receptors coupled by an intracellular downstream activation pathway of AKT, MAPK, and MEK proteins compared to parental cells. HER2 amplified cells were treated with several combinations of drugs directed against HER receptors, such as anti-EGFR antibodies of first, second and third generation (cetuximab, SYM004 and MM151); trastuzumab, pertuzumab and lapatinib directed against HER2 receptor; and duligotuzumab direct against HER3. Subsequently, both cells were treated with drugs directed against MEK and PI3KCA proteins, such as refametinib and pictilisib. Among these therapeutic options, the combination of refametinib and pictilisib have shown the most synergist anti-proliferative activity. The in vivo xenograft CRC models have confirmed the synergistic antitumor activity of this combined treatment. Moreover, PDTX HER amplified CRC models will be used to validate the previous results.

Conclusions: These results suggest that the treatment with refamentinib and pictilisib could be a strategy for patients with HER2 amplification that do not receive clinical benefit from standard anti-EGFR therapies.

Legal entity responsible for the study: Università Degli Studi della Campania Luigi Vanvitelli.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

597P Predictive value of in-vitro testing anti-cancer therapy sensitivity on 3D micro-tumors (tumoroids) from patients with metastatic colorectal cancer: A feasibility study

L.H. Jensen[1], C. Dam[1], G. Hagel[2], C. Hansen[1], H. Harling[3], B.M. Havelund[1], A. Jakobsen[1], J. Lindebjerg[1], S. Rafaelsen[1], O. Thastrup[4], T.F. Hansen[1]

[1]Danish Colorectal Cancer Center South, Center of Clinical Excellence, Vejle Hospital, Institute of Regional Health Research, University of Southern Denmark, Vejle, Denmark, [2]Laboratory, 2cureX, Copenhagen, Denmark, [3]Surgery, Bispebjerg Hospital, Copenhagen, Denmark, [4]2cureX, University of Copenhagen - Department of Drug Design and Pharmacology, Copenhagen, Denmark

Background: The treatment of cancer may be improved by testing the chemo sensitivity of cancer cells obtained from the patient's tumor. 3D culture represents a promising method for modeling of patient tumors in vitro. The purpose of this study was to test the feasibility of a clinical trial offering patients with metastatic colorectal cancer treatment based on in-vitro testing anti-cancer therapy sensitivity.

Methods: Main inclusion criteria were stage IV colorectal cancer, PS 0-1, previous exposure to 5FU, oxaliplatin, irinotecan, bevacizumab and, if RAS/RAF wild-type, an EGFR inhibitor. Fresh cancer tissues from metastases were cultivated as tumoroids. The culturing protocol which was originally developed for resected tissue was optimized for the smaller tissue amounts received from needle biopsies. Ten patients were to be included and at least five of them to have clinically applicable results in order for the procedure to be feasible.

Results: Ten patients were included from September to December 2017 in one institution. Biopsies were from liver (6), peritoneum (2), retroperitoneum (1) and lung (1). Rebiopsies were allowed and a total of 19 biopsy sessions were performed with ultrasound (14), CT (3) or sigmoidoscopy (2). In seven cases, the biopsy, tumorsphere formation and sensitivity testing was successful. Median time from biopsy to result was 34 days (range 19-50). A notable challenge was obtaining sufficient viable tumor tissue resulting in increased culture times or the need for re-biopsies.

Conclusions: This is the first clinical study of its kind. The method of selecting last-line treatment of colorectal cancer based on fresh biopsies was feasible as results were obtained in seven out of ten cases. The trial is now extended to a phase II trial with PFS as the primary endpoint.

Clinical trial identification: NCT03251612.

Legal entity responsible for the study: Lars Henrik Jensen.

Funding: 2cureX.

Disclosure: L.H. Jensen: Travel grants: Roche, Amgen, Bayer. G. Hagel, H. Harling, O. Thastrup: 2cureX. All other authors have declared no conflicts of interest.

598P Macrophage migration inhibitory factor overexpression is a mechanism of acquired resistance to anti-EGFR inhibitor cetuximab in human colorectal cancer cell line

N. Matrone[1], A. Chambery[2], R. Russo[2], P.V. Pedone[2], V. Belli[1], S. Napolitano[1], E. Martinelli[1], E.F. Giunta[1], V. De Falco[1], N. Zanaletti[1], P. Vitale[1], M. Terminiello[1], C. Cardone[1], F. Ciardiello[1], T. Troiani[1]

[1]Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [2]Dipartimento di Scienze e Tecnologie Ambientali, Biologiche e Farmaceutiche, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: The anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) cetuximab and panitumumab are effective in a subset of RAS/BRAF wild-type (WT) metastatic colorectal cancers (mCRCs) patients. Despite an accurate RAS-driven selection, not all patients will respond to EGFR inhibitors and the onset of secondary resistance limits their clinical benefit.

Methods: With the aim of developing effective preclinical models for testing possible strategies to overcome acquired resistance to EGFR blockade, we have generated a series of human colon cancer cell lines with in vitro and in vivo acquired resistance to anti-EGFR inhibitors. To better investigate the differentially expressed proteins involved in EGFR resistance, we applied an advanced quantitative proteomic approach based on TMT isobaric labeling and nano-liquid chromatography coupled with high resolution tandem mass spectrometry (MS/MS).

Results: To evaluate changes in protein expression we have used human CRC cell line cetuximab-sensitive GEO, as well as its derived cell line with acquired resistance to cetuximab GEO-CR. By MS/MS, we have identified and quantified 2455 proteins; 53 proteins were found to be differentially expressed in GEO-CR compared to GEO cells. Only 11 proteins were found to be high regulated in GEO-CR, among these we focused our attention on the inhibition factor of macrophage migration (MIF) for its relevance in CRC tumorigenesis. To explore its involvement in resistance to cetuximab in CRC cell line, we have performed an MTT assay with two MIF-antagonists, ISO1 a cell-permeable inhibitor of MIF tautomerase and 4-IPP, a selective MIF inhibitor that blocks MIF and its receptor, CD74, internalization. GEO-CR cell line was treated with two MIF antagonists alone and in combination with cetuximab. Only the combined treatment with cetuximab and 4-IPP induced a synergistic antiproliferative and apoptotic effects.

Conclusions: These results suggest that MIF overexpression is involved in acquired resistance to cetuximab and the inhibition of EGFR and MIF could be a strategy for overcoming anti-EGFR resistance in patients with CRC.

Legal entity responsible for the study: Università Degli Studi della Campania "Luigi Vanvitelli".

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

599P Efficacy and safety of a recombinant soluble human thrombomodulin (ART-123) in preventing oxaliplatin induced peripheral neuropathy (OIPN): Results of a placebo-controlled, randomized, double-blind phase II study

T. Kato[1], M. Kotaka[2], H. Satake[3], A. Makiyama[4], Y. Tsuji[5], K. Shinozaki[6], T. Fujiwara[7], T. Mizushima[8], Y. Harihara[9], N. Nagata[10], N. Kurihara[11], Y. Kagawa[12], G. Kusakawa[13], T. Sakai[13], Y. Uchida[13], M. Takamoto[13], S. Asami[13], M. Ando[14], Y. Saito[15], I. Hyodo[16]

[1]Colorectal Surgery, National Hospital Organization Osaka National Hospital, Osaka, Hyogo, Japan, [2]Gastrointestinal Cancer Centre, Sano Hospital, Kobe, Hyogo, Japan, [3]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan, [4]Department of Hematology, Japan Community Healthcare Organization Kyushu Hospital, Kita-Kyusyu, Japan, [5]Medical Oncology, Tonan Hospital, Sapporo, Japan, [6]Division of Clinical Oncology, Hiroshima Prefectural Hospital, Hiroshima, Japan, [7]Department of Gastroenterological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [8]Department of Gastrointestinal Surgery, Osaka University Graduate School of Medicine, Suita, Japan, [9]Department of Surgery, NTT Medical Center Tokyo, Tokyo, Japan, [10]Department of Surgery, Kitakyushu General Hospital, Kitakyushu, Japan, [11]Department of Surgery, Nerima General Hospital, Tokyo, Japan, [12]Department of Colorectal Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [13]Clinical Development Center, Asahi Kasei Pharma Corporation, Tokyo, Japan, [14]Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan, [15]Department of Anesthesiology, Shimane University Faculty of Medicine, Izumo, Japan, [16]Department of Gastroenterology, University of Tsukuba, Tsukuba, Japan

Background: OIPN is a common adverse event leading to early discontinuation of oxaliplatin. This was the first exploratory trial for proof of concept of whether ART-123 prevented OIPN.

Methods: Patients with pStage II or III colon cancer who planned adjuvant chemotherapy with mFOLFOX6 were randomly allocated to the following 3 groups in a double-blind manner; placebo group (placebo saline on day 1-3), 1-day ART-123 group (ART-123 380U/kg on day 1 and placebo on day 2-3), and 3-day ART-123 group (ART-123 on day 1-3). Study drug was given intravenously for 30 min immediately before oxaliplatin. The severity of OIPN was evaluated using NCI-CTCAE by physicians and FACT/GOG-NTX-12 (score range 0-48, lower values more severe) by patients. NCI-CTCAE was assessed at baseline, day 1-3 of every cycle, and 14 and 42 days after the last treatment with oxaliplatin. FACT/GOG-NTX-12 was assessed at baseline, day 1 and 8 of every cycle, and 14 and 42 days after the last treatment with oxaliplatin.

Results: Eighty patients were randomized, and 79 (28 placebo, 27 1-day ART-123, and 24 3-day ART-123) patients were analyzed. Both 1-day and 3-day ART-123 tended to reduce the cumulative incidence of NCI-CTCAE grade 2 or higher OIPN and prevent worsening of FACT/GOG-NTX-12 scores, compared to placebo (Table). No substantial differences in other adverse events were noted.

Table: 599P

		Placebo (n = 28)	1-day ART-123 (n = 27)	3-day ART-123 (n = 24)
Sensory neuropathy NCI-CTCAE (% grade 2 or higher)	Baseline	0%	0%	0%
	at 6th cycle	39%	19%	17%
	at 12th cycle	64%	41%	46%
Overall scores in FACT/GOG-NTX-12 (the least square mean (SE))	Baseline	46 (0.4)	47 (0.5)	46 (0.5)
	at 6th cycle	35 (1.6)	39 (1.6)	38 (1.6)
	at 12th cycle	29 (1.9)	36 (1.9)	32 (2.0)
Median total dose of oxaliplatin (mg/m^2)(range)		819 (84-1000)	849 (331-1037)	921 (255-1012)

Conclusions: ART-123 showed promising efficacy in delaying and reducing OIPN without serious safety concerns.

Clinical trial identification: NCT02792842.

Legal entity responsible for the study: Asahi Kasei Pharma Corporation.

Funding: Asahi Kasei Pharma Corporation.

Disclosure: G. Kusakawa: Employee, Stockholder: Asahi Kasei Pharma;. T. Sakai, Y. Uchida, M. Takamoto, S. Asami: Employee: Asahi Kasei Pharma. M. Ando, Y. Saito, I. Hyodo: Advisory board: Asahi Kasei Pharma. All other authors have declared no conflicts of interest.

600P Development of a nomogram for predicting survival in microsatellite stable patients with resected colorectal cancer

Y. Li[1], J. Peng[1], T. Hou[2], H. Han-Zhang[3], H. Liu[3], J. Xiang[3], L. Zhang[3], X. Ma[1], D. Huang[4], S. Cai[1]

[1]Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China, [2]Bioinfo, Burning Rock Biotech, Guangzhou, China, [3]Medicine, Burning Rock Biotech, Guangzhou, China, [4]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The benefits of adjuvant chemotherapy remain controversial in microsatellite stable (MSS) stage II resected colorectal cancer (CRC) patients. In this study, we constructed an overall survival (OS) prediction model for this subgroup, integrating a combination of molecular and clinical predictors.

Methods: Variables with p-values < 0.05 were entered into multivariate analyses using Cox stepwise regression model to select independent predictors as input for OS prediction nomogram. A final model was selected using a backward step-down process, which used Akaike Information Criterion as a stopping rule. The probability of 3-year and 5-year survival can be obtained by summing up the total score and locating it on the total point scale.

Results: We performed targeted sequencing on surgically resected tumor tissue of 122 stage II MSS patients, defined as having less than 15% length-instable loci, using a panel which allows for simultaneous detection of MSI status and mutation in 41 CRC-related genes. Among them, 23, 30 and 69 patients were diagnosed with proximal, distal and rectal cancer, respectively. To predict the probability of 3-year and 5-year survival, we constructed a nomogram incorporating the significant prognostic factors, including APC, ATM, BRAF, PTEN, TP53 (LOF), mutation count (high: >3, low: <=3), age, CEA, and the location of the tumor. The actual and predicted survivals were in an excellent agreement, reflected by a C-index of 0.887 (95% CI: 0.816-0.957). Furthermore, Kaplan-Meier curves for survival outcomes showed significant distinction ($p < 0.001$) after stratifying our cohort into low, median and high risk groups according to total score obtained from our nomogram. Our data also demonstrated high risk patients who received adjuvant chemotherapy are associated with a better OS ($p = 0.004$). Low and median risk patients did not benefit from adjuvant chemotherapy, reflected by comparable OS.

Conclusions: We developed a nomogram model for predicting survival of MSS patients with stage II resected CRC. It can potentially serve as complementary method for clinicians to identify subgroups necessitating adjuvant therapy.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.

Funding: Has not received any funding.

Disclosure: T. Hou, H. Han-Zhang, H. Liu, J. Xiang, L. Zhang: Burning Rock Biotech. All other authors have declared no conflicts of interest.

601P Germline mutations in Chinese colorectal cancer patients with mismatch repair deficiency

Y. Yuan[1], L. Zhu[1], D. Xu[2], C. Liu[3], X. Mao[4]

[1]Medical Oncology, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China, [2]Surgical Oncology, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, [3]Bioinformatics, Burning Rock Biotech, Guangzhou, China, [4]Medicine, Burning Rock Biotech, Guangzhou, China

Background: Mismatch repair deficiency (dMMR) due to germline mutations in DNA repair genes including MLH1, MSH2, MSH6 and PMS2, or somatic aberrant silencing of MLH1, is a well-established feature for Lynch syndrome, a major type of hereditary colorectal cancer (CRC). The purpose of this study is to derive prevalence of germline MMR gene mutations in Chinese population with dMMR CRC.

Methods: ColonCore panel is designed for simultaneous detection of microsatellite instabiligy (MSI) status of 22 regions and mutations in 38 CRC-related genes. Whole exons of the 38 genes were covered by the panel. The MSI phenotype detection method was a read-count-distribution-based approach. It utilized the coverage ratio of a specific set of repeat lengths as the main characteristic of each microsatellite locus, and categorized a locus as unstable if the coverage ratio was less than a given threshold. The MSI status of a sample was determined by the percentage of unstable loci in the given sample.

Results: Among 1394 postsurgical CRC patients whose MMR status were detected by immunohistochemistry (IHC), 99 patients were dMMR, accounting for 7.1%. The concordance rate was 92.3% between MSI and IHC. Next, we investigated the germline mutation spectrum of dMMR patients. About 26.3% patients harbored pathogenic germline MMR gene mutations, with 13%, 6%, 5% and 2% of patients carrying pathogenic MLH1, MSH2, MSH6 and PMS2 mutations, respectively. Specially, about 30% pathogenic MLH1 mutation occured in splice region. Among patients with pathogenic MMR gene mutations, their first cancer was diagnosed ranging from 22 to 69 years old

with median age at diagnosis was 50, and only 57% have a family history of ≥ 1 relative with Lynch syndrome related cancers. Furthermore, 3% harbored pathogenic mutations in other genes. Approximately, 17% of patients harbored MMR gene variants of unknown significance (VUS) and 26% harbored other VUS. The remaining 28% of patients had no pathogenic or VUS mutations from this panel.

Conclusions: The prevalence rate of germline pathogenic mutations is 26% in dMMR CRC patients, accounting for 1.8% of all resectable CRC patients. Median age at diagnosis of Lynch syndrome related cancers is 50 years old and nearly 40% Lynch syndrome patients have no family history.

Legal entity responsible for the study: Ying Yuan.

Funding: Burning Rock Biotech.

Disclosure: C. Liu: Burning Rock Biotech. All other authors have declared no conflicts of interest.

602P Kynurenine 3-monooxygenase as a potential biomarker for colorectal cancer

C-Y. Liu[1], C-H. Lee[1], J-L. Chen[1], T-T. Huang[1], S-H. Yang[2], J-K. Jiang[2], W-S. Chen[2], K-D. Lee[3], H-W. Teng[1]

[1]Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, [2]Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, [3]Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan

Background: Colorectal cancer (CRC) is the third most common cancer and the cause of cancer-related deaths worldwide. Due to the lack of highly sensitive and specific biomarkers, colorectal cancer often identified at the late stages in most patients when diagnosed. Identifying the potential cancer marker and understanding the mechanisms of metastasis and progression behind colorectal cancer is crucial for human CRC. Kynurenine 3-monooxygenase (KMO) is a monooxygenase participating in tryptophan metabolism. Previous studies showed that KMO related to metastasis and proliferation in hepatocellular carcinoma. However, the biological role of KMO in human CRC is still unclear.

Methods: The expression level of KMO in patients with CRC was examined using immunohistochemistry (IHC). The correlation between KMO expression and patient survival rate was analyzed using The Cancer Genome Atlas (TCGA) database. CRC cell lines were used to perform functional assays. UPF 648, a potent KMO inhibitor, and RNAi against KMO and luciferase were used for in vitro studies. Cell viability was analyzed by MTT assay. Cells motility was examined by transwell assay. Stemness properties were assessed by sphere assay and the expression of cancer stem cells markers.

Results: IHC data showed that the expression of KMO was upregulated in CRC tumor tissues compared with normal counterparts of CRC. Furthermore, higher level of KMO transcript was associated with worse overall survival in CRC patients in TCGA database. Knockdown of KMO inhibited the expression of cancer stem cells markers, including CD44 and Nanog, as well as abilities of migration and invasion of CRC cells. Furthermore, the effect of KMO activity inhibition in cell viability was cell lines specific whereas the abilities of cell migration, invasion and sphere formation in CRC cells were significantly suppressed by UPF 648 treatment.

Conclusions: Our data suggests that KMO may serve as a potential biomarker and play tumor-promoting role in CRC.

Legal entity responsible for the study: Chun-Yu Liu.

Funding: Has not received any funding.

Disclosure: C. Liu, X. Mao: Employee of Burning Rock Biotech. All other authors have declared no conflicts of interest.

603TiP Induction chemotherapy plus chemoradiotherapy with or without aspirin in high risk rectal cancer (ICAR)

J.C.E.S.O.D. Souza[1], R. Araujo[2], M. Valadão[2], C. Carrara[3], M.Á. Barbosa[3], R. Guimarães[4], J. Carvalho[4], G. Kovaleski[5], I. Small[6], A. Marins[5], A.P. Victorino[1], R. Gil[1], J.P. Jesus[2], L.H. de Araujo[1], A.C. de Melo[5]

[1]Oncology Department, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [2]Surgery Department, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [3]Radiology Department, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [4]Radiotherapy Department, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [5]Clinical Research Department, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [6]Biostatiscs Department, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil

Background: Induction chemotherapy followed by chemoradiation is an attractive approach, with more favorable compliance and toxicity profiles. Furthermore, the benefit of aspirin in cancer of the colon and rectum is already known. Recently, it was described its potential activity during chemoradiotherapy. The aim is to evaluate the efficacy of total neoadjuvant treatment and the aspirin use during chemoradiotherapy for high-risk rectal cancer.

Trial design: Randomized trial to evaluate induction treatment with XELOX and Capecitabine-based chemoradiotherapy with or without aspirin in a high risk population selected by MRI. High-risk will be defined by presence of at least one of the following criteria on high-resolution thin-slice MRI: tumors within 1 mm of or beyond the mesorectal fascia; tumor extending 5 mm or more into perirectal fat; resectable cT4 tumors; lower third; nodal involvement; extramural vascular invasion. Primary objective is to evaluate the tumor downstaging after total neoadjuvant treatment with or without aspirin. All the patients enrolled in the study will receive XELOX every 21 days for four cycles, unless unacceptable toxicity or progression is detected. After this treatment, patients will be randomized to receive Capecitabine-based chemoradiotherapy with aspirin or placebo (Capecitabine 850 mg/m^2 5 days per week combined with radiotherapy with total dose of 50.4 Gy in 28 days). Random assignment of treatment will be stratified by MRI tumour regression grade. After 8-10 weeks, they will be evaluated by MRI. Patients with complete clinical response will be managed with "watch and wait" approach. The sample size was calculated according to Simon's optimal two-stage design. Accordingly, 11 patients must be included in each group during the first stage. If 3 patients or fewer show downstaging, the trial will be stopped (interim efficacy analysis). Inclusion of patients will continue until 31 patients are included, in order to detect a difference of 26% or greater in downstaging. A treatment regimen will be considered effective if more than 10 patients of the total 31 show downstaging (final analysis), reaching 90% power with an alpha of 0.05 level of significance.

Clinical trial identification: NCT03170115.

Legal entity responsible for the study: INCA- Instituto Nacional de Câncer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

604TiP Phase II study of surgery after S-1 + oxaliplatin +bevacizumab therapy for unresectable rectal cancer by organ-preserved TME

T. Yoshida[1], T. Miura[1], Y. Sakamoto[1], H. Morohashi[1], H. Fujita[2], K. Sato[1], K. Hakamada[1]

[1]Gastroenterological Surgery, Hirosaki University Hospital, Hirosaki, Japan, [2]Radiology, Hirosaki University Hospital, Hirosaki, Japan

Background: For unresectable locally advanced rectal cancer (ULARC), long-course preoperative neoadjuvant chemoradiotherapy (NACRT) was recommended by ESMO guideline. However, ULARC had the risk of not only local recurrence but also subsequent metastatic disease. In these circumstances, preoperative neoadjuvant intense chemotherapy without radiotherapy (NAC) are being investigated in multiple trials. The recent trials suggested equivalent local down staging and pCR rates of NAC using doublet therapy + bevacizumab as compared with standard NACRT. On the other hands, the addition of bevacizumab could be associated with anastomotic insufficiency or rectal perforation. Therefore, the strategy of the safe and sufficient introduction of preoperative doublet therapy + bevacizumab has been required for ULARC.

Trial design: Primary end point: T down-staging rate (The rate of pT0, pTis, pT1 and pT2) Inclusion criteria: 1. Clinical stage T3 or T4, any N without distant metastases. 2. Unresectable rectal cancer by organ-sparing TME which was judged by high resolution MRI. The features include CRM < =1mm, T4b, and lateral lymph node metastasis. Exclusion criteria: 1. Over 75 years old. 2. The patients had thromboembolism or significant abnormal electrocardiogram or cardiovascular disease. Protocol: S-1 is administered orally at 80mg/m2/day for 14 consecutive days followed by a 7 day rest. L-OHP is given intravenously on days 1, at a dose of 130mg/m2/day. Bevacizumab is given intravenously on days 1, at a dose of 7.5mg/kg/day. 21 days are assumed 1 course, and chemotherapy consisted of 4 courses. Surgery is carried out in 8 to 12 weeks after the end of chemotherapy. The type of surgery was defined by high resolution MRI after preoperative chemotherapy within 2 weeks before the date of surgery. Target sample: 32 patients Features of this trial: Paying attention to the safety and efficacy of bevacizumab compared with prior trials according to the following points; 1. long interval between surgery and the administration of bevacizumab. 2. The transverse loop colostomy is required before NAC in case of stenosis. 3. The diverting stoma are necessary after intestinal reconstruction.

Clinical trial identification: UMIN Clinical Trials Registry: UMIN000031626

Release date: 2018/03/08.

Legal entity responsible for the study: Aomori Colorectal Cancer Study (ACCS) group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

605TiP Phase II study of resection of primary colorectal cancer and synchronous liver metastasis after S-1 + oxaliplatin (SOX) + bevacizumab (Bmab) therapy and adjuvant S-1 chemotherapy

T. Miura, H. Morohashi, Y. Sakamoto, T. Yoshida, K. Sato, K. Ishido, D. Kudo, N. Kimura, K. Hakamada

Gastroenterological Surgery, Hirosaki University Hospital, Hirosaki, Japan

Background: For resectable colorectal liver metastasis, perioperative adjuvant chemotherapy was suggested to prolong disease-free survival. However, the relapse rate was still high even after doublet therapy. To decrease the relapse rate, doublet + targetted therapy was tried but the efficacy and perioperative safety of the targetted therapy have not been significantly shown. These failures might be caused by inappropriate indication, timing of preoperative chemotherapy and short interval between chemotherapy

and surgery. In these circumstances, we designed a preoperative doublet + bevacizumab therapy in high-risk patients such as synchronous liver metastasis before simultaneous resection of primary and liver metastasis.

Trial design: Primary end point: Disease-free survival. Inclusion criteria: 1. Clinical any T and any N with only liver metastases. Exclusion criteria: 1. Over 75 years old. 2. The patients had thromboembolism or significant abnormal electrocardiogram or cardiovascular disease. Protocol: S-1 is administered orally at 80mg/m^2/day for 14 consecutive days followed by a 7-day rest. Oxaliplatin (L-OHP) was given intravenously on days 1, at a dose of 130mg/m^2/day. Bevacizumab is given intravenously on days 1, at a dose of 7.5mg/kg/day. 21 days were assumed 1 course, and chemotherapy consisted of 4 courses. Surgery was carried out 8 to 12 weeks after the end of chemotherapy. Adjuvant chemotherapy of S-1 at 80mg/m^2/day for 14 consecutive days followed by a 7-day rest was initiated within 6-8 weeks after surgery. Target sample: 28 patients. Features of this trial: Paying attention to the safety and efficacy of bevacizumab compared with prior trials according to the following points; 1. Long interval between surgery and the administration of bevacizumab. 2. Preoperative chemotherapy was administered prior to resection of primary colorectal cancer in order to increase the intensity of chemotherapy. 3. The loop ostomy is required before neoadjuvant chemotherapy in case of stenosis.

Clinical trial identification: UMIN000032102, release date: 2018/04/04.

Legal entity responsible for the study: Aomori Colorectal Cancer Study (ACCS) Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

606TiP Randomized phase II study of FOLFIRI plus ramucirumab (Rmab) versus FOLFOXIRI plus Rmab as first-line treatment for patients with metastatic colorectal cancer (mCRC): WJOG9216G

Y. Kito[1], T. Yamada[2], T. Matsumoto[3], H. Yasui[4], K. Murata[5], A. Makiyama[6], H. Hara[7], E. Baba[8], K. Nishio[9], K. Yoshimura[10], S. Hironaka[11], K. Muro[12], K. Yamazaki[13]

[1]Medical Oncology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan, [2]Gastroenterology, University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan, [3]Internal Medicine, Himeji Red Cross Hospital, Himeji Hyogo Pref, Japan, [4]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Fushimi-ku, Japan, [5]Department of Colorectal Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [6]Department of Hematology/Oncology, Japan Community Healthcare Organization Kyushu Hospital, Fukuoka, Japan, [7]Department of Gastroenterology, Saitama Cancer Center, Ina, Japan, [8]Comprehensive Clinical Oncology, Kyushu University Hospital, Fukuoka, Japan, [9]Department of Genome Biology, Kindai University, Osaka, Japan, [10]Innovative Clinical Research Center, Kanazawa University, Kanazawa, Ishikawa, Japan, [11]Medical Oncology & Hepatology, Oita University Faculty of Medicine, Yufu, Chiba, Japan, [12]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan, [13]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

Background: Rmab, an anti-VEGFR-2 antibody, inhibits VEGF-A, -C, -D binding and endothelial cell proliferation, while bevacizumab (Bmab) binds to and blocks circulating VEGF-A. The RAISE trial showed the survival benefit of FOLFIRI plus Rmab compared with FOLFIRI plus placebo as second-line treatment for patients with mCRC. The TRIBE trial demonstrated that FOLFOXIRI plus Bmab improved overall response rate (ORR), progression-free survival and overall survival compared with FOLFIRI plus Bmab as induction therapy followed by maintenance therapy with fluorouracil (5-FU), l-leucovorin (l-LV) and Bmab. However, little is known about the role of Rmab in first-line setting and the comparison of induction followed by maintenance therapy with continuous therapy continued until progressive disease (PD) or unacceptable toxicity.

Trial design: WJOG9216G is an open-label, randomized phase II study evaluating FOLFIRI plus Rmab until PD (arm A) versus FOLFOXIRI plus Rmab for 8 to 12 cycles followed by maintenance therapy with 5-FU, l-LV and Rmab (arm B) for patients with mCRC. Eligibility criteria include histologically confirmed unresectable colorectal adenocarcinoma, age of 20-75 years, ECOG PS of 0 or 1, without UGT1A1 *6/ *6, *28/ *28 or *6/ *28, no history of prior chemotherapy for mCRC, and adequate organ function. Stratification criteria are institution, RAS status, history of adjuvant chemotherapy, and primary tumor location. Arm A comprises Rmab 8 mg/kg, irinotecan (IRI) 180 mg/m^2, l-LV 200 mg/m^2, and bolus 5-FU 400 mg/m^2 followed by a 46-hour continuous infusion (ci) of 5-FU 2400 mg/m^2 every 2 weeks until PD. Arm B consists of 8 to 12 cycles of FOLFOXIRI plus Rmab (Rmab 8 mg/kg, IRI 165 mg/m^2, oxaliplatin 85 mg/m^2, l-LV 200 mg/m^2, and 5-FU ci 3200 mg/m^2) as induction therapy followed by 5-FU/l-LV plus Rmab until PD. Primary endpoint is ORR, and main secondary endpoints are PFS, PFS2, OS and safety. Sample size was calculated to be 120 (60 patients per arm), with a one-sided alpha of 10% and a power of 80%, assuming ORR of 50% in arm A and of 70% in arm B. This study has enrolled 23 patients as of April 28th, 2018.

Clinical trial identification: UMIN000026527 (Release date: March 13th, 2017).

Legal entity responsible for the study: West Japan Oncology Group.

Funding: Eli Lilly Japan K.K.

Disclosure: H. Yasui: Honoraria: Taiho Pharmaceutical, Chugai Pharma, Yakult Honsha, Bristol-Myeres Squibb Japan, Takeda, Kyowa Hakko Kirin, Medicon, Ono Pharmaceutical, Daiichi Sankyo, Lilly Japan, Merk Serono, Terumo, Becton Dickinson, Nihonkayaku. H. Hara: Consulting or advisory role: Ono Pharmaceutical, Chugai Pharma, Merck Serono, and MSD; Honoraria from Chugai Pharma, Taiho Pharmaceutical, Merck Serono, Yakult Honsha, Lilly, Ono Pharmaceutical, Takeda; Author's institution has received research funding: AstraZeneca, Chugai Pharma, Merck Serono, MSD, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda, Boehringer Ingelheim, Dainippon Sumitomo Pharma, Daiichi Sankyo, Lilly, Pfizer, LSK BioPharma, Eisai, Incyte. E. Baba: Honoraria: Chugai Pharma, Lilly Pharma; Author's institution has received research funding: Chugai Pharma, Lilly Pharma, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda, Merck Serono Ltd. K. Yoshimura: Honoraria: Chugai Pharma, Lilly, Astra Zeneca, Taiho Pharmaceutical, Boehringer Ingelheim, Takeda, Eisai. S. Hironaka: Consulting or advisory role: Astra Zeneca; Honoraria: Lilly, Bristol-Myers Squibb Japan, Ono Pharmaceutical, Taiho Pharmaceutical, Yakult Honsha, Daiichi Sankyo. K. Muro: Honoraria: Takeda, Chugai Pharma, Yakult Honsha, Merck Serono, Taiho Pharmaceutical, Lilly, Ono Pharmacutical; Research funding: Ono Pharmaceutical, MSD, Daiichi Sankyo, Shionogi Pharma, Kyowa Hakko Kirin, Gilead Sciences. K. Yamazaki: Honoraria: Chugai Pharma, Daiichi Sankyo, Yakult Honsha, Takeda, Bayer, Merck Serono, Bristol-Myers Squibb Japan, Taiho Pharmaceutical, and Lilly; Author's institution has received research funding: Taiho Pharmaceutical. All other authors have declared no conflicts of interest.

607TiP BIG BANG study: A multicenter phase II study of the MEK inhibitor binimetinib + BRAF inhibitor encorafenib + anti-EGFR antibody cetuximab in patients with BRAF non-V600E mutated metastatic colorectal cancer (EPOC 1703)

D. Kotani[1], H. Bando[1], T. Masuishi[2], Y. Komatsu[3], K. Yamaguchi[4], T.E. Nakajima[5], T. Satoh[6], T. Nishina[7], T. Esaki[8], S. Nomura[9], S. Sakamoto[9], S. Iida[9], S. Matsuda[9], M. Yonemura[9], N. Fuse[9], A. Sato[9], S. Fujii[10], H. Ebi[11], A. Ohtsu[1], T. Yoshino[1]

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [2]Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan, [3]Cancer Chemotherapy, Hokakido University Cancer Center, Sapporo, Japan, [4]Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan, [5]Department of Clinical Oncology, St Marianna University School of Medicine, Kawasaki City, Japan, [6]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Osaka, Japan, [7]Department of Gastrointestinal Medical Oncology, Shikoku Cancer Center, Matsuyama, Japan, [8]Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan, [9]Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [10]Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [11]Division of Oncological Pathology, Aichi Cancer Center Research Institute, Nagoya, Japan

Background: While BRAF mutations occur in 10-15% of metastatic colorectal cancer (mCRC), BRAF Non-V600E mutations was recently reported with ranging 2.2 - 5.2%. We have reported that BRAF Non-V600E could be a negative impact on survival outcome as well as anti-EGFR antibody treatment for pretreated mCRC patients (Shinozaki E, et al. Br J Cancer 2017). In addition, simultaneous inhibitions of MEK, BRAF and EGFR exhibited most potent anti-tumor activities in BRAF Non-V600E mutant cell lines and xenografted models (unpublished data).

Trial design: BIG BANG study is a multicenter phase II study to assess efficacy, safety and proof-of-concept of the triple combinations of binimetinib (BINI) + encorafenib (ENCO) + cetuximab (CETUX) in patients with BRAF Non-V600E mutated mCRC, identified by either tumor tissue-based analysis (primary analysis cohort) or circulating tumor DNA (ctDNA) analysis (liquid biopsy cohort). Key eligibility criteria includes ECOG PS $\leq$ 1; mCRC with BRAF Non-V600E mutant and RAS wild-type; refractory or intolerant to at least one fluoropyrimidine-based regimen (including irinotecan or oxaliplatin) and no prior history of anti-EGFR antibody and regorafenib. Enrolled patients receive BINI (45 mg, BID), ENCO (300 mg, QD), and CETUX (initially 400 mg/m^2, and subsequently 250 mg/m^2, QW), which are same recommended doses as the BEACON CRC trial (NCT02928224). In addition, the natural history data of patients with BRAF Non-V600E mutations who do not meet the eligibility criteria are collected as a historical control. The primary endpoint is the objective response rate (ORR) for primary analysis cohort. A sample size of the primary analysis cohort is calculated to be 21 on the hypothesis that the threshold ORR is 6% and expected ORR is 30%, with a significant level of 2.5% (one-sided) and power of 80%. Furthermore, paired tissue and blood samples will be obtained for pharmacodynamics analysis before study treatment, pre-dose of second cycle, and after disease progression. To our best knowledge, this is the first study targeting BRAF Non-V600E mutated mCRC.

Clinical trial identification: UMIN000031857 and 000031860.

Legal entity responsible for the study: Hideaki Bando.

Funding: The Japan Agency for Medical Research and Development.

Disclosure: H. Bando: Research funding: AstraZeneca, Sysmex, Falco biosystemes. T.E. Nakajima: Personal financial interests: Eli Lilly, Sanofi, Chugai, Sawai, Bayer, Bristol, Taiho, Merck, Ono, Takeda, Mochida, MSD; Institutional financial interests: Ono, Taiho, A2 Health Care, JCRO, Daiichi-Sankyo, Mediscience Planning. T. Nishina: Grants, honoraria: Ono, Merck Serono, Yakult, Taiho, Chugai. T. Esaki: Grant: Taiho, Eli Lilly, Eisai, Daiichi-Sankyo, DS Pharma, Merck Serono, Ono, Nihon Kayaku, Novartis, AstraZeneca, Boehringer, MSD, Astellas, Bayer, Pfizer, Yakult; Personal fees: Taiho, Bristol, Eli Lilly, Eisai, Daiichi-Sankyo, Merck Serono, Chugai, Ono, Takeda,

Kyowa-Kirin, Nihon Kayaku. S. Nomura: Honoraria: Taiho. T. Yoshino: Grant: MSD, Sanofi, Sumitomo Dainippon Pharma, Chugai, GlaxoSmithKline, Nippon Boehringer Ingelheim; Personal fees: Sanofi, Chugai, Eli Lilly, Merck Serono. All other authors have declared no conflicts of interest.

608TiP BRAVERY study: A multicenter phase II study of eribulin in patients with BRAF V600E mutant metastatic colorectal cancer (EPOC1701)

T. Masuishi[1], H. Taniguchi[2], D. Kotani[3], H. Bando[3], Y. Komatsu[4], K. Yamaguchi[5], T.E. Nakajima[6], T. Satoh[7], T. Nishina[8], T. Esaki[9], M. Wakabayashi[10], S. Nomura[10], S. Sakamoto[10], H. Ono[10], N. Hirano[10], N. Fujishiro[10], N. Fuse[10], A. Sato[10], A. Ohtsu[3], T. Yoshino[3]

[1]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan, [2]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [3]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [4]Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan, [5]Department of Gastrointestinal Oncology, Cancer Institute Hospital of JFCR, Tokyo, Japan, [6]Department of Clinical Oncology, St Marianna University School of Medicine, Kawasaki City, Japan, [7]Department of Frontier Science for Cancer and Chemotherapy, Osaka University, Osaka, Japan, [8]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [9]Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan, [10]Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan

Background: BRAF V600E mutations are present in 5-10% of metastatic colorectal cancer (mCRC) patients, associated with aggressive biology and limited response to standard chemotherapy, especially in second line and beyond. BRAF V600E mutant CRCs have different patterns of gene expression from the BRAF wild-type, and preclinical evidence suggests that microtubule inhibitors have a potential antitumor effect on xenograft models of BRAF V600E mutant CRC; among them, eribulin has greater growth inhibitory activity than either vinblastine or paclitaxel in vitro. In addition, we have experienced a hint of activity for BRAF V600E mutant CRC patients with tumor shrinkage following eribulin treatment (Masuishi T, et al. Ann Oncol, 2018).

Trial design: BRAVERY study is a multicenter phase II study to evaluate the efficacy and safety of eribulin in patients with BRAF V600E mutant mCRC detected in either tumor tissue (primary analysis cohort) or circulating tumor DNA (ctDNA) assay (liquid biopsy cohort). Key eligibility criteria are refractory or intolerant to at least one regimen (including irinotecan or oxaliplatin) containing fluoropyrimidine, an age of 20 years or older, and ECOG performance status of 0–1. Eribulin is administered intravenously at a dose of 1.4 mg/m^2 on Days 1 and 8, repeated every 21 days. Primary endpoint is confirmed objective response rate (ORR) by investigator's assessment. A sample size of the primary analysis cohort is calculated 27 using two-stage design with ORR of 25% deemed promising and 5% unacceptable (one-sided α, 0.05; β, 0.1). Secondary endpoints include progression-free survival, time to treatment failure, disease control rate, overall survival and adverse events. Furthermore, pretreated tissue and serial blood samples are collected for biomarker analysis; especially focused on gene expression associated with BRAF mutant-like CRC as a predictive marker, BRAF mutant allele frequency in ctDNA as early detection of efficacy, and acquired gene alteration as resistant mechanism to eribulin. At the end of April 2018, four patients have been enrolled in primary analysis cohort since March 2018. Clinical trial information: UMIN000031221 and 000031552.

Clinical trial identification: UMIN000031221 and 000031552. 26/March/2018.

Legal entity responsible for the study: Hiroya Taniguchi.

Funding: Japan Agency for Medical Research and Development.

Disclosure: T. Esaki: Grant and personal fees: Eisai. All other authors have declared no conflicts of interest.

609TiP Intermittent or continuous panitumumab (PAN) plus FOLFIRI for first-line treatment of patients (pts) with RAS/BRAF wild-type (WT) metastatic colorectal cancer (mCRC): A randomized phase II trial (IMPROVE)

A. De Stefano[1], G. Nasti[2], A. Febbraro[3], G. Rosati[4], F. Giuliani[5], D. Santini[6], G. Aprile[7], M. Scartozzi[8], F. Silvestris[9], G. Luppi[10], I. Lolli[11], C. Mastroianni[12], S. Leo[13], V. Montesarchio[14], C. Gridelli[15], C. Pozzo[16], E. Sperti[17], D. Giannarelli[18], A. Budillon[19], A. Avallone[1]

[1]Clinical Experimental Abdominal Oncology Unit, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [2]SSD Innovative Therapies for Abdominal Metastases - Abdominal Oncology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [3]Medical Oncology, Ospedale "Sacro Cuore di Gesù" Fatebenefratelli, Benevento, Italy, [4]Oncology, Ospedale San Carlo, Potenza, Italy, [5]Medical Oncology, Istituto Tumori Giovanni Paolo II, Bari, Italy, [6]Oncology, Campus Bio-Medico di Roma, Rome, Italy, [7]Medical Oncology, ULSS 8 Berica - Vicenza, Vicenza, Italy, [8]Oncology, University Hospital and University of Cagliari, Cagliari, Italy, [9]Department of Biomedical Sciences and Human Oncology – University of Bari, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy, [10]Medical Oncology, Azienda Ospedaliero Universitaria di Modena, Modena, Italy, [11]Medical Oncology Unit, IRCCS Saverio de Bellis, Castellana Grotte, Italy, [12]Medical Oncology, Azienda Ospedaliera di Cosenza, Cosenza, Italy, [13]Medical Oncology, Ospedale Vito Fazzi, Lecce, Italy, [14]Medical Oncology, Azienda Ospedaliera dei Colli-Monaldi, Naples, Italy, [15]Medical Oncology, Azienda Ospedaliera S. Giuseppe Moscati, Avellino, Italy, [16]Oncologia Medica - Fondazione Policlinico Gemelli - IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy, [17]Medical Oncology, Ordine Mauriziano Hospital, Turin, Italy, [18]Statistica, IFO Regina Elena Roma, Rome, Italy, [19]Clinical Pharmacology Experimental, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy

Background: Anti-EGFR treatment demonstrated a clinical benefit limited to RAS-wt mCRC pts. In the FIRE-3 trial the depth of response was significantly associated with survival and the median time to tumor nadir was of 3.6months in the FOLFIRI plus anti-EGFR arm. These data suggest that further exposure to combined treatment may not result in an outcome improvement, but only in an increase of side effects. Therefore, a drug holiday strategy could increase adherence to therapy and quality of life. The feasibility of intermittent use of FOLFIRI in first line was showed by the GISCAD study, but no data are available on the optimal duration of anti-EGFR monoclonal antibodies (moAbs). This issue is of particular interest given the dermatologic toxicities of anti-EGFR moAbs and the emergence of drug resistant clones. In mCRC pts recent data suggest a molecular adaptation of tumor to an intermittent drug schedule with anti-EGFR moAbs. On this basis, we designed a multicenter phase II randomized two arms study with intermittent PAN plus FOLFIRI compared to the same regimen given continuously until disease progression (PD) in the first line treatment of pts with WT RAS and BRAF unresectable mCRC, with a prospective genetic analysis of both tumor tissue and cfDNA.

Trial design: PFS on treatment (PFS_{OT}) at 12months is the primary endpoint. Assuming a p0=30% (corresponding to a median PFS of 7months), and a p1=43% (corresponding to a median PFS of 10months), setting the significance level at 10% with a power of 80% a total of 68 pts will be enrolled in each arm. At the time of enrollment, pts will be immediately randomized to one of the two arms: standard continuous or exploratory intermittent treatment. All pts will receive an induction treatment with 8 cycles of PAN plus FOLFIRI, given every two weeks, at the standard dosage. After the induction treatment, non-progressing pts will receive continuous PAN plus FOLFIRI until PD, unacceptable toxicity or informed consent withdrawal (Standard ARM) or observe a treatment free interval until PD followed by up to 8 cycles of PAN plus FOLFIRI (Experimental ARM). Treatment cycling will continue till any PD on treatment.

Clinical trial identification: EudraCT: 2017-003628-65.

Legal entity responsible for the study: Istituto Nazionale Tumori Fondazione G. Pascale - Naples, Italy.

Funding: Amgen; Istituto Nazionale Tumori Fondazione G. Pascale - Naples, Italy

Disclosure: A. De Stefano: Advisory boards: Amgen, Roche. G. Rosati: Advisory role: Amgen, Roche, Bayer, Merck Serono. A. Avallone: Advisory role: Roche, Amgen, Celgene, Sanofi; Research funding: Bayer. All other authors have declared no conflicts of interest.

610TiP Preoperative nivolumab in patients(pts) with locally advanced colon cancer (T3 or T4): A window-of-opportunity study (NICOLE)

A. Avallone[1], P. Delrio[1], G. Nasti[2], A. Cassata[1], L. Silvestro[1], A. De Stefano[1], S. Lastoria[3], R. Casaretti[1], C. Romano[1], A. Ottaiano[4], E. Di gennaro[5], A. Nappi[1], P. Maiolino[6], E. Cavalcanti[7], A. Petrillo[3], F. Tatangelo[7], D. Giannarelli[8], J. Galon[9], P.A. Ascierto[10], A. Budillon[5]

[1]Abdominal Oncology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy, [2]SSD Innovative Therapies for Abdominal Metastases - Abdominal Oncology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy, [3]Radiology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy, [4]SSD Innovative Therapies for Abdominal Metastases - Abdominal Oncology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [5]Clinical Pharmacology Experimental, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy, [6]Pharmacology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy, [7]Pathology, Istituto Nazionale Tumori, IRCCS, Fondazione "G. Pascale", Naples, Italy, [8]Statistica, IFO Regina Elena Roma, Rome, Italy, [9]Pathology, National Institute of Health and Medical Research, Paris, France, [10]Melanoma, Cancer Immunotherapy and Innovative Therapy Unit, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy

Background: Colorectal cancer (CRC) is one of the most common malignancies, and a leading cause of cancer death worldwide. Surgery is the only curative therapy available for locally advanced colon cancer (LACC), however, the disease is associated with a significant recurrence rate and even with adjuvant therapy its prognosis is far from satisfactory. Preoperative treatment strategy is an attractive concept in LACC because it has the theoretical advantages to eradicate micrometastases, to reduce tumor cell shedding during surgery, to allow the assessment of initial tumor response and could be better tolerated than adjuvant treatment. The results of the recently reported FOxTROT trial has shown that preoperative chemotherapy in LACC is feasible with no increase in surgical morbidity or mortality. The immune contexture of solid tumors has become an emerging hallmark of cancers. Recent evidences indicate that immune infiltrate (immunoscore) is an informative prognostic indicator in LACC. Moreover, it was demonstrated that immunoscore is also a stronger predictor of patient survival than microsatellite instability. Based on these considerations, we designed a window of opportunity study to determine the feasibility of nivolumab in the preoperative setting in pts with LACC.

Trial design: Pts will receive nivolumab at a flat dosage of 240 mgs every two weeks on Day -28 and Day-14 (+/- one day) prior to planned surgery on Day 0 or up to + 7 days. An initial 6-pts safety run-in cohort will be followed by an expansion cohort, with a planned accrual of 16 pts. Postoperatively, standard adjuvant chemotherapy will be administered as recommended by guidelines. Primary objective is to determine the safety and feasibility of Nivolumab in the preoperative setting. The exploratory primary objective is the rate of pathological complete tumor regression, as well as correlative studies to determine molecular and immunophenotypic changes in tumor and peripheral blood samples as potential biomarkers of toxicity/efficacy. Secondary objective are tumor response rate defined by RECIST, postoperative complications, relapse-free survival, overall survival and metabolic response changes evaluated by FDG-PET-CT scan prior to surgery.

Clinical trial identification: EudraCT: 2017-003739-12.

Legal entity responsible for the study: Società Campana di Immunoterapia Oncologica (SCITO).

Funding: Società Campana di Immunoterapia Oncologica (SCITO) with funding from BMS.

Disclosure: All authors have declared no conflicts of interest.

611TiP AVEVAC: A phase I-II trial with avelumab plus autologous dendritic cell (ADC) vaccine in pre-treated mismatch repair-proficient (MSS) metastatic colorectal cancer (mCRC) patients (GEMCAD 16-02)

M. Español Rego[1], V. Alonso[2], J. Aparicio[3], E. Elez Fernandez[4], P. Escudero[5], C. Fernández-Martos[6], N. Rodríguez[7], A. Ruiz Casado[8], J. Cid[9], R. Cabezón[1], M. Lozano[10], A. Ginés[11], L. Bianchi[12], J. Garcia-Corbacho[13], X. García de Albéniz[14], J. Maurel[15], D. Benitez Ribas[1]

[1]Immunology, Hospital Clínic of Barcelona, Barcelona, Spain, [2]Medical Oncology Service, Hospital Miguel Servet, Zaragoza, Spain, [3]Medical Oncology Service, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [4]Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Medical Oncology Service, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain, [6]Medical Oncology Service, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [7]Medical Oncology, H. U. Funjdación Alcorcón, Madrid, Spain, [8]Medical Oncology, Hospital Puerta de Hierro, Majadahonda, Spain, [9]Biomedical Diagnostic Center, Hospital Clínic of Barcelona, Barcelona, Spain, [10]Hemotherapy, Hospital Clínic of Barcelona, Barcelona, Spain, [11]Gastroenterology, Hospital Clínic of Barcelona, Barcelona, Spain, [12]Radiodiagnosis, Hospital Clínic of Barcelona, Barcelona, Spain, [13]Oncology and Hematology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [14]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA, [15]Medical Oncology, Hospital Clínic of Barcelona, Barcelona, Spain

Background: Monoclonal antibodies against checkpoint inhibitors (CHKPNT) such as pembrolizumab showed clinical benefit in patients with microsatellite instability (MSI) in mCRC but not in MSS patients. Cancer vaccines with ADC could be a complementary therapeutic approach to CHKPNT. We previously conducted a negative randomized phase II trial in mCRC patients refractory to standard therapy, with ADC compared to the best supportive (Eur J Cancer 64:167-74, 2016). A phase I-II multicentric trial with avelumab (anti-PD-L1) plus ADC vaccine in pre-treated MSS mCRC patients began in April 2018 (NCT03152565).

Trial design: The study is designed to evaluate the safety, tolerability, pharmacodynamics and anti-tumour effects of the combination in pre-treated MSS mCRC patients. In the phase I, patients are assigned using a standard 3x3 de-escalation criteria (level -1 if dose limiting toxicity (DLT) with avelumab 3 mg/kg every 2 weeks) to received avelumab at a dose of 10 mg/kg every 2 weeks combined to ADC vaccine at days 1, 14, 28, 42 and 56, and thereafter every 6 months until disease progression (maximum of 6 additional doses) or unacceptable toxicity. Biopsies to prepare tumour lysate will be obtained from primary tumour or metastatic disease. The primary objective is to determine the maximum tolerated dose (MTD) and the efficacy of the combination. To detect at least a 20% difference in PFS at 6 months (from 20% to 40%), 33 patients are needed (80% power, alpha equals 5%, two sided). An interim analysis (Simon's two stage) when the first 18 patients are accrued is planned. Secondary objective includes pharmacodynamics (a) NanoString 360 gene immune-signature from archival biopsy, at study entry and at 2 months therapy (b) cytokine and chemokine determination (at study entry and at 2 months therapy) and (c) Autologous tumour mixed leucocyte reaction to test the polarisation of the immune response against the combination (at study entry and at 2 months therapy).

Clinical trial identification: NCTO3152565.

Legal entity responsible for the study: Grupo Español Multidisciplinar de Melanoma.

Funding: Merck.

Disclosure: All authors have declared no conflicts of interest.

612TiP Phase I studies assessing the safety and clinical activity of multiple doses of a NKG2D-based CAR-T therapy, CYAD-01, in metastatic colorectal cancer

A. Flament[1], A. Hendlisz[2], L. Shaza[2], S. Aspeslagh[2], M. Vouche[3], V. Donckier[3], A. Awada[2], J-P. Machiels[4], M. van den Eynde[4], J-L. Canon[5], J. Carrasco[6], C. Lonez[1], F.F. Lehmann[1]

[1]Clinical Development, Celyad SA, Mont Saint Guibert, Belgium, [2]Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, [3]Department of Radiology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, [4]Oncology, Cliniques Universitaires St. Luc, Brussels, Belgium, [5] Service d'Oncologie-Hématologie, Grand Hopital de Charleroi Site Notre Dame, Charleroi, Belgium, [6]Medical Oncology, Grand Hopital de Charleroi Site Notre Dame, Charleroi, Belgium

Background: Chimeric antigen receptor T-cell (CAR-Ts) therapies have yet to demonstrate positive results in the context of solid tumors likely because of the inability of classical CAR-Ts to infiltrate into the tumor and overcome the hostile immune suppressive tumor microenvironment (TME). CYAD-01, a NKG2D receptor-based CAR-T, is currently evaluated in the ongoing THINK study (NCT03018405) without preconditioning therapy in both hematologic and solid indications, and demonstrated encouraging signs of clinical stabilization in refractory metastatic colorectal (mCRC) and ovarian cancer patients. These preliminary results prompted us to design a clinical development plan evaluating CYAD-01 in multiple settings.

Trial design: To improve the likeliness to observe clinical activity of CYAD-01 in metastatic solid tumors, the SHRINK (NCT03310008) and the LINK (NCT03370198) trials have been designed to address, respectively, the challenge related to the immunosuppressive TME and difficulty of CAR-T cells to access the site of metastases. The SHRINK trial is evaluating the multiple infusion CYAD-01 treatment i.v. administered concurrently to a standard-of-care FOLFOX neoadjuvant treatment for the treatment of mCRC disease with potentially resectable liver metastases, with the aim to (i) favor infiltration into the immunosuppressive TME but also (ii) provide an opportunity for the CYAD-01 cells to better engraft due to the lymphodepletion induced by the FOLFOX, and likely (iii) increase the NKG2D ligand expression in tumor tissues targeted by CYAD-01. The LINK trial is evaluating multiple hepatic transarterial administrations of CYAD-01 in mCRC patients with unresectable liver metastases with the potential advantage of a lower systemic toxicity and higher and more persistent concentration of the infused cells on the TME compared to systemic administration and difference in blood supply between uninvolved liver parenchyma and metastases. Finally, the boosting of the adaptive immune response by CYAD-01 might control distant lesions due to a possible abscopal effect. Both studies were initiated in 2018 and the first patients were successfully enrolled.

Clinical trial identification: NCT03310008, EudraCT: 2017-000616-41; NCT03370198, EudraCT 2017-000959-11.

Legal entity responsible for the study: Celyad SA.

Funding: Celyad SA.

Disclosure: A. Flament, F.F. Lehmann, C. Lonez: Employee: Celyad SA. All other authors have declared no conflicts of interest.

613TiP Serum levels of interleukin 8 (IL-8) and other cytokines as predictors of the efficacy of aflibercept in combination with FOLFIRI in metastatic colo-rectal cancer patients: The FLIBER study

C. Buonerba[1], S. Vecchiarelli[2], F. Cappuzzo[2]

[1]Dipartimento di Medicina Clinica e Chirurgia, Università Federico II, Naples, Italy, [2]UOC Oncologia Medica, Ospedale Civile di Ravenna - S.ta Maria delle Croci, Ravenna, Italy

Background: The VELOUR study (Van Cutsem, et al. 2012) showed that the addition of aflibercept to irinotecan-based chemotherapy (FOLFIRI) in patients with metastatic colorectal cancer (mCRC) refractory to oxaliplatin-based chemotherapy was associated with improved progression-free and overall survival. IL-8 enhances cell proliferation and survival and promotes tumor angiogenesis (Lee, et al. 2012). In the randomized phase II AFFIRM study, conducted in mCRC patients treated with oxaliplatin-based chemotherapy with or without aflibercept, high serum levels of circulating IL-8 were significantly associated with reduced PFS (Lambrechts, et al. 2015). While in patients treated without aflibercept, PFS was independent on IL-8 levels, patients treated with aflibercept with IL-8 levels $\leq$ vs. $>$ 19 pg ml−1 presented a median progression free survival of 9.3 (7.52–11.10) vs. 4.1 (2.33–8.54) months. The FLIBER trial aims to explore the predictive value of serum levels of IL-8 and other cytokines in a population of mCRC patients receiving aflibercept plus FOLFIRI.

Trial design: The FLIBER trial is a phase IV single arm study which plans to enroll 124 patients with mCRC resistant to or progressed after an oxaliplatin-containing regimen who are planned to start aflibercept in combination with FOLFIRI as per standard clinical practice and decision by their treating oncologist. Patients will be assessed for a serum cytokine panel at baseline, after 2 months of treatment and at radiologic progression. The primary end point is progression free survival (PFS), with the objective to estimate the difference in PFS between the two groups defined on the basis of their baseline IL-8 levels ($>=$ vs. $<$ than median). The secondary endpoints are Radiologic Response Rate (rRR), Overall Survival (OS) and Safety profile and their relationship with IL-8 levels and the other cytokines assessed. Assessed cytokines include PDGF, IL-1b, IP10, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, bFGF, GCSF, GMCSF, IFNg, MCP1, MIP1a, MIP1b, RANTES, TNFa and VEGF, VEGFA, T-cad, VEGFR3, SAP, VDBP, neuropilin1, CRP, endoglin, PlGF.

Clinical trial identification: EudraCT: 2017-003509-16.

Legal entity responsible for the study: Fondazione Ricerca Traslazionale (FoRT).

Funding: Sanofi Genzyme.

Disclosure: C. Buonerba: Research support to Institution, Consultancy. All other authors have declared no conflicts of interest.

614TiP UCGI 28 Panirinox: A randomized phase II study assessing Panitumumab + FOLFIRINOX or mFOLFOX6 in RAS and BRAF wild type metastatic colorectal cancer patients (mCRC) selected from circulating DNA analysis

T. Mazard[1], F. Ghiringhelli[2], C. Mollevi[3], E. Assenat[4], C. Gavoille[5], D. Smith[6], V. Pezzella[7], R. Meddeb[8], B. Pastor[8], M. Ychou[1], A.R. Thierry[8]

[1]Medical Oncology, ICM Regional Cancer Institute of Montpellier, Montpellier, France, [2]Medical Oncology Unit, Centre Georges-François Leclerc, Dijon, France, [3]Biometry Unit, ICM Regional Cancer Institute of Montpellier, Montpellier, France, [4]Medical Oncology, CHU Saint Eloi, Montpellier, France, [5]Oncology Department, Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandoeuvre les Nancy, France, [6]Service d'Oncologie, CHU Bordeaux Hopital St. André, Bordeaux, France, [7]R&D – UCGI Group, UNICANCER, Paris, France, [8]Integrative Cancer Research for Personalized Medecine in Digestive Oncology, IRCM, Montpellier, France

Background: A majority of patients with mCRC are not suitable for potentially curative resection and their management consists in palliative-intended chemotherapy (CT). Nevertheless, it is described that in patients who achieve complete response (CR) with CT alone or after multimodality treatment, median overall survival is significantly longer than in other patients. In combination with CT, anti-EGFR antibodies appear to be the biological agents of choice in order to reach the best response rate as long as tumors are RAS wild-type.To determine RAS and BRAF mutational status, we have already demonstrated the clinical validity and utility of circulating DNA (ctDNA) analysis using IntPlex® method. Selecting patients with this technology, we aim to investigate response rate and outcomes reached with panitumumab in combination with a standard (mFOLFOX6) or an intensified CT regimen (FOLFIRINOX) in RAS and BRAF wild-type (WT) metastatic patients.

Trial design: This is a national multicentric open-label randomized phase II trial. Key inclusion criteria are age between 18 and 75 years, ECOG PS 0 and 1, untreated synchronous or metachronous metastatic disease deemed unresectable with curative intent, RAS and BRAF WT tumor according to analysis of ctDNA by Intplex® technology. 209 patients will be randomized 2:1 to either FOLFIRINOX-panitumumab ($N = 139$) or mFOLFOX6-panitumumab ($N = 70$)(12 planned cycles in each arm). For each arm, two strata are planned according to disease-extent (non/liver limited disease). Primary endpoint is the CR rate defined as complete disappearance of metastatic lesions and CEA level normalization. It can be reached with CT alone or with a multimodal approach. Secondary endpoints are progression-free and overall survival, secondary resection rate, early tumor shrinkage, depth of response, safety, diagnostic performance of ctDNA analysis. On-treatment, an ancillary study assesses appearance of RAS mutations in ctDNA detected by Intplex® technology. The first patient was enrolled in October 2017 and $>$ 20 sites are planned to recruit patients.

Clinical trial identification: NCT02980510.

Legal entity responsible for the study: UNICANCER GI.

Funding: Amgen.

Disclosure: T. Mazard: Research funding: Roche and Amgen; Honoraria: Amgen, Sanofi, BMS; Travel accommodations, expenses: Amgen. All other authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii205–viii270, 2018
doi:10.1093/annonc/mdy282

GASTROINTESTINAL TUMOURS, NON-COLORECTAL

615O Randomized phase III study of gemcitabine, cisplatin plus S-1 (GCS) versus gemcitabine, cisplatin (GC) for advanced biliary tract cancer (KHBO1401-MITSUBA)

D. Sakai[1], M. Kanai[2], S. Kobayashi[3], H. Eguchi[4], H. Baba[5], S. Seo[6], A. Taketomi[7], T. Takayama[8], H. Yamaue[9], C. Ishioka[10], M. Sho[11], Y. Takeyama[12], J. Fujimoto[13], M. Toyoda[14], J. Shimizu[15], T. Goto[16], K. Yoshimura[17], E. Hatano[13], H. Nagano[18], T. Ioka[19]

[1]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan, [2]Department of Clinical Oncology and Pharmacogenomics, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [3]Department of Surgery, Osaka International Cancer Institute, Osaka, Japan, [4]Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Japan, [5]Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan, [6]Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [7]Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [8]Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan, [9]Second Department of Surgery, Wakayama Medical University, School of Medicine, Wakayama, Japan, [10]Department of Clinical Oncology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan, [11]Department of Surgery, Nara Medical University, Nara, Japan, [12]Department of Surgery, Kinki University Faculty of Medicine, Osaka-sayama, Japan, [13]Department of Surgery, Hyogo College of Medicine, Nishinomiya, Japan, [14]Division of Medical Oncology/Hematology, Kobe University Graduate School of Medicine, Kobe, Japan, [15]Department of Surgery, Osaka Rosai Hospital, Osaka, Japan, [16]Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Asahikawa, Japan, [17]Innovative Clinical Research Center, Kanazawa University, Kanazawa, Japan, [18]Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, [19]Department of Cancer Survey and Gastrointestinal Oncology, Osaka International Cancer Institute, Osaka, Japan

616PD Quality-of-life (QoL) results from RAINFALL: A randomized, double-blind, placebo (PL)-controlled phase III study of cisplatin (Cis) plus capecitabine (Cape) or 5FU with or without ramucirumab (RAM) as first-line therapy for metastatic gastric or gastroesophageal junction (G-GEJ) cancer

I. Chau[1], S-E. Al-Batran[2], A. Luft[3], R.D. Kowalyszyn[4], C.A. Hernandez[5], P. Pfeiffer[6], E. Wojcik[7], G. Bodoky[8], A. Madi[9], B. Brenner[10], F. De Vita[11], G. Folprecht[12], K. Peltola[13], S. Lorenzen[14], C. Denlinger[15], A. Liepa[16], M. Das[16], R. Wei[16], C.S. Fuchs[17]

[1]Department of Medicine, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, UK, [2]GI Oncology, Nordwest-Krankenhaus, Frankfurt am Main, Germany, [3]Department of Thoracic Surgery, St. Petersburg Regional Clinic and Hospital, St. Petersburg, Russian Federation, [4]Oncology, IMO Instituto Multidisciplinario Oncologico, Viedma, Argentina, [5]Clínica Osmo, Oaxaca Site Management Organization SC, Oaxaca, Mexico, [6]Experimental research in Medical Cancer Therapy, Odense University Hospital, Odense, Denmark, [7]Department of Oncology and Chemotherapy, NZOZ Centrum Medyczne HCP, Poznan, Poland, [8]Oncology, St. László Hospital, Budapest, Hungary, [9]The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine, University of Liverpool, Wirral, UK, [10]Oncology, Institute of Oncology, Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petach Tiqva, Israel, [11]Medical Oncology, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy, [12]University Cancer Center, Medical Department I, Universitätsklinikum Dresden, Dresden, Germany, [13]Comprehensive Cancer Centre, Helsinki University Hospital, Helsinki, Finland, [14]Medical Clinic, Heidelberg University Hospital, Munich, Germany, [15]Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [16]Oncology, Eli Lilly and Company, Indianapolis, IN, USA, [17]Yale Cancer Center, Yale University, New Haven, CT, USA

617PD A phase III study of nivolumab (nivo) in previously treated advanced gastric or gastric esophageal junction (G/GEJ) cancer (ATTRACTION-2): Two-years update data

T. Satoh[1], L-T. Chen[2], Y-K. Kang[3], Y. Chao[4], K. Kato[5], H.C. Chung[6], J-S. Chen[7], K. Muro[8], W.K. Kang[9], T. Yoshikawa[10], S.C. Oh[11], T. Tamura[12], K-W. Lee[13], N. Boku[14]

[1]Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Osaka, Japan, [2]Internal Medicine, National Cheng-Kung University Hospital, Tainan, Taiwan, [3]Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [4]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, [5]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [6]Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea, [7]School of Medicine, Chung Gung University, Tao Yuan, Taiwan, [8]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan, [9]Hematology-Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [10]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, [11]Division of Hematology/Oncology, Internal Medicine Department, Korea University Guro Hospital, College of Medicine, Korea University, Seoul, Republic of Korea, [12]Department of Medical Oncology, Kindai University Faculty of Medicine, Osakasayama, Japan, [13]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea, [14]Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

618PD Progression-free survival and recurrence results for AGITG DOCTOR: Pre-op cisplatin, 5FU & DOCetaxel +/-radiotherapy after poor early response to cisplatin & 5FU for resectable oesophageal adenocarcinoma

A.P. Barbour[1], E.T. Walpole[2], G.T. Mai[3], L. Barnes[4], D.I. Watson[5], S.P. Ackland[6], V. Wills[7], J. Martin[8], M. Burge[9], C.S. Karapetis[10], J. Shannon[11], L.M. Nott[12], V. Gebski[13], M. Oostendorp[14], K. Wilson[14], J. Thomas[15], G. Lampe[16], J.R. Zalcberg[17], J. Simes[18], M. Smithers[1]

[1]Department of Surgery, Princess Alexandra Hospital, Woolloongabba, Australia, [2]Department of Medical Oncology, Princess Alexandra Hospital, Woolloongabba, Australia, [3]Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Australia, [4]Biostatistics, NHMRC Clinical Trials Centre, Sydney, Australia, [5]Department of Surgery, Flinders Medical Centre, Adelaide, Australia, [6]Department of Medical Oncology, Calvary Mater Hospital Newcastle, Newcastle, Australia, [7]Department of Surgery, John Hunter Hospital, New Lambton Heights, Australia, [8]Department of Radiation Oncology, Calvary Mater Hospital Newcastle, Newcastle, Australia, [9]Department of Medical Oncology, Royal Brisbane and Women's Hospital, Brisbane, Australia, [10]Department of Medical Oncology, Flinders Centre for Innovation in Cancer, Bedford Park, Australia, [11]Department of Medical Oncology, Nepean Cancer Care Centre, Kingswood, Australia, [12]Department of Medical Oncology, Royal Hobart Hospital, Tasmania, Australia, [13]Biostistics, NHMRC Clinical Trials Centre, Sydney, Australia, [14]Oncology, NHMRC Clinical Trials Centre, Sydney, Australia, [15]Clinical Trials Research, Mater Misericodiae Research Institute, South Brisbane, Australia, [16]Department of Anatomical Pathology, Princess Alexandra Hospital, Woolloongabba, Australia, [17]Department of Medical Oncology, Alfred Hospital, Melbourne, Australia, [18]Clinical Trials Research, The NHMRC Clinical Trials Centre, Camperdown, Australia

620PD **Influence of enteral nutrition on nutritional status, treatment toxicities, and short-term outcomes in esophageal carcinoma patients treated with concurrent chemoradiotherapy: A prospective, multicenter, randomized controlled study**

T. Li[1], J. Lyu[1], G. Zhu[2], J. Li[3], R. Zhao[4], S. Zhu[5], J. Wang[6], L. Xing[7], D. Yang[8], C. Xie[9], L-F. Shen[10], H-P. Shi[11], J. Lang[1]

[1]Department of Radiotherapy, Sichuan Cancer Hospital & Institute, Chengdu, China, [2]Department of Radiotherapy, China-Japan Friendship Hospital, Beijing, China, [3]Department of Radiotherapy, Shanxi Cancer Hospital, Taiyuan, China, [4]Department of Radiotherapy, General Hospital of NingXia Medical University, Yinchuan, China, [5]Department of Radiotherapy, Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [6]Department of Radiotherapy, Henan Cancer Hospital, Zhengzhou, China, [7]Department of Radiotherapy, Shandong Cancer Hospital, Beijing, China, [8]Department of Radiotherapy, First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [9]Department of Radiotherapy, Zhongnan Hospital of Wuhan University, Wuhan, China, [10]Department of Radiotherapy, Xiangya Hospital Central South University, Changsha, China, [11]Surgery, Beijing Center Century Altar Hospital Affiliated to the Capital Medical University, Beijing, China

621PD **Phase II trial of tepotinib vs sorafenib in Asian patients (pts) with advanced hepatocellular carcinoma (HCC)**

B-Y. Ryoo[1], Z. Ren[2], T-Y. Kim[3], H. Pan[4], K-M. Rau[5], H.J. Choi[6], J-W. Park[7], J.H. Kim[8], C-J. Yen[9], B-H. Kim[10], D. Zhou[11], J. Straub[12], C. Zhao[13], S. Qin[14]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Liver Cancer Institute, Department of Hepatic Oncology, Zhongshan Hospital, Fudan University, Shanghai, China, [3]Division of Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea, [4]School of Medicine, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China, [5]Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Taiwan, China, [6]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [7]Center for Liver Cancer, National Cancer Center, Goyang-si, Republic of Korea, [8]Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea, [9]Department of Internal Medicine, National Cheng Kung University Hospital, Taiwan, China, [10]Department of Internal Medicine, Kyung Hee University Hospital, Seoul, Republic of Korea, [11]GBEM, Merck Serono Pharmaceutical R&D Co, Beijing, China, [12]Global Early Development, Merck KGaA, Darmstadt, Germany, [13]Global Clinical Development Oncology, EMD Serono Inc, Billerica, MA, USA, [14]Medical Oncology Department, PLA Cancer Center, Nanjing Bayi Hospital, Nanjing, China

622PD Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated alpha-fetoprotein (AFP) following first-line sorafenib: Patient reported outcome results across two phase III studies (REACH-2 and REACH)

A.X. Zhu[1], R.S. Finn[2], P.R. Galle[3], J.M. Llovet[4], J.F. Blanc[5], T. Okusaka[6], I. Chau[7], D. Cella[8], A. Girvan[9], J. Gable[10], L. Bowman[10], Y. Hsu[11], P.B. Abada[12], M. Kudo[13]

[1]Department of Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA, [2]Los Angeles Medical Center, University of California, Los Angeles, CA, USA, [3]First Department of Internal Medicine, Universitätsmedizin Mainz, Mainz, Germany, [4]Barcelona Clinic Liver Cancer Group, Hospital Clinic Barcelona, Barcelona, Spain, [5]Department of Hepato-Gastroenterology and Medical Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France, [6]Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, [7]Deaprtment of Medicine, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, UK, [8]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA, [9]Global Health Outcomes, Eli Lilly and Company, Indianapolis, IN, USA, [10]Global Patient Outcomes, Eli Lilly and Company, Indianapolis, IN, USA, [11]Statistics, Eli Lilly and Company, New York, NY, USA, [12]Oncology, Eli Lilly, Indianapolis, IN, USA, [13]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan

623PD The nationwide cancer genome screening project in Japan, SCRUM Japan GISCREEN: Efficient identification of cancer genome alterations in advanced biliary tract cancer

C. Morizane[1], Y. Komatsu[2], H. Takahashi[3], M. Ueno[4], J. Furuse[5], T. Kudo[6], S. Itoh[7], S. Shimizu[8], K. Nakamura[9], K. Kamata[10], K. Ohtsubo[11], T. Mizukami[12], Y. Kagawa[13], S. Nomura[14], T. Kuwata[15], S. Fujii[16], W. Okamoto[17], K. Shitara[18], A. Ohtsu[18], T. Yoshino[18]

[1]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, [2]Division of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan, [3]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [4]Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan, [5]Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan, [6]Department of Frontier Science for Cancer and Chemotherapy, Gradeate School of Medicine Osaka University, Suita, Japan, [7]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [8]Department of Gastroenterology, Saitama Cancer Center, Kitaadachigun, Japan, [9]Department of Gastroenterology, Chiba Cancer Center, Chiba, Japan, [10]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Ina, Japan, [11]Division of Medical Oncology, Cancer Research Institute, Kanazawa University, Kanazawa, Japan, [12]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan, [13]Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [14]Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [15]Department of Pathology and Clinical Laboratories, National Cancer Center Hospital East, Kashiwa, Japan, [16]Division of Pathology, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Kashiwa, Japan, [17]Biobank Translational Research Support Section, Translational Research Management Division, Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [18]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

624PD **Preliminary results of a ph2a study to evaluate the clinical efficacy and safety of erdafitinib in Asian patients with biomarker-selected advanced cholangiocarcinoma (CCA)**

Y-Y. Chen[1], J.O. Park[2], W-C. Su[3], D-Y. Oh[4], K-P. Kim[5], Y-H. Feng[6], L. Shen[7], H. Liao[8], J. Nie[9], M. Qing[10], J. Li[11], P. De Porre[12]

[1]Department of Haemato-Oncology, Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung, Taiwan, [2]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [3]Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, [4]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [5]Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [6]Division of Hematology and Oncology, Chi-Mei Medical Center, Tainan, Taiwan, [7]Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China, [8]Statistics & Decision Sciences, Janssen China R&D Center, Shanghai, China, [9]Clinical Pharmacology, Janssen China R&D Center, Beijing, China, [10]Department of Biomarker, Janssen China R&D Center, Shanghai, China, [11]Early Development, Janssen China R&D Center, Shanghai, China, [12]BE Clinical Oncology, Janssen R&D BE, Beerse, Belgium

625PD Pembrolizumab for advanced biliary adenocarcinoma: Results from the multicohort, phase II KEYNOTE-158 study

M. Ueno[1], H.C. Chung[2], A. Nagrial[3], A. Marabelle[4], R.K. Kelley[5], L. Xu[6], J. Mahoney[6], S.K. Pruitt[6], D-Y. Oh[7]

[1]Hepatobiliary and Pancreatic Oncology Division, Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan, [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Medical Oncology Specialists, Blacktown University of Sydney, Sydney, Australia, [4]Département d'Innovation Thérapeutique et d'Essais Précoces, Gustave Roussy, Université Paris-Saclay, Villejuif, France, [5]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA, [6]MRL, Merck & Co., Inc., Kenilworth, NJ, USA, [7]Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

626PD Randomized, phase III trial comparing adjuvant gemcitabine (Gem) versus Gem plus chemoradiation (CCRT) in curatively resected pancreatic ductal adenocarcinoma (PDAC): A Taiwan cooperative oncology group study

H-J. Chang[1], Y-F. Chiu[1], J-S. Chen[2], C-P. Li[3], C-L. Ho[4], Y-M. Shyr[5], W-C. Chiou[6], C-N. Yeh[7], R-K. Hsieh[8], Y-L. Lin[9], Y-W. Tien[10], T-L. Hwang[7], Y-S. Shan[11], L-T. Chen[12]

[1]National Institute of Cancer Research, National Health Research Institutes, Miaoli, Taiwan, [2]Hematology and Oncology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [3]Medical Oncology, Taipei Veterans General Hospital, Taipei City, Taiwan, [4]Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan, [5]Surgery, Taipei Veterans General Hospital, Taipei City, Taiwan, [6]Internal Medicine, Chung Gung University, Tao Yuan, Taiwan, [7]Surgery, Chung Gung University, Tao Yuan, Taiwan, [8]Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan, [9]Oncology, National Taiwan University Hospital, Taipei, Taiwan, [10]Surgery, National Taiwan University Hospital, Taipei, Taiwan, [11]Medical Oncology, National Cheng Kung University, Tainan, Taiwan, [12]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

627P The nationwide cancer genome screening project in Japan, SCRUM-Japan GI-SCREEN: Efficient identification of cancer genome alterations in advanced esophageal cancer

K. Kato[1], T. Kojima[2], H. Saeki[3], H. Hara[4], T. Kajiwara[5], S. Hironaka[6], H. Nakatsumi[7], S. Kadowaki[8], Y. Kagawa[9], T. Esaki[10], T. Moriwaki[11], T. Kobayashi[12], N. Izawa[13], S. Nomura[14], T. Kuwata[15], S. Fujii[16], W. Okamoto[17], K. Shitara[18], A. Ohtsu[18], T. Yoshino[18]

[1]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa-shi, Japan, [3]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [4]Department of Gastroenterology, Saitama Cancer Center, Ina, Japan, [5]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [6]Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan, [7]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [8]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [9]Department of Colorectal Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [10]Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan, [11]Division of Gastroenterology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [12]Department of Medical Oncology, Kyorin University Faculty of Medicine, Mitaka, Japan, [13]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan, [14]Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [15]Department of Pathology and Clinical Laboratories, National Cancer Center Hospital East, Kashiwa, Japan, [16]Division of Pathology, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Kashiwa, Japan, [17]Biobank Translational Research Support Section, Translational Research Management Division, Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [18]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in advanced non-colorectal gastrointestinal (GI) cancer (aNon-CRC), called as the SCRUM-Japan GI-SCREEN. The objective is to evaluate the frequency of cancer genome alterations and to identify patients who are candidate for clinical trial for corresponding targeting agents.

Methods: This study is ongoing with the participation of 23 major cancer centers. Patients with aNon-CRC, including advanced esophageal cancer (aEC), who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from formalin-fixed paraffin embedded (FFPE) tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect mutations, copy number variant (CNV) and fusion genes in a CLIA certified CAP accredited lab. The detected genomic variant data were classified according to genetic drivers of cancer, including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase.

Results: By the end of March 2017, a total of 220 aEC samples were analyzed. The sequence with the OCP was successfully performed in 144 (65.5%). Out of 144 patients, the proportion of sample and histology type is followed; surgical specimen 52.1%, squamous cell carcinoma 92.4%. The frequently detected mutations were TP53(76.4%), NFE2L2 (38.2%), CDKN2A (9.7%), PIK3CA (6.3%), RB1 (5.6%), and CNVs were CCND1 (38.2%), EGFR (7.6%), ATP11B (6.9%), SOX2 (6.9%). ERBB2 amplification was identified in 3 cases (2.1%) and FGFR3-TACC3 fusion was identified in one case (0.7%). Five patients with druggable genomic alterations (PIK3CA($n = 2$), EGFR($n = 2$), FGFR3-TACC fusion($n = 1$)) were enrolled for clinical trials of targeting therapies.

Conclusions: This nationwide screening system is efficient to detect rare gene alterations in aEC. This novel knowledge provides an intriguing background to investigate new target approaches in these patients and to progress precision medicine. Clinical trial information: UMIN000016344 (Non-CRC).

Clinical trial identification: UMIN000016344.

Legal entity responsible for the study: SCRUM JAPAN.

Funding: 15 SCRUM-Japan collaborating pharmaceutical companies, AMED, NCC.

Disclosure: K. Kato: Other: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: AMED; Other: NCC, during the conduct of the study; Grants: Shionogi, Ono Pharmaceuticals, Merck & Co., Merck Serono. T. Kojima: Grants: Shionogi, Ono Pharmaceutical, MSD, Oncolys BioPharma, Astellas, Amgen, BioPharama, outside the submitted work. H. Saeki, H. Hara, S. Kadowaki, Y. Kagawa, S. Hironaka, N. Izawa, S. Fujii, K. Shitara, A. Ohtsu: Other: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: AMED; Other: NCC, during the conduct of the study. T. Kajiwara: Other: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: AMED, other: NCC, during the conduct of the study; Grants and personal fees: Taiho Pharmaceutical Co., Ltd.; Grants and personal fees: Chugai Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., Merck Serono Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Yakult Honsha Co.,Ltd., Medical & Biological Laboratories Co., Ltd., outside the submitted work. H. Nakatsumi: Other: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: AMED; Other: NCC, during the conduct of the study; Personal fees: Ono Pharmaceutical, Bayer Yakuhin, Lilly Japan, outside the submitted work. T. Esaki: Other: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: AMED; Other: NCC, during the conduct of the study; Grants and personal fees: Taiho; Eli Lilly, Eisai, Daiichi-Sankyo, Merck Serono, Nihon Kayaku, Ono; Personal fees: Chugai, Bristol-Myers Squibb, Takeda, Kyowa-Kirin; Grants: DS Pharma, Novartis, AstraZeneca, Boehringer Ingelheim, MSD, Astellas, Bayer, Pfizer, Yakult, outside the submitted work. T. Moriwaki: Grants: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: AMED, during the conduct of the study; Grants and personal fees: Takeda, Chugai, Yakult; Personal fees: Taiho, Sanofi; Grants: MSD Oncology, outside the submitted work. T. Kobayashi: Grants: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: J-Pharma, Taiho, Sumitomo Dainippon, Janssen, Daiichi Sankyo, MSD, Yakult, Takeda, Chugai, Ono, Astellas, Zeria, Novartis, Nanocarrier, Shionogi, Onco Therapy Science, Eli Lilly Japan, Bayer, Bristol-Myers Squibb, Merck Serono, Kyowa Hakko Kirin, Eisai, Mochida, Baxalta, Sanofi, during the conduct of the study. S. Nomura: Other: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: AMED; Other: NCC, during the conduct of the study; Personal fees: Taiho, outside the submitted work. T. Kuwata: Other: 15 SCRUM-Japan collaborating pharmaceutical companies; Grants: AMED; Other: NCC, during the conduct of the study; Personal fees: Chugai Pharm; Grants and personal fees: Daiichi-Sankyo, outside the submitted work. W. Okamoto: Grants: MSD, outside the submitted work. T. Yoshino: Grants: MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co., Ltd; Grants and personal fees: Sanofi K.K., Chugai Pharmaceutical Co., Ltd; Personal fees: Eli Lilly Japan K.K, Merck Serono Co., Ltd., outside the submitted work.

628P Signal transduction pathway activity during neoadjuvant treatment in esophageal adenocarcinomas

A. Creemers[1], S.L. Meijer[2], M. Stoffels[3], G.K.J. Hooijer[2], L. Holtzer[3], H. van Ooijen[3], A. Van Brussel[3], E.M.G. Aussems-Custers[3], M. van Berge Henegouwen[4], M.C.C.M. Hulshof[5], K.K. Krishnadath[6], A. van de Stolpe[7], M.F. Bijlsma[8], H.W.M. van Laarhoven[1]

[1]Medical Oncology, Academic Medical Center (AMC), Amsterdam, Netherlands, [2]Pathology, Academic Medical Center (AMC), Amsterdam, Netherlands, [3]Precision and Decentralized Diagnostics, Philips Research, Eindhoven, Netherlands, [4]Surgery, Academic Medical Center, Amsterdam, Netherlands, [5]Radiotherapy, Academic Medical Center (AMC), Amsterdam, Netherlands, [6]Gastroenterology, Academic Medical Center (AMC), Amsterdam, Netherlands, [7]Research, Philips, Eindhoven, Netherlands, [8]LEXOR, Academic Medical Center (AMC), Amsterdam, Netherlands

Background: Little is known about signaling pathway activity in esophageal adenocarcinomas. Using a new methodology we have delineated the activity of key pathways involved in tumor growth during neoadjuvant treatment. The aim is to use this knowledge to personalize, and thereby improve, treatment strategies.

Methods: We included all patients with esophageal adenocarcinomas between 2004 and May 2013 in the AMC. Paired tumor samples were obtained before start of neoadjuvant chemoradiation therapy according to the CROSS regimen and at surgical resection of the esophagus. Using a custom-built device, digital annotations of whole slide H&E scans were transferred to a hematoxylin-stained slide, which was subsequently deparaffinized. Marked tumor areas were scraped for RNA extraction and qPCR. qPCR data were subjected to stringent QC prior to determining the signaling pathway activity scores of the AR-, ER-, FOXO/PI3K-, HH-, TGF-β- and WNT pathway, using a combined mRNA-Bayesian model-based method (Verhaegh et al, Cancer Res, 2014). Pathway activity scores were correlated to pathological response to treatment (Mandard score).

Results: Based on a test set of esophageal tumor tissue samples, we determined that tumor areas of $\geq 2mm^2$ were eligible for RNA isolation and pathway activity analysis. We provide a analysis of 288 currently processed samples. FOXO activity was significantly higher in post-treatment resection specimen compared to matched pre-treatment biopsies ($p < 0.001$). Patients with high FOXO activity in post-treatment resection specimen showed better response to treatment ($p = 0.019$).

Conclusions: The assessment of pathway activity is feasible on small amounts of tumor. Marked dynamics in FOXO activity are observed during nCRT in esophageal adenocarcinomas. Patients with high FOXO activity post-nCRT show better response to treatment. An active PI3K pathway blocks FOXO transcriptional activity. To increase FOXO transcriptional activity, patients might benefit from the addition of PI3K-inhibitors to the nCRT regimen.

Legal entity responsible for the study: AMC.

Funding: Royal Philips.

Disclosure: M. Stoffels, L. Holtzer, A. Van Brussel: Employee: Royal Philips; Research funding: Royal Philips. H. van Ooijen: Employee: Royal Philips; Patents, royalties or other intellectual property: Royal Philips. E.M.G. Aussems-Custers. A. van de Stolpe: Employee, Funded: Royal Philips. M. van Berge Henegouwen: Research funding: Olympus. M.F. Bijlsma: Research funding: Celgene. H.W.M. van Laarhoven: Consultant: Philips, Celgene, Lilly, Nordic; Unrestricted research funding: Philips, Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Roche. All other authors have declared no conflicts of interest.

629P Hypoxia gene expression defines a poor prognostic sub-group in oesophageal adenocarcinoma

R.V. Douglas, C. McKinney, L. Stevenson, L. Cairns, R.D. Kennedy, J.K. Blayney, R.C. Turkington

Queen's University Belfast, Health Science Building, Belfast, UK

Background: The incidence of Oesophageal Adenocarcinoma (OAC) has risen 6-fold in the western world in the last forty years but survival is poor. Increased molecular understanding of this heterogeneous disease is needed to improve treatment selection and develop novel therapies. This study uses gene expression data to perform unbiased molecular subtyping and identify prognostic subgroups in OAC.

Methods: Transcriptional profiling of 274 treatment naïve OAC biopsies was performed using the Almac Diagnostics Xcel array™. All patients received platinum-based neo-adjuvant chemotherapy prior to surgical resection at four United Kingdom centres between 2004-2012. Iterative semi-supervised clustering based on gene expression level variability was performed followed by functional enrichment using DAVID. Cluster membership was assessed for independence of known prognostic factors using Cox proportional hazards regression for relapse-free (RFS) and overall survival (OS). Clustering was repeated with a published 51-gene hypoxia signature with validation in the TGCA OAC ($n = 65$) and oesophageal squamous cell carcinoma ($n = 45$) cohorts.

Results: Patients were clustered into two groups with significantly different RFS ($HR = 0.54$, $p = 0.05$) and OS ($HR = 0.52$, $p = 0.04$). There were no significant differences in known prognostic factors such as pathological response, lymphovascular invasion and resection margin. Pathway analysis revealed the PI3K-AKT, p53, Tumour Necrosis Factor and Hypoxia Inducible Factor 1 (HIF-1) signalling pathway to be upregulated in the poor prognostic group. To further investigate the role of the HIF-1 pathway, a hypoxia 51-gene signature was applied. Patients were stratified into hypoxia low and high groups with improved RFS (HR 0.64, 95% CI 0.42-0.97; $p = 0.04$) and OS (HR 0.67, 95% CI 0.44-1.02; $p = 0.06$) in the hypoxia-low group. Increased OS for the hypoxia-low group was also observed in the TCGA cohort (HR 0.49, 95% CI 0.24-0.97; $p = 0.04$). There was a significant association between membership of the poor prognostic and hypoxia-low cluster groups ($p < 0.001$).

Conclusions: Molecular stratification and application of a hypoxia gene signature identifies a poor prognostic group of OAC patients characterised by upregulation of hypoxia signalling.

Legal entity responsible for the study: Queen's University Belfast.

Funding: Northern Ireland Health and Social Care Research and Development Division.

Disclosure: R.D. Kennedy: Global VP of Biomarker Development for Almac Diagnostics and have patent declarations. All other authors have declared no conflicts of interest.

630P Neoadjuvant radio-chemotherapy for esophageal cancer: A multicenter European study comparing paclitaxel/carboplatin, 5FU/cisplatin and FOLFOX

P. Allemann[1], S. Mantziari[1], M. Winiker[1], A.D. Wagner[2], A. Digklia[2], M. van Berge Henegouwen[3], S.S. Gisbertz[3], A. Slaman[3], R. van Hillegersberg[4], J.P. Ruurda[4], H. Brenkman[4], M. Nilsson[5], K. Satoshi[5], G. Piessen[6], D. Collet[7], C. Gronnier[7], N. Carrere[8], A. Marinho[8], N. Demartines[1], M. Schafer[1]

[1]Visceral Surgery, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, [2]Medical Oncology, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, [3]Surgery, Academic Medical Center, Amsterdam, Netherlands, [4]Surgery, University Medical Center Utrecht, Utrecht, Netherlands, [5]Surgical Gastroenterology, Karolinska Institute, Huddinge, Sweden, [6]Chirurgie Digestive, C.H.U. Claude Huriez, Lille, France, [7]Digestive Surgery, University Hospital Bordeaux, Bordeaux, France, [8]Oncological Surgery, CHU Toulouse, Toulouse, France

Background: Different regimens of neoadjuvant radio-chemotherapy are concurrently used prior to surgery for resectable, locally advanced esophageal cancer. Comparative data are scarce and to some extent conflicting, regarding toxicity and long-term outcomes when treating different subtypes. This study aimed to assess clinical tolerances and long-term survival of three commonly used combinations of neoadjuvant therapies.

Methods: Patients operated from January 2004 to December 2014 who underwent neoadjuvant radio-chemotherapy with Paclitaxel/Carboplatin, or 5FU/Cisplatin, or FOLFOX for adenocarcinoma or squamous cell carcinoma were included. Seven European centers colligated data of 1188 patients. Cases with missing data ($n = 147$) or death <30 days postoperative ($n = 51$) were excluded. The primary outcome was the overall survival; secondary outcomes were the completeness and toxicity of neoadjuvant treatment, the disease free survival and the recurrence timing and pattern.

Results: Of the 990 eligible patients, Paclitaxel/Carboplatin was used in 598 patients (60%), 5FU/Cisplatin in 331 (33%) and Folfox in 61 (7%). The groups received a median radiation dose of 41.4 Gy, 45 Gy and 45 Gy ($p = 0.65$). Adenocarcinoma was the most frequent subtype (69%). No differences were detected in median overall survival (41 months, 34 months and 46 months, $p = 0.251$). Comparing the overall survival of the three regimens for adenocarcinoma vs squamous cell carcinoma, no difference was observed as well. There were no differences in chemotherapy-related morbidity (13%, 11% and 9%, $p = 0.57$), chemotherapy completeness (85%, 88% and 90%, $p = 0.542$) and radiotherapy completeness (98%, 99% and 96%, $p = 0.9$) between the three groups. Recurrence rates were similar (42%, 46% and 34%, $p = 0.169$), but median disease-free survival was improved in the 5FU/Cisplatin group (10 months, 18 months and 13 months, $p < 0.001$).

Conclusions: The overall survival did not differ between different neoadjuvant treatments. Moreover, no advantage of one regimen for specific cancer subtypes was observed. At most, a modest clinical advantage of 5-FU/Cisplatin was observed for disease-free survival.

Clinical trial identification: Research Registry number: 2157.

Legal entity responsible for the study: NeoTEC study group, Lausanne University Hospital, Lausanne, Switzerland.

Funding: Has not received any funding.

Disclosure: A.D. Wagner: Research funding: Roche; Consultant or advisory: Lilly, Celgene, Merck, Bristol-Myers Squibb, Pfizer, Servier Shire. M. van Berge Henegouwen: Medtronic, Olympus research grant (other studies). All other authors have declared no conflicts of interest.

631P Neoadjuvant therapy for esophageal adenocarcinoma: A propensity score-matched comparison of paclitaxel and carboplatin chemoradiotherapy with cisplatin and 5-fluoruracil-based chemo- or chemoradiotherapy

A.P. Barbour[1], S. Brosda[1], B. Wijnhoven[2], S. van Hootgem[2], J.J.B. Lanschot[3], S. Barbour[4], S. Lagarde[2], L. Krause[1], D. Pryor[5], J. Thomas[6], E.T. Walpole[7], A. van der Gaast[8], M. Smithers[6]

[1]Diamantina Institute, The University of Queensland, Woolloongabba, Australia, [2]Department of Surgery, Erasmus Medical Center, Rotterdam, Netherlands, [3]Department of General Surgery, Erasmus Medical Center, Rotterdam, Netherlands, [4]Radiation Oncology Centre, Greenslopes Private Hospital, Greenslopes, Australia, [5]Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Australia, [6]Department of Surgery, Princess Alexandra Hospital, Woolloongabba, Australia, [7]Medical Oncology, Princess Alexandra Hospital, Woolloongabba, Australia, [8]Medical Oncology, Erasmus University Medical Center, Rotterdam, Netherlands

Background: Multimodality treatments of patients with esophageal adenocarcinoma (EAC) improve survival, but the optimal treatment strategy remains undetermined. This study aimed to compare response, local recurrence and survival outcomes in patients undergoing neoadjuvant paclitaxel and carboplatin chemoradiotherapy with 41Gy (CROSS) with neoadjuvant cisplatin and 5-fluoruracil (CF)-based chemoradiotherapy with 45Gy (CFRT) or CF chemotherapy followed by oesophagectomy for EAC.

Methods: Patients who underwent CROSS, CFRT or CF followed by surgery for EAC were identified from two single institution prospective databases from Australia and the Netherlands (2000-2018) and included in this study. After pair-wise propensity score matching (caliper 0.2) using pre-treatment variables (age, gender, year of treatment, tumor length and site, and clinical T stage), we compared the impact of the treatments on pathological outcomes, patterns of recurrence and overall survival.

Results: Of the 637 eligible patients, 429 patients were analysed following propensity score matching. This resulted in 143 patients in each group with median follow up 61 months. CROSS and CFRT demonstrated significantly higher pathological complete response rates ($p < 0.001$), lower ypT stage ($p < 0.001$) and lower ypN stage ($p < 0.001$) compared with CF. There were no statistically significant differences in 5-year local recurrence-free survival between the three treatment groups: CROSS 76% (95%CI: 68-85); CFRT 71% (95%CI: 64-81); and CF 66% (95%CI: 65-76). Similarly, there were no significant differences in 5-year overall survival rates between groups: CROSS 52% (95%CI: 44-62); CFRT 40% (95%CI: 32-49); and 46% (95%CI: 38-55)($p = 0.18$, log rank). Median overall survival for CROSS was 69 months (95%CI: 47-139), for CFRT 32 months (95%CI: 26-52), and for CF 47 months (95%CI: 33-66) ($p = 0.33$, log rank).

Conclusions: In this study, there were higher pathological response rates and lower pathological stage associated with CROSS and CFRT. However, overall survival and local recurrence was similar for CROSS, CF and CFRT.

Legal entity responsible for the study: The University of Queensland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

632P Induction chemotherapy for locally advanced esophageal cancer

G. Harada, R.R.D.C.C. Bonadio, F.C.C. de Araújo, C.R. Victor, F.R. Takeda, R.A.A. Sallum, U.R. Junior, I. Cecconello, T.B. de Castria

Medical Oncology, ICESP - Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

Background: The concurrent chemoradiotherapy followed by surgery is the standard treatment for locally advanced esophageal cancer (LAEC) and the role of induction chemotherapy (IC) remains unclear. We aimed to study if the addition of IC to standard treatment increases the rate of pathologic complete response (pCR).

Methods: We assembled a retrospective analysis of patients (pts) diagnosed with LAEC and treated with preoperative chemoradiotherapy followed by esophagectomy (CRT+S), preceded or not by IC, between 2009 and 2017. Patients' characteristics, tumor variables and treatment outcomes were evaluated. Kaplan-Meier method was used to estimate overall survival and Cox proportional hazard model to evaluate prognostic factors.

Results: 103 pts were studied, with a median age of 62 years (range 37-84). Seventy-five pts (73%) were male, 67 (65%) had squamous cell carcinoma and 31 (30%) adenocarcinoma. Forty-three pts (41,7%) received IC followed by CRT+S (IC+CRT+S). The most frequent IC consisted of paclitaxel and platinum (38 pts – 90%) and the median number of cycles was 2 (range 1-6). All pts received CRT+S. Concurrent chemotherapy was a combination of paclitaxel and platinum in 94 pts (91%). The median radiation dose was 41.4 Gy (range 39.6-50.4). There was no statistically significant difference in pCR between the IC group and the standard CRT+S group. The pCR was 41.9% and 46.7% in the IC+CRT+S and CRT+S group ($p = 0,628$), respectively. In the multivariate analysis, pCR was an independent prognostic factor for failure free survival (FFS) (HR 0.35, 95% CI 0.14-0.85, $p = 0.021$), but not for overall survival (OS) ($p = 0.863$). The factor that significantly affected OS in the multivariate analysis was positive lymph node (HR 5.9, 95% CI 1.23-28.27, $p = 0.026$). IC, histology, histologic grade, radiation dose, T stage were not identified as independent prognostic factors for neither OS nor FFS.

Conclusions: Our data suggest that the addition of IC to standard CRT+S does not increase the pCR rate in LAEC. No difference in OS was observed between pts that received or not IC. Regardless of the treatment received, pts achieving a pCR presented improved FFS.

Legal entity responsible for the study: Guilherme Harada.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

633P The role of comprehensive evaluation for clinical complete response in predicting pathologic complete response in patients treated with neoadjuvant chemoradiation for esophageal squamous cell carcinoma (ESCC)

H-S. Im[1], J. Kang[2], Y-H. Kim[3], H.R. Kim[3], J.H. Kim[4], H-Y. Jung[5], G-H. Lee[5], H.J. Song[5], D.H. Kim[5], K.D. Choi[5], J.H. Lee[5], J.Y. Ahn[5], J-S. Ryu[6], K-J. Cho[7], S-B. Kim[8], S.R. Park[8]

[1]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Oncology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [3]Department of Thoracic Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [4]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [5]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [6]Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [7]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [8]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Neoadjuvant chemoradiation (nCRT) followed by surgery is the preferred treatment for locally advanced ESCC. But a recent trial suggested close observation might be a reasonable option in patients achieving clinical complete response (CR) to nCRT. For this strategy, accurate clinical assessment for predicting pathologic CR (pCR) is essential. In NCCN guidelines PET/CT is recommend as response assessment, whereas endoscopy is optional after nCRT.

Methods: In 234 patients who received nCRT (46–50.4Gy) plus surgery for locally advanced ESCC at Asan Medical Center from 2007 to 2014, the performance of endoscopy and PET/CT which were done 4-8 weeks after nCRT for predicting pCR was evaluated. Metabolic CR (mCR) was defined as complete resolution of FDG uptake within all lesions, making them indistinguishable from surrounding tissue, and endoscopic CR (eCR) as no residual mucosal lesions except for scar change.

Results: pCR (ypT0N0) was achieved in 108 patients (46.2%), and ypT0N+ in 17 (7.3%). Among patients who underwent PET/CT ($n = 231$), mCR was obtained in 102 (44.2%), and non-mCR in 81 (35.1%), whereas metabolic response could not be assessed due to diffuse esophagitis in 48 (20.8%). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of mCR for pCR was 56.6%, 46.4%, 58.8%, and 71.6%, respectively. Among patients who underwent endoscopy ($n = 229$), eCR was obtained in 42 (18.3%), and the sensitivity, specificity, PPV, and NPV of eCR for pCR only in primary tumor site (ypT0N+/-) was 29.5%, 94.4%, 85.7%, and 54.0%, respectively. When adding endoscopic response to metabolic response, the sensitivity, specificity, PPV, and NPV of clinical CR for pCR was 27.9%, 94.3%, 80.6%, and 60.5%, respectively, and the positive likelihood ratio for pCR was 4.9 (95% CI 2.2–10.6).

Conclusions: The addition of endoscopic evaluation to metabolic response after nCRT improved specificity and PPV for pCR compared to metabolic response alone, which could help in applying surveillance strategy without immediate surgery in patients achieving clinical CR after nCRT for ESCC.

Legal entity responsible for the study: Asan Medical Center.

Funding: Asan Medical Center.

Disclosure: All authors have declared no conflicts of interest.

634P Prognostic impact of inflammation-based scores in esophageal cancer patients achieving pathologic complete response after neoadjuvant chemoradiotherapy followed by surgery

J. Kang[1], H-S. Im[2], Y-H. Kim[3], H.R. Kim[3], J.H. Kim[4], H-Y. Jung[5], G-H. Lee[5], H.J. Song[5], D.H. Kim[5], K.D. Choi[5], J.H. Lee[5], J.Y. Ahn[5], J-S. Ryu[6], K-J. Cho[7], S-B. Kim[8], S.R. Park[2]

[1]Division of Hematology/Oncology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Department of Oncology, Asan Medical Center, Seoul, Republic of Korea, [3]Department of Thoracic Surgery, Asan Medical Center, Seoul, Republic of Korea, [4]Department of Radiation Oncology, Asan Medical Center, Seoul, Republic of Korea, [5]Department of Gastroenterology, Asan Medical Center, Seoul, Republic of Korea, [6]Department of Nuclear Medicine, Asan Medical Center, Seoul, Republic of Korea, [7]Department of Pathology, Asan Medical Center, Seoul, Republic of Korea, [8]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Patients achieving pathologic complete response (pCR) after neoadjuvant chemoradiotherapy (NCRT) followed by surgery for locally advanced esophageal squamous cell carcinoma (ESCC) have a favorable prognosis. However, about 20–30% of the patients still suffer recurrences, and there are few studies evaluating prognostic factors in these patients. This retrospective analysis was performed to identify the prognostic factors in ESCC patients with pCR after NCRT followed by surgery.

Methods: Among 234 patients with ESCC who were treated with NCRT followed by surgery between 2007 and 2014 at Asan Medical Center in South Korea, 108 patients who achieved pCR ($n = 108$, 46.2%) were included in this analysis. Clinical, pathologic, treatment, and laboratory factors including inflammation-based scores such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and modified Glasgow prognostic score (mGPS) were included in univariate and multivariate analysis using the Cox-proportional hazards model.

Results: With the median follow-up duration of 84.5 months (range, 1.3–139.9), 10 patients (9.2%) had recurrent disease. The 5-year overall survival (OS) and relapse-free survival (RFS) rates were 71.9% and 71.5%, respectively. In multivariate analysis, advanced clinical T stage (T3/4 vs.1/2: HR = 2.7; 95% CI, 1.37–5.16; $p = 0.004$), higher post-NCRT PLR ($\geq$167.4: HR = 2.0; 95% CI, 1.01–3.78; $p = 0.048$), and age $\geq$65 years (HR = 2.4; 95% CI, 1.25–4.71; $p = 0.009$) were independent poor prognostic factors for OS. Advanced clinical T stage (T3/4 vs.1/2: HR = 2.7; 95% CI, 1.31–5.65; $p = 0.007$), higher post-NCRT PLR ($\geq$167.4: HR = 2.1; 95% CI, 1.00–4.20; $p = 0.049$), and age $\geq$65 years (HR = 2.1; 95% CI, 1.02–4.21; $p = 0.044$) were also significant adverse prognostic factors for RFS. The 5-year OS rates according to number of risk factors (0/1 vs. 2 vs. 3) were 84.9%, 59.1%, and 43.6%, respectively.

Conclusions: Post-NCRT PLR together with age and pretreatment clinical T stage might be useful in identifying patients with a poor prognosis even after achieving pCR with NCRT plus surgery.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

635P Association of sarcopenia with dose-limiting toxicities and survival in oesophageal adenocarcinoma treated with neoadjuvant chemotherapy

J.M.J. Weaver[1], C. Cipriano[1], A. McWilliam[2], Z. Kordatou[3], M. Abraham[3], T. Germetaki[4], G. Papaxoinis[5], W. Mansoor[1]

[1]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [2]Department of Cancer Sciences, University of Manchester, Manchester, UK, [3]Nutrition & Dietetics, The Christie NHS Foundation Trust, Manchester, UK, [4]Medical & Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [5]Medical Oncology, Laiko General Hospital of Athens, Athens, Greece

Background: Despite several recent studies the association of sarcopenia with outcomes in oesophageal adenocarcinoma (OAC); in particular overall survival and dose limiting toxicity (DLT), remains unclear likely due to the heterogeneity of the populations included. There is therefore a need for studies of sarcopenia utilising large homogenously treated cohorts.

Methods: We retrospectively collected data on DLT from 197 OAC patients treated with neoadjuvant chemotherapy at a single institution between August 2009 and September 2016. CT scans were visualised using the Worldmatch software package skeletal muscle at the L3 level was manually segmented. Published sex-specific cut-offs for skeletal muscle index (SMI) were used to classify patients as sarcopenic. Patients were further classified as sarcopenically obese if they had both sarcopenia and a BMI $\geq$ 30. Statistical analysis was completed using RStudio, Kaplan-Meier curves were plotted and differences in survival between sarcopenic and non-sarcopenic patients was analysed using a cox proportional hazards model. The Chi-squared test was used to analyse differences in toxicity between groups.

Results: Sarcopenia was observed in 81% of patients. There was no correlation with age and SMI ($r = -0.1$). Average SMI was greater in men than women (44.2 cm^2/m^2 versus 33.7 cm^2/m^2, male versus female). Sarcopenic patients had a worse overall survival than non-sarcopenic patients (median OS, 28.0 months versus 19.3 months, $p = 0.0225$). In contrast patients with sarcopenic obesity showed no difference in OS, in keeping with

previous data. There was no significant difference between rates of DLT in patients with sarcopenia and those without (16.4% and 13.2% respectively, $p > 0.05$). There was a non-significant trend towards increasing rates of completion of 6 cycles of perioperative chemotherapy in non-sarcopenic patients (47% Vs 37%).

Conclusions: In our large homogenously treated cohort of patients undergoing neoadjuvant chemotherapy for OAC sarcopenia was associated with poorer OS confirming recent studies of smaller mixed populations.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

636P Survival benefit of re-irradiation in esophageal cancer patients with locoregional recurrence: A propensity score matched analysis

K. Xiangquan, Y. Huang, B. Zheng, Q. Zhuang, X. Zhang, L. Tang, J. Li, J. Wu

Department of Radiation Oncology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, Fujian, China

Background: To investigate the prognostic factors of esophageal squamous cell carcinoma (ESCC) with locoregional recurrence and to explore whether re-irradiation(re-RT) improves outcomes.

Methods: We retrospectively analyzed 87 ESCC patients with locoregional recurrence. All patients received radiotherapy in the initial treatment. The failure patterns were classified into regional lymph node recurrence only (LN) and local failure with/without regional lymph node recurrence (LF). A propensity score model was utilized to balance baseline covariates: RT group ($n = 33$) comprising patients who underwent re-RT and non-RT group ($n = 33$) without re-RT. Outcomes measure including overall survival (OS) and toxicities.

Results: Median follow-up was 87 months (range 2-206). Of the 87 included patients, 39 received re-RT. Failure pattern and re-RT were the independent prognostic factors of OS ($P = 0.040$ and 0.015) by Cox multivariate analysis. Further subgroup analysis did not demonstrate a survival benefit with re-RT combined with chemotherapy as compared to re-RT alone ($P = 0.70$). After propensity score matching, no differences were found between two groups' characteristics by Chi-square tests. Similarly, Cox model demonstrated failure pattern and re-RT as the prognostic factors, with hazard ratio (HR) 0.319 (95% confidence interval [CI] 0.117–0.869, $P = 0.025$) and HR 0.375 (95% CI 0.201–0.701, $P = 0.002$) in the matched chort. Also, significant differences in OS ($P = 0.004$) were presented in failure pattern (LN vs. LF, $P = 0.004$) and re-RT (RT vs. non-RT, $P < 0.001$). In terms of toxicities, there were 9.09% and 3.03% of tracheoesophageal fistulas, 15.15% and 3.03% of pericardial/pleural effusion in the RT and non-RT group, respectively ($P > 0.05$). The RT group had a higher rate of radiation pneumonitis (24.24% vs. 6.06%, $P = 0.039$), but no pneumonia related deaths occurred.

Conclusions: Re-irradiation might improve the long-term prognosis of locoregional recurrent ESCC with a radiation history. Though the radiation pneumonitis is more frequent, re-irradiation is well tolerated.

Legal entity responsible for the study: Junxin Wu.

Funding: National Clinical Key Specialty Construction Program.

Disclosure: All authors have declared no conflicts of interest.

637P Magnetic resonance imaging in oesophageal (oes) cancer: Results from the STO3 MRI substudy

M. Davidson[1], M. Nankivell[2], D. Cunningham[1], N. Starling[1], D-M. Koh[3], G. Brown[3], W. Allum[1], A. Wotherspoon[4], E. Smyth[1], L. Ly[2], N. Kleovoulou[2], R. Langley[2], A. Riddell[3]

[1]Gastrointestinal Research, Royal Marsden Hospital NHS Foundation Trust, London, UK, [2]Medical Research Council Clinical Trials Unit at UCL, University College London, London, UK, [3]Radiology Department, Royal Marsden Hospital NHS Foundation Trust, London, UK, [4]Histopathology Department, Royal Marsden Hospital NHS Foundation Trust, London, UK

Background: A key aim of neoadjuvant therapy in oes cancer is to increase the chance of complete R0 resection. Microscopic residual disease after surgery is reported in around 30% cases, mainly involving the circumferential resection margin (CRM), with current staging techniques unable to accurately identify pts at risk of residual tumour at the CRM. Previous small single site studies have shown that high res T2-weighted MRI achieves detailed imaging of oes anatomy and has the potential to serve as an additional non-invasive staging modality.

Methods: As part of the UK STO3 trial pts from participating centres with operable lower oes and type I/II OGJ adenoca were enrolled in the MRI observational sub-study. All pts underwent standard staging investigations, with additional MRI scans pre and post neoadjuvant chemo, followed by surgery. MRI parameters were consistent across sites and included CRM, T/N staging and apparent diffusion coefficient (ADC) assessment. Scans were reviewed locally and centrally to assess interobserver variability. Chemo response and association with pathological outcome were recorded.

Results: Between Aug 2011 and Mar 2015 57 pts were recruited from 11 sites. Of these 32 had matched pre and post chemo scans and 28 had corresponding pathological outcome data available. Negative CRM status was correctly identified on post chemo MRI in 17/19 (89%) cases; positive CRM in 3/9 (33%) cases. When compared to pathological staging there was concordance between MRI T staging in 36% cases, with overstaging in 43% and understaging in 21%. Concordance between MRI and CT for T/N staging was 66% and 77% respectively. Tumour size reductions and ADC increases were observed during chemo. Local sites predicted significantly more CRM involvement than central review (48 vs 19%).

Conclusions: This represents the first prospective, multi-centre, national trial of MRI in oes cancer and is the first report of interobserver variability between treatment centres. Although limited by small numbers, MRI showed promising specificity to identify negative surgical margins and reasonable correlation with pathological outcome. Discrepancy between local and central review was observed, suggesting that more standardised methods of MRI assessment in oes cancer are required.

Clinical trial identification: EudraCT: 2006-000811-12.

Legal entity responsible for the study: Medical Research Council, UK.

Funding: Cancer Research UK, Clinical Trials Awards Advisory Committee.

Disclosure: D. Cunningham: Research funding: Amgen, AstraZeneca, Bayer, Celgene, Merck-Serono, Medimmune, Merrimack, Novartis, Roche, Sanofi. N. Starling: Research funding: AZ, BMS, Merck; Honoraria: AZ. All other authors have declared no conflicts of interest.

638P Prognostic value of pretreatment diffusion weighted magnetic resonance imaging based texture in concurrent chemo-radiotherapy of esophageal squamous cell cancer

B. Li[1], Z. Li[2], C. Han[3]

[1]Radiation Oncology, Cancer Hospital and Institute of Shandong, Jinan, China, [2]Radiation Oncology, Shandong Cancer Hospital, Jinan, China, [3]Radiation Oncology, Hebe Cancer Hospital, Shijiazhuang, China

Background: The aim of this study was to explore the prognostic value of diffusion-weighted magnetic resonance imaging (DWI) 3D texture features in esophageal squamous cell carcinoma (ESCC) patients undergoing concurrent chemo-radiotherapy (CRT).

Methods: We prospectively enrolled 82 cases with ESCC into a cohort study which underwent DWI before CRT. All MR examinations included axial T2WI, T1WI and diffusion-weighted sequences ($b = 0$, $b = 600$ s/mm^2). Two groups of tumor features were examined: (1) clinical features (eg, TNM stage, age and gender) and demographics; (2) spatial texture features of apparent diffusion coefficient (ADC), which characterize tumor intensity range, spatial patterns and distribution and associated changes resulting from CRT. A reproducible and no redundant feature set was statistically filtered and validated. The prognostic value of each parameter for overall survival was investigated using Kaplan-Meier and Cox regression models for univariate and multivariate analyses, respectively.

Results: Both univariate and multivariate Cox model analyses showed that the radiation dose; IHIST_energy, m_contrast_1, m_clustershade_2, Diff_ClusetrTendency_2, Diff_homogeneity_2, m_Inversevariance_2, high intensity small zone emphasis (HISE) and low intensity large zone emphasis (LILE) associated significantly with survival. Our study showed seven 3D texture parameters extracted from ADC maps could distinguish high, median and low risk groups (Log-rank $c^2 = 9.7$, $P = 0.00773$).

Conclusions: The ADC 3D texture features can be useful biomarkers to predict the survival of ESCC patients who received CRT. The combination of DWI texture and conventional prognostic factors can be used to generate robust predictive models for survival rate.

Legal entity responsible for the study: Shandong Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

639P Volume reduction rate of the primary tumor of esophageal squamous cell carcinoma after neoadjuvant chemotherapy: Could this measurement be a surrogate end point for survival before surgery?

S. Nagasawa[1], T. Ogata[1], K. Hara[1], Y. Shimoda[1], M. Nakazono[1], Y. Kumazu[1], T. Hayashi[1], T. Yamada[1], Y. Rino[2], M. Masuda[2], T. Yoshikawa[3], T. Oshima[1]

[1]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, [2]Surgery, Yokohama City University, Yokohama, Japan, [3]Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan

Background: Neoadjuvant chemotherapy (NAC) followed by surgery is regarded as a standard treatment for Stage II and III resectable thoracic esophageal squamous cell carcinoma (ESCC) in Japan. In general, therapeutic effect of NAC against the primary tumor is estimated microscopically with resected specimen after surgery. Then, this microscopic assessment is validated as surrogating survival. However, as this assessment needs resected specimen, therapeutic effect could not be evaluated before surgery. The aim of this study was to investigate whether therapeutic effects in imaging findings obtained by calculating tumor volume reduction could be a surrogating survival or not.

Methods: This retrospective study examined the patients who fulfilled the following criteria; (1) thoracic ESCC, (2) underwent esophagectomy following NAC between

January 2011 and December 2015, and (3) clinical Stage II or III. Tumor volume was calculated by multiplying length and thickness in the lateral view of esophagography. The reduction rate of tumor volume was calculated as follow; (pre NAC tumor volume – post NAC tumor volume) / pre NAC tumor volume . The cut off value of volume reduction ratio was determined as 50%, 60%, and 70% respectively. Patients were divided into an effective group and an ineffective group in each cut off value, and examined relationship with 3-year relapse-free survival (3yRFS). The hazard ratio (HR) for 3yRFS in each cut off value was estimated for selecting optimal cut off surrogating survival.

Results: In total, 93 patients were included in this study. 3yRFS of the effective group / ineffective group and HR of ineffective group for effective group in each cut off were 70.2% / 39.4% (HR = 0.469 [95% CI = 0.253 - 0.868], p = 0.0136) in 50%, 73.5% / 40.3% (HR = 0.418 [95% CI = 0.216 - 0.809] , p = 0.00752) in 60%, and 80.4% / 42.8% (HR = 0.427 [95% CI = 0.199 - 0.916], p = 0.0243) in 70%.

Conclusions: Therapeutic effect of NAC evaluated by imaging finding was reflected in 3-year relapse free survival. Especially for optimal surrogate of 3yRFS, the optimal cut off point was 60% volume reduction after NAC.

Legal entity responsible for the study: Kanagawa Cancer Center.

Funding: Has not received any funding.

Disclosure: T. Hayashi: Personal fee: MDS, Chugai, Ono. T. Yoshikawa: Personal fee: MDS, Chugai, Ono, Taiho. All other authors have declared no conflicts of interest.

640P A model using computed tomography-based compactness to predict prognosis after multimodal treatment for esophageal squamous cell carcinoma

Q. Wang[1], B. Cao[1], J. Chen[2], T. Li[3], J. Lang[3], Z. Xiao[4]

[1]Radiation Oncology, Sichuan Cancer Hospital & Institution, Sichuan Cancer Center, School of Medicine, University of Electronic, Chengdu, China, [2]Radiation Oncology, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital, Fuzhou, China, [3]Department of Radiotherapy, Sichuan Cancer Hospital & Institute, Chengdu, China, [4]Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: We aimed to establish a risk model using computed tomography-based compactness to predict overall survival (OS) and progression-free survival (PFS) after multimodal treatment for esophageal squamous cell carcinoma (ESCC).

Methods: We extracted pre-treatment CT-based tumor data (volume, surface area, and compactness) for 512 cases of ESCC that were treated at 3 centers. A risk model based on compactness was trained using Cox regression analyses of 83 cases, and then the model was validated using two independent cohorts (98 patients and 283 patients). The largest cohort (283 patients) was then evaluated using the risk model to predict response to radiotherapy with or without chemotherapy.

Results: In the three datasets, the pre-treatment compactness risk model provided good accuracy for predicting OS (P = 0.012, P = 0.022, and P = 0.003) and PFS (P < 0.001, P = 0.003, and P = 0.005). Patients in the low-risk group did not experience a significant OS benefit from concurrent chemoradiotherapy (P = 0.099). Furthermore, after pre-operation concurrent chemoradiotherapy, the OS outcomes were similar among patients in the low-risk group who did and did not achieve a pathological complete response (P = 0.127). Compactness was correlated with clinical T stage but was more accurate for predicting prognosis after treatment for ESCC, based on higher C-index values in all three datasets.

Conclusions: Our compactness-based risk model was effective for predicting OS and PFS after multimodal treatment for ESCC. Therefore, it may be useful for guiding personalized treatment.

Editorial acknowledgement: Michelle Doctorate/Evolutionary Biology/University of Exeter/Exeter, UK/2008.

Legal entity responsible for the study: Sichuan Cancer Hospital.

Funding: This work was supported by the National Key Projects of Research and Development of China [grant number 2016YFC0904600], the National Natural Science Foundation of China [grant number 81272512], the Capital Clinical Characteristic Application Research of China [grant number Z121107001012004], and the Capital Health Research and Development of Special of China [grant number 2016-2-4021].

Disclosure: All authors have declared no conflicts of interest.

641P Clinical significance of 18F-fluorodeoxyglucose-positron emission tomography-positive lymph nodes to outcomes of trimodal therapy for esophageal squamous cell carcinoma

Y. Hamai[1], M. Emi[1], Y. Ibuki[1], M. Okada[2]

[1]Surgical Oncology, Institute of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan, [2]Surgical Oncology, Hiroshima University, Hiroshima, Japan

Background: The clinical significance of lymph node (LN) status determined by preoperative ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) has not been investigated in patients with locally advanced esophageal squamous cell carcinoma (ESCC) treated with neoadjuvant chemoradiotherapy (NCRT) followed by surgery (trimodal therapy).

Methods: We reviewed 132 consecutive patients with ESCC who were preoperatively evaluated using FDG-PET before and after NCRT to analyze associations among LN status according to PET findings, pathological LN metastasis and the prognosis of ESCC after trimodal therapy.

Results: PET-positive LN both before and after NCRT comprised significant predictive markers of pathological LN metastasis (sensitivity, specificity and accuracy: 84.5%; 40.5%; 59.8% [p = 0.002] before, and 27.6%, 87.8% and 61.4% [p = 0.02] after NCRT, respectively). The numbers of LN evaluated using PET before and after NCRT and of pathological metastatic LN were significantly associated. Univariate and multivariable analyses selected LN status determined by PET before NCRT as a significant independent predictor of both recurrence-free (LN negative vs. positive: hazard ratio [HR], 1.90; 95% confidence interval [CI], 1.02 – 3.23; p = 0.045) and overall survival (HR, 2.62; 95% CI, 1.29 – 5.30, p = 0.01).

Conclusions: The status of LN determined by preoperative FDG-PET is significantly associated with pathological LN status and the prognosis of ESCC with trimodal therapy. Thus, FDG-PET is a useful diagnostic tool with which to preoperatively predict pathological LN metastasis and survival among patients with ESCC.

Legal entity responsible for the study: Hiroshima University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

642P Phase I study results from an esophageal squamous cell carcinoma (ESCC) cohort treated with M7824 (MSB0011359C), a bifunctional fusion protein targeting transforming growth factor β (TGF-β) and PD-L1

C-C. Lin[1], T. Doi[2], K. Muro[3], M-M. Hou[4], T. Esaki[5], H. Hara[6], H-C. Chung[7], M. Osada[8], C. Helwig[9], S. Kondo[10]

[1]Department of Oncology, National Taiwan University Hospital, Taipei City, Taiwan, [2]Division of Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [3]Department of Endoscopy, Aichi Cancer Center Hospital, Nagoya, Japan, [4]Division of Hematology-Oncology, Chang Gung Memorial Hospital-Linkou, Taoyuan, Taiwan, [5]Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan, [6]Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan, [7]Medical Oncology, Severance Hospital, Seoul, Republic of Korea, [8]Medical Oncology, Merck Serono, Tokyo, Japan, [9]Medical Oncology, Merck KGaA, Darmstadt, Germany, [10]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Inhibition of the TGF-β pathway, which promotes tumor immunosuppression, may enhance the clinical response to PD-(L)1 monoclonal antibodies (mAbs). M7824 is an innovative first-in-class bifunctional fusion protein composed of a human anti–PD-L1 IgG1 mAb fused with 2 extracellular domains of the TGFβ receptor II to function as a TGF-β "trap". We report on the safety and efficacy of M7824 in a cohort of Asian patients (pts) with ESCC. Esophageal cancer is the sixth most common type of cancer in Eastern Asia, with ESCC accounting for ≈90% of cases. ESCC represents an area of high unmet need. Additionally, no immunotherapies have been yet approved for this patient population, and monochemotherapy with a taxane or irinotecan remains the 2L standard of care (ORRs, ≤16%).

Methods: In this expansion cohort of the ongoing, phase 1 trial NCT02699515, Asian pts with ESCC unselected for PD-L1 expression, for which no standard therapy exists or has failed, received M7824 1,200 mg q2w until disease progression, unacceptable toxicity, or trial withdrawal. The primary objective is safety and tolerability; secondary objectives include best overall response per RECIST v1.1.

Results: As of January 4, 2018, 30 pts received M7824 for a median of 6.1 (range, 2.0–44.1) weeks; 4 pts remained on treatment. 76.7% of patients had received ≥2 prior lines of treatment. The most common TRAEs were hypothyroidism, maculopapular rash (both 16.7%), rash (13.3%), and interstitial lung disease (ILD; 10.0%). Grade 3 TRAEs occurred in 4 pts (13.3%; eczema, increased amylase, lip SCC, maculopapular rash, rash); 2 grade 4 TRAEs were observed (6.7%; ILD, increased blood creatine phosphokinase). 3 treatment discontinuations, but no deaths, due to TRAEs occurred. 6 pts (confirmed ORR, 20.0%; unconfirmed ORR, 26.7%) had a partial response (duration of response, 1.4+, 2.8+, 4.2+, 4.2+, 5.8, and 7.0 months); 5 pts had stable disease (disease control rate, 36.7%) by investigator read.

Conclusions: M7824 had a manageable safety profile and promising preliminary efficacy in heavily pretreated Asian pts with ESCC and no/limited treatment options.

Clinical trial identification: NCT02699515.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA.

Disclosure: T. Doi: Consultancy: Lilly Japan, Chugai Pharma, Kyowa Hakko Kirin, Merck Sharp and Dohme Corp, Daiichi Sankyo, Amgen, Sumitomo Dainippon, Taiho Pharmaceutical; Research funding: Taiho Pharmaceutical, Novartis, Merck Serono, Astellas Pharma, Merck Sharp and Dohme Corp, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Lilly Japan, Sumitomo Group, Chugai Pharma, Kyowa Hakko Kirin,

Daiichi Sankyo, Celgene, Bristol-Myers Squibb, Abbvie Quintiles. M-M. Hou: Employee: Chang Gung Memorial Hospital. H. Hara: Honoraria: Chugai Pharma, Taiho Pharmaceutical, Merck Serono, Yakult Honsha, Lilly, Ono Pharmaceutical, Takeda; Consulting or advisory role: Ono Pharmaceutical, Chugai Pharma, Merck Serono, Merck Sharp & Dohme Corp; Research funding: AstraZeneca, Chugai Pharma, Merck Serono, Merck Sharp & Dohme Corp, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda, Boehringer Ingelheim, Dainippon Sumitomo Pharma, Daiichi Sankyo, Lilly, Pfizer, LSK BioPharma, Eisai, Incyte. H-C. Chung: Employee: Yonsei University College of Medicine; Consultancy: Taiho, Celltrion, Merck Sharp and Dohme Corp, Lilly, Quintiles, Bristol-Myers Squibb, Merck-Serono; Research funding: Lilly, GlaxoSmithKline, Merck Sharp and Dohme Corp, Merck-Serono, Bristol-Myers Squibb/Ono, Taiho; Speakers bureau: Merck-Serono, Lilly, Foundation Medicine. M. Osada: Employee: Merck Serono. C. Helwig: Employee: Merck KGaA. All other authors have declared no conflicts of interest.

643P M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-*β*, in patients with post-platinum esophageal adenocarcinoma (EAC): Preliminary results from a phase I cohort

B. Tan[1], A. Khattak[2], E. Felip[3], K. Kelly[4], P. Rich[5], D. Wang[6], C. Helwig[7], I. Dussault[8], L. Ojalvo[9], N. Isambert[10]

[1]Medical Oncology, Washington University School of Medicine, Saint Louis, MO, USA, [2]Medical Oncology, Fiona Stanley Hospital, Murdoch, Australia, [3]Medical Oncology Service (Lung Cancer Unit), Vall d'Hebron University Hospital, Barcelona, Spain, [4]Hematology Oncology, University of California Davis Cancer Center, Sacramento, CA, USA, [5]Medical Oncology, Cancer Treatment Centers of America, Newnan, GA, USA, [6]Medical Oncology, Henry Ford Hospital, Detroit, MI, USA, [7]Biostatistics, Merck KGaA, Darmstadt, Germany, [8]Clinical Biomarkers, Immuno-Oncology, EMD Serono, Billerica, MA, USA, [9]Immuno-Oncology, EMD Serono, Billerica, MA, USA, [10]Medical Oncology, Centre Georges-François Leclerc, Dijon, France

Background: TGF-β and PD-(L)1 are 2 mechanisms of immune suppression in the tumor microenvironment; blocking both may enhance antitumor activity. M7824 is an innovative first-in-class bifunctional fusion protein composed of an anti–PD-L1 mAb fused with 2 extracellular domains of TGF-βRII (a TGF-β "trap"). Advanced EAC is treated per gastric cancer guidelines, with ORRs ≤14% with 2L SoC taxane monotherapy. We report results in patients (pts) with EAC that progressed on ≥ 1 platinum-based therapy. Emerging data with immunotherapies show clinical activity in advanced EAC, though none are currently approved in these pts.

Methods: In the ongoing trial NCT02517398, pts with advanced, post-platinum EAC received M7824 1200 mg q2w until confirmed PD per RECIST v1.1, unacceptable toxicity or trial withdrawal. The primary endpoint is BOR per RECIST; secondary endpoints include safety/tolerability. Biomarker analysis included tumor cell PD-L1 expression (antibody clone 73-10).

Results: As of August 23, 2017 (median follow-up, 14.4 [range, 1.3–43.3] weeks), 30 pts with advanced EAC (80% had ≥2 prior lines of therapy) received M7824. The median therapy duration was 6.1 (range, 2.0–40.0) weeks; treatment was ongoing in 4 pts (13.3%). 19 pts (63.3%) had TRAEs; 7 pts (23.3%) experienced grade 3 TRAEs (anemia [2 pts], Bowen's disease, cancer pain, generalized rash, hemorrhagic gastritis, hypophysitis, hypopituitarism, and skin SCC [1 pt each]). No grade 4 TRAEs, study discontinuations, or deaths due to a TRAE were observed. 6 pts (confirmed ORR 20.0%) had a PR with 3 responses ongoing per RECIST (DOR, 1.4+, 2.0, 2.8, 2.9+, 3.6, 6.5+ months), and 4 pts (13.3%) had SD per RECIST by independent committee read. 9 pts (31.0% of 29 evaluable) had PD-L1 + (≥1%) tumors. ORR was 22.2% in pts with PD-L1+ and 20.0% in pts with PD-L1– tumors.

Conclusions: These preliminary data show that M7824 resulted in a manageable safety profile in pts with advanced EAC. Early signs of clinical efficacy in this heavily pretreated population are encouraging, with an ORR of 20%, irrespective of PD-L1 expression. Updated efficacy data and biomarker analysis will be presented.

Clinical trial identification: NCT02517398.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: A. Khattak: Employee: Fiona Stanley Hospital; Consultancy: Merck, Bristol-Myers Squibb; Research funding: MSD, Cancer Council WA; Honoraria: MSD, Merck, Bristol-Myers Squibb, Novartis; Speakers bureau: MSD, Merck, Bristol-Myers Squibb, Novartis. E. Felip: Consultancy: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Guardant Health, MSD, Novartis, Pfizer, Roche, Takeda, Abbvie, Merck; Speakers bureau: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Guardant Health, MSD, Novartis, Pfizer, Roche, Takeda, Abbvie, Merck. C. Helwig: Employee, Equity ownership: Merck KGaA, Germany. I. Dussault: Employee: EMD Serono Consultancy (Includes expert testimony). L. Ojalvo: Employee: EMD Serono. N. Isambert: Travel, accommodations, expenses: Roche, MedImmune, AstraZeneca, Novartis, Celgene, Pharmara. All other authors have declared no conflicts of interest.

644P The nationwide cancer genome screening project in Japan, SCRUM-Japan GI-SCREEN: Efficient identification of cancer genome alterations in advanced pancreatic cancer

N. Izawa[1], C. Morizane[2], H. Takahashi[3], M. Ueno[4], Y. Kawamoto[5], N. Okano[6], S. Shimizu[7], K. Sudo[8], S. Itoh[9], A. Asagi[10], Y. Kagawa[11], K. Kamata[12], T. Kudo[13], S. Nomura[14], T. Kuwata[15], S. Fujii[16], W. Okamoto[17], K. Shitara[18], A. Ohtsu[18], T. Yoshino[18]

[1]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan, [2]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [4]Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan, [5]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [6]Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan, [7]Department of Gastroenterology, Saitama Cancer Center, Ina, Japan, [8]Department of Gastroenterology, Chiba Cancer Center, Chiba, Japan, [9]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [10]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [11]Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [12]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osakasayama, Japan, [13]Department of Frontier Science for Cancer and Chemotherapy, Gradeate School of Medicine Osaka University, Suita, Japan, [14]Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [15]Department of Pathology and Clinical Laboratories, National Cancer Center Hospital East, Kashiwa, Japan, [16]Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Kashiwa, Japan, [17]Biobank Translational Research Support Section, Translational Research Management Division, Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [18]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: We initiated the Nationwide Cancer Genome Screening Project in Japan since February 2014. From October 2015, we have introduced the Next Generation Sequencing to detect cancer genome alterations in advanced pancreatic cancer (aPC), called as the SCRUM-Japan GI-SCREEN.

Methods: This study is ongoing with 20 major cancer centers. Patients with aPC who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from formalin-fixed paraffin embedded (FFPE) tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect mutations, copy number variant (CNV) and fusion genes in a CLIA certified CAP accredited lab. The detected genomic variant data were classified according to genetic drivers of cancer, including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase.

Results: As of March 31st in 2017, total of 270 aPC patients were enrolled and 209 samples were analyzed. The sequence was successfully performed in 136 tumors (65.1%). The origin of samples included the primary site of 65.4%, metastatic site of 34.6%. The tissue samples were obtained by surgical resection 32.4%, needle biopsy 33.8%, EUS-FNA 27.9%, and other 5.9%. Rate for success sequence of EUS-FNA was 56.7%. The frequently detected mutations (≥ 2%) in 136 samples of which results were available were KRAS (91.9%), TP53 (62.5%), CDKN2A (14.0%), SMAD4 (10.3%), GNAS (4.4%), TET2(4.4%), PIK3CA(3.7%), ATM (2.9%), STK11 (2.9%), BRCA2 (2.2%). Most frequently detected CNVs (≥ 7copies) was MYC (2.9%), and no gene fusion was detected. We will show the clinical outcome based on certain key cancer genome alterations.

Conclusions: This nationwide screening system is efficient to detect rare gene alterations in aPC. This novel knowledge provides an intriguing background to investigate new targeted approaches in these patients and to progress precision medicine.

Clinical trial identification: UMIN000016344.

Legal entity responsible for the study: SCRUM-Japan GI-Screen.

Funding: 15 SCRUM-Japan collaborating pharmaceutical companies, AMED, NCC.

Disclosure: N. Izawa: Consulting or advisory role: Taiho Pharmaceutical Co., Ltd., Merck Serono Co., Ltd. C. Morizane: Honoraria: Pfizer, Novartis, Yakult Honsha, Eli Lilly Japan K.K, Nobelpharma, Fujifilm, Teijin Pharma, Taiho Pharmaceutical Co., Ltd.; Consulting or advisory role: Yakult Honsha, Novartis, Taiho Pharmaceutical; Research funding (Recipient: my institution): Pfizer, Nobelpharma, Eisai, Yakult Honsha, Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd. H. Takahashi: Honoraria: Taiho Pharmaceutical Co., Ltd.; Research funding: Bayer Pharmaceutical, Bristol-Myers Squibb. M. Ueno: Honoraria: Taiho Pharmaceutical Co., Ltd., Yakult Honsha, AstraZeneca, Novartis, Eli Lilly Japan K.K, Teijin Pharma, Shire, Ono Pharmaceutical Co., Ltd.; Research funding: Taiho Pharmaceutical, Shire, Daiichi Sankyo, Eisai, AstraZeneca, Ono Pharmaceutical Co., Ltd., MSD, Merck Serono Co., Ltd., NanoCarrier, Dainippon Sumitomo Pharma, Incyte. N. Okano: Honoraria: Taiho Pharmaceutical Co., Ltd., Merck Serono Co., Ltd. S. Shimizu: Honoraria: Novartis, Taiho Pharmaceutical Co., Ltd. S. Itoh: Speakers' bureau: Otsuka Pharmaceutical, Asahi Kasei Phama; Consulting or Advisory Role: Asahi Kasei Phama, Takeda; Research funding (Recipient: our institution): Taiho Pharmaceutical Co., Ltd., Sumitomo Dainippon, Daiichi Sankyo, MSD, Yakult Honsha, Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd., Astellas, CSL Behring, Novartis, Shionogi, Eli Lilly Japan K.K, Bayer, Merck Serono Co., Ltd., Kyowa Hakko Kirin, Sanofy, Pfizer, Boehringer Ingelheim, Asahi Kasei Phama, Taisho Toyama Pharmaceutical, Kaken Pharmaceutical, Hisamitsu Pharmaceutical, Nihon Pharmaceutical, Nihon Blood Products Organization, Kowa Company, Medtronic, Johnson and Johnson. T. Kudo:

Research grants: Yakult Honsha, Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd. S. Nomura: Honoraria: Taiho Pharmaceutical Co., Ltd. T. Kuwata: Honoraria: Chugai Pharmaceutical Co., Ltd, Daiichi-Sankyo Research funding (to institution): Daiichi-Sankyo. W. Okamoto: Grants: MSD. K. Shitara: Consulting or advisory role: Astellas Pharma, Eli Lilly Japan K.K, Bristol-Myers Squibb, Takeda, Pfizer, Ono Pharmaceutical Co., Ltd.; Personal fees: Novartis, AbbVie, Yakult Honsha; Research funding (to institution): Eli Lilly Japan K.K, Ono Pharmaceutical Co., Ltd., Dainippon Sumoitomo Pharma, Daiichi Sankyo, Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd, MSD. A. Ohtsu: Honoraria: Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb; Research funding: Bristol-Myers Squibb. T. Yoshino: Grants: MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co., Ltd, Sanofi K.K., Chugai Pharmaceutical Co., Ltd; Personal fees: Eli Lilly Japan K.K, Merck Serono Co., Ltd, Sanofi K.K., Chugai Pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

645P Spatial genomic heterogeneity from multi-region endoscopic biopsies in primary gastric cancer: Implications for precision therapy

S.J. Klempner[1], J. Chao[2], K. Kim[3], K-M. Kim[4], S-T. Kim[3], J. Lee[3], H. Lee[5]

[1]Medical Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA, [2]Department of Medical Oncology and Therapeutics, City of Hope, Duarte, CA, USA, [3]Medicine, Samsung Medical Center, Seoul, Republic of Korea, [4]Pathology, Samsung Medical Center, Seoul, Republic of Korea, [5]Gastroenterology, Samsung Medical Center, Seoul, Republic of Korea

Background: The responses and benefit from targeted therapies in gastric cancer (GC) remain limited and improved biologic understanding is needed. Both inter-tumoral and intra-tumoral heterogeneity for HER2 and EGFR has been observed in small datasets and may limit efficacy of targeted therapies. Broader heterogeneity assessment has not been studied. We sought to explore intra-tumoral heterogeneity in GC by multi-region sampling of primary gastric tumors with subsequent interrogation of mutational differences via next generation sequencing (NGS) and cell-free DNA (cfDNA) analyses.

Methods: Patients with newly diagnosed advanced GC underwent endoscopic mapping and pre-determined 8-region biopsy of the primary with concurrent plasma cfDNA sampling. Biopsy samples were subjected to NGS using a 32-gene custom panel and plasma cfDNA analyzed via 28-gene cfDNA assay. Clinicopathologic features and genomic alterations (GA) were abstracted and descriptive statistics were used to compare samples.

Results: All six initial patients underwent multi-region biopsy and NGS. Within a given patient the average number of GA observed in all biopsies (shared GA) was 3.3 with an average of 12.8 non-shared alterations ($p = < 0.05$). There was no significant difference in the average mutant allele frequency (MAF) or MAF variability between shared and non-shared GA in the primary tumor ($p = > 0.05$). Cell free DNA analyses identified GA not found in each respective case's multi-region primary tumor analysis, likely reflective of GA derived from metastatic sites. An updated cohort will be presented.

Conclusions: Endoscopic multi-region biopsy of GC is feasible and significant genomic heterogeneity existed within the primary in all patients. Paired cfDNA analyses should also be included to complement studies of intra-tumoral heterogeneity. Standardized methods to determine intra and inter-tumoral heterogeneity are needed and stratification by heterogeneity score in prospective trials may inform optimal patient selection, particularly in targeted therapies.

Legal entity responsible for the study: Samsung Medical Center.

Funding: Samsung Medical Center.

Disclosure: S.J. Klempner: Consulting, Advisory: Lilly Oncology, Boston Biomedical, Astellas, Merck. J. Chao: Consulting, Advisory: Boston Biomedical, Merck, Five Prime Therapeutics. All other authors have declared no conflicts of interest.

646P EGFR amplification (amp) and survival in the REAL-3 trial

E. Smyth[1], K. Kouvelakis[2], D. Cunningham[1], J.C. Hahne[3], C. Peckitt[2], G. Vlachogiannis[3], D. Watkins[1], S. Rao[1], N. Starling[1], S.H. Wilson[3], T.S. Waddell[4], A. Okines[1], T. Crosby[5], W. Mansoor[4], J. Wadsley[6], G. Middleton[7], A. Wotherspoon[8], I. Chau[9], N. Valeri[3]

[1]Gastrointestinal Oncology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [2]R&D, Royal Marsden Hospital NHS Foundation Trust, London, UK, [3]Molecular Pathology, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, UK, [4]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [5]Oncology, Velindre Cancer Centre, Cardiff, UK, [6]Oncology, Weston Park Hospital Cancer Research Centre, Sheffield, South Yorkshire, UK, [7]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK, [8]Histopathology, Royal Marsden Hospital NHS Foundation Trust, Sutton, UK, [9]Department of Medicine, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, UK

Background: EGFR amp occurs in 6-10% of gastroesophageal adenocarcinomas (OGA). The effect of EGFR amp on survival in advanced chemotherapy treated OGA is unknown. We evaluated EGFR amp in tissue and plasma in patients (pts) treated in the REAL3 trial.

Methods: REAL3 was a randomised, open-label phase 3 trial in treatment naïve, advanced OGA pts assessing the addition of panitumumab (P) to epirubicin, oxaliplatin and capecitabine (EOX) (HR 1.37 (95% CI 1.07-1.76) $p = 0.013$; EOX-P vs EOX). DNA was extracted from pre-treatment biopsies and plasma. EGFR copy number was assessed by ddPCR using probes for EGFR and reference probe CNTNAP2 (Ch7). EGFR:CNTNAP2 copy number assessment allowed detection of EGFR amp and exclusion of Ch7 polysomy. The association between EGFR amp and progression free and overall survival (PFS/OS) was assessed by the Kaplan-Meier method and Cox regression.

Results: 271 pts (of a total 553 pts treated) had tissue analysed. EGFR ratio was ≥2 in 19/271 (7.0%); 14/271 (5.2%) had ratio ≥5. Plasma was analysed in 370 pts; 23/370 (6.2%) had EGFR ratio ≥2 and 10/370 (2.7%) had ratio ≥5. EGFR amp pts were balanced according to clinicopathological variables. Of 14 EGFR amp tissue samples 7 plasma samples (50%) were concordant; all had EGFR ratio ≥ 5. OS and PFS by EGFR amp are shown in the table. Results were similar for ratio ≥5. Multivariate analysis adjusted for age, gender, PS and histology demonstrated a similar prognostic trend in each arm.

Table: 646P OS and PFS by arm and EGFR amp

	EGFR	n	Median OS (95% C.I.)	HR (95% C.I.)
EOX OS				
Tissue	<2	120	12.5 (9.5-15.7)	Ref
	≥2	7	11.5 (na)	1.2 (0.5-2.8)
Plasma	<2	163	11.8 (10.5-14.6)	Ref
	≥2	4	11.5 (na)	1.6 (0.5-5.0)
EOX PFS				
Tissue	<2	120	7.6 (6.4-8.9)	Ref
	≥2	7	6.6 (na)	1.4 (0.6-3.2)
Plasma	<2	163	7.1 (6.2-8.6)	Ref
	≥2	4	6.5(na)	1.2 (0.4-3.2)
EOX-P OS				
Tissue	<2	113	8.5 (7.0-9.7)	Ref
	≥2	10	5.7 (1.7-12.9)	1.3 (0.7-2.4)
Plasma	<2	169	9.7 (8.5-11.8)	Ref
	≥2	18	7.8 (3.9-12.9)	1.6 (0.8-3.1)
EOX-P PFS				
Tissue	<2	113	5.7 (4.5-6.3)	Ref
	≥2	10	2.7 (1.6-12.2)	1.2 (0.6-2.3)
Plasma	<2	169	6.9 (6.0-8.6)	Ref
	≥2	18	5.3 (2.6-10.0)	1.28 (0.8-2.1)

Conclusions: Liquid biopsy using ddPCR can detect EGFR amp in advanced OGA patients; higher levels of EGFR tissue amp may predict plasma status. EGFR amp appears to be negatively prognostic, however due to low biomarker prevalence this difference was not significant.

Clinical trial identification: NCT00824785.

Legal entity responsible for the study: Royal Marsden.

Funding: Royal Marsden National Institute for Health Research Biomedical Research Centre.

Disclosure: E. Smyth: Honoraria for advisory role: Servier, BMS, Five Prime Therapeutics, Gritstone Oncology, Celgene. D. Cunningham: Research funding (Inst): Amgen, AstraZeneca, Bayer, Celgene, MedImmune, Merck Serono, Merrimack, Sanofi. S. Rao: Honoraria: Shire Pharmaceuticals, Celgene, Lilly, Amgen, BMS; Travel/accommodation: Celgene, Amgen, Bayer. T.S. Waddell: Honoraria: BMS, Pfizer, Ipsen, Roche. A. Okines: Honoraria (speakers fee): Roche. T. Crosby: Honoraria for advisory role: Lilly. W. Mansoor, J. Wadsley: Honoraria: Novartis, Merck; Travel/accommodation: Ipsen, Merck. G. Middleton: Research funding: Kael-Gemvax. I. Chau: Honoraria: Amgen, Gilead Sciences, Lilly, Pfizer, Taiho Pharmaceutical; Consulting, Advisory role: Bayer, Bristol-Myers Squibb, Five Prime Therapeutics, Lilly, MSD Oncology, Roche/Genentech, Sanofi; Research funding (Inst): Janssen-Cilag, Lilly, Merck Serono, Sanofi; Travel, accommodations, expenses: Bristol-Myers Squibb, Lilly, Merck Serono, MSD, Sanofi. N. Valeri: Honoraria: Bayer, Merck, Eli Lilly. All other authors have declared no conflicts of interest.

647P The role of FGFR2 amplification and expression in patients with advanced or metastatic gastric cancer receiving fluoropyrimidine-based chemotherapy

M.M. Skupinska[1], M. Jesiotr[2], P. Chrom[3], A. Mroz[4], S. Cierniak[2], M. Winiarek[5], L.S. Wyrwicz[5], J. Pieczykolan[6], M. Wieczorek[7], A. Stanczak[1], L. Bodnar[3]

[1]Preclinical Development Departament, Celon Pharma, Warsaw, Poland, [2]Department of Pathology, Military Institute of Medicine, Warsaw, Poland, [3]Department of Oncology, Military Institute of Medicine, Warsaw, Poland, [4]Department of Pathology and Laboratory Diagnostics, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [5]Department of Oncology and Radiotherapy, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [6]Preclinical Development Departament, Celon Pharma, Lomianki, Poland, [7]Celon Pharma S.A., Lomianki, Poland

Background: Fibroblast growth factors (FGF) and their receptors are complex intracellular pathway that controls cellular proliferation and tumour growth and invasion. FGFR alterations have been shown to be associated with the initiation and progression of gastric cancer (GC). We investigated the correlations of the FGFR2 amplification and expression with clinicopathological characteristics and outcomes in advanced/ metastatic gastric cancer patients who received systemic chemotherapy based on fluoropyrimidine.

Methods: FFPE tumor samples were obtained from patients with advanced/ metastatic gastric cancer who received systemic chemotherapy based on fluoropyrimidine diagnosed at 2 cancer centers between 2010 and 2016. FGFR2 gene copy number was assessed by FISH method using probes specific for the 10q26 locus and the chromosome 10 centromere (CEN10). FGFR2 amplification was defined as FGFR2/CEN10 $\geq$2.0. FGFR2 protein expression was determined by immunohistochemistry. Overexpression was defined as complete membrane staining intensity $\geq$2 + (graded from 0 to 3+) in cancer cells.

Results: From the cohort consists of 186 GC patients, FFPEs were available from 123 pts. FGFR2 amplification was found in 4/123 (3,3%) patients with FGFR2/CEN10 median 1,16 +1,77 and range 0,8-20,0. FGFR2 overexpression was observed in 5/123 (4,1%) patients. FGFR2 amplification had no significantly impact on overall survival (OS) and progression free survival (PFS) in compare those without FGFR2 amplification (respectively, HR = 1.43, 95% CI 0.54 to 4.04, p = 0.4426 and HR = 3.06, 95%CI 0.94 to 9.97, p = 0.0628). There was no prognostic significance observed for FGFR2 overexpression on OS and PFS (respectively, HR = 1.27, 95%CI 0.52 to 3.15, p = 0.5961 and HR = 2.44, 95%CI 0.88 to 6.78, p = 0.0863).

Conclusions: The rate of GC patients with tumors positive for FGFR2 amplification or expression was consistent with the data published in the literature. However FGFR2 amplification and overexpression has no prognostic significance in advanced/ metastatic gastric cancer patients who received systemic chemotherapy based on fluoropyrimidine. Therefore, further investigation on a larger population is required.

Legal entity responsible for the study: Celon Pharma.

Funding: National Centre for Research and Development (Poland); Celon Pharma.

Disclosure: M.M. Skupinska, J. Pieczykolan, A. Stanczak: Employee: Celon Pharma. M. Wieczorek: CEO: Celon Pharma. All other authors have declared no conflicts of interest.

648P Changes in CpG methylation of APC, CDH13, MLH1, MGMT, P16 and RASSF1A in gastric adenocarcinoma

N.N. Timoshkina[1], O.I. Kit[2], D.I. Vodolazhskiy[1], N.V. Soldatkina[2], Y.A. Gevorkyan[2], N.S. Samoylenko[2], D.A. Kharagezov[2], M.N. Duritskiy[3], A.V. Dashkov[2], D.O. Kaymakchi[2], D.S. Petrov[2], S.A. Ilchenko[2], V.A. Sustretov[3], L.Y. Vladimirova[4]

[1]Laboratory of Molecular Oncology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [2]Department of Surgical Oncology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [3]Clinical Diagnostic Department, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [4]Medical Department, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Background: Stomach cancer (SC) is one of the most common cancers and the third leading cause of cancer-related deaths; however, it is often diagnosed at later stages. Literature data on epigenetic changes in stomach cancer and precancer, in particular on hypermethylation of tumor suppressor genes, indicate its important role in gastric tissue malignization.

Methods: Bisulfite pyrosequencing was used to study the CpG methylation in promoter sites of 6 tumor suppressor genes (APC, CDH13, MLH1, MGMT, P16 and RASSF1A). The study included paired bioptates of tumors and intact tissues obtained from 35 patients (25 men, 10 women, median age 67 years) with stomach cancer (G2-3 adenocarcinoma, T3-4N0-2M0).

Results: The rates of hypermethylation of the MGMT, P16 and RASSF1A genes amounted to 23%, 14% and 11% respectively. Increased methylation in the promoter site of the MLH1 gene was observed in one case only (11% vs 4%). Regulatory sites of CDH13 and APC genes in intact tissues were atypically hypermethylated in 80% of cases, which was obviously associated with functional characteristics of the gastric mucosa. However, the methylation of the promoter site of the CDH13 gene in non-tumor tissue was 2 times lower compared to the local tumor (p = 0.002) and 1.5 times lower compared to the tumor with lymph node metastases (p = 0.012). An association between the methylation of the P16 and RASSF1A genes and higher tumor grade G (p = 0.046) and increasing tumor sizes (T-classification, p = 0.028) was registered.

Conclusions: We observed hypermethylation of the promoter sites of the MGMT, P16 (CDKN2A) and RASSF1A genes in malignant stomach tissues compared to intact tissues which demonstrated the importance of disorders of repair processes (MGMT and RASSF1A) and mechanisms of regulation of the cell cycle (CDKN2A) in the malignization of stomach tissues. The methylation status of these genes can be a useful biomarker for early diagnosis of stomach cancer or possible therapeutic targets.

Legal entity responsible for the study: Ministry of Health of the Russian Federation.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

649P The level of somatic mutations as an indicator of overall survival in gastric cancer

T. Kekeeva[1], A.S. Tanas[2], L. Khashimov[3], V. Lyadov[4], Y. Andreeva[5], G. Frank[5], L. Zavalishina[5], D.V. Zaletaev[6], V.V. Strelnikov[7]

[1]Laboratory of Epigenetics, Research Centre for Medical Genetics, Moscow, Russian Federation, [2]Epigenetics, Research Centre for Medical Genetics, Moscow, Russian Federation, [3]Pathology, Russian Medical Academy of Postgraduate Education, Moscow, Russian Federation, [4]Surgery, Treatment and Rehabilitation Center, Moscow, Russian Federation, [5]Pathology Department, Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation, [6]Laboratory of Medical Genetics, Sechenov First Moscow State Medical University, Moscow, Russian Federation, [7]Epigenetics, Institute of Molecular Medicine, Moscow, Russian Federation

Background: Gastric cancer (GC) is a leading cause of cancer deaths. Tumor staging has been conceived as the best predictor of patient survival. Nevertheless, TNM classification has limited power to fully reflect the complicated progression events. Prognosis varies from individual to individual even though the two patients stay in a similar tumor stage, therefore the molecular biology of the individual tumor might be the key point to better understand the nature of GC. The identification of somatic mutations (SM) has the potential to offer diagnostic and prognostic information. The present study is focusing on implementation of clinical exome sequencing for SM identification.

Methods: 18 gastric cancer specimens and 18 corresponding adjacent normal gastric specimens were obtained from GC patients with stages from Ia to IV. Paired-ended sequencing was performed using Trusight one sequencing panel (Illumina) on a NEXTSEQ500 platform. 94,5% of the target regions were represented with an average sequencing depth of 20-fold. A somatic variant list was generated for each patient by using MuTect.

Results: Tumor and normal library targeted 4,813 genes associated with known clinical phenotypes were sequenced with mean coverage of 99x. Mean number of detected variations was 7613 per sample. After MuTect filtration the amount of SM was varied from 2 to 414 per sample. We found 692 SM: 5 pathogenic mutations in TP53, ARID1A and HER2 genes, 40 were described in COSMIC and dbSNP database, the rest were novel mutations. By the time of 2 years follow-up, 5 patients (27.8%) died, all of them had intermediate grade adenocarcinoma. Importantly, all of them had dramatic number of SM (from 37 to 414). At the operation moment 3 of them had III stage, 2 of them had 1b and IIa stages. For patients with overall survival (OS) > 2 years the number of SM increases with disease stage: I-II stage from 2 to 12, III stage – from 2 to 20, IV stage – from 12 to 43. For patients with OS < 2 years the number of SM was high nevertheless stage.

Conclusions: We found more than 600 novel mutations, from them 18 mutations were localized in genes previously associated with gastric cancer pathogenesis. In the current moment of the investigation patients with high level of SM have unfavorable prognosis (OS less than 2 year) regardless of stage.

Legal entity responsible for the study: Research Center of Medical Genetics, Moscow, Russia.

Funding: State assignment of FASO Russia.

Disclosure: All authors have declared no conflicts of interest.

650P Mechanisms of G9a on promoting tumor invasion and metastasis of gastric cancer

B. Liu[1], L. Hu[2]

[1]Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]Surgery, Shanghai Ruijin Hospital, Shanghai Jiao Tong University, College of Medicine, Shanghai, China

Background: Histone methyltransferase G9a is up-regulated in a wide variety of human tumors. The aims of this study are to clarify G9a expression in tumor tissues and its adjacent normal tissues of gastric cancer, to investigate the effect of G9a on tumor invasion and metastasis of gastric cancer by up-regulating and down-regulating the expression of G9a in gastric cancer cells, and to validate it in animal model.

Methods: IHC was used to detect the expression of G9a in gastric cancer tissues and its adjacent non-tumor tissues and to analyze the relationship between G9a and

clinicopathological parameters. After overexpressing or knock-down G9a stable gastric cancer cell lines were constructed, the effect of G9a on tumor invasion and metastasis of gastric cancer cells was detected by transwell assay, ankylosis resistance assay, soft agar formation assay and adhesion assay, nude mice model of cell peritoneal transplantation used to validate the in vitro results. The expression of related pathway gene was detected by WB, the interaction between the protein and the promoter region was detected by double luciferase reporter assay and ChIP and Co-IP was used to detect the interaction between proteins.

Results: G9a highly expressed in GC tissues. G9a expression level was correlated with advanced stage and shorter overall survival. Silencing G9a attenuate the peritoneal metastasis-relevant traits activities of GC cells, ectopic overexpression of G9A contributes to promote tumor metastasis. G9a expression can be induced by Reg IV via p-erk/p-SP1 pathway. SP1 directly binds to G9A promoter and promote its expression. G9a can form a transcriptional activator complex with P300 and GR to participate in ITGB3 expression induced by DEX. G9a participates in ITGB3 expression induced by DEX was independent on the SET domain and methyltransferase activity of G9a.

Conclusions: The expression of G9a in gastric cancer was significantly up-regulated. Overexpression of G9a in gastric cancer cells promoted tumor invasion and metastasis behavior of cancer cells and vise versa. G9a was involved in the process of tumor invasion and metastasis of gastric cancer through the regulation of ITGB3.

Legal entity responsible for the study: Bingya Liu.

Funding: The National Natural Science Foundation of China, China (Nos. 91529302, 81572798, 81602160), The National Key Technology R&D Program of China (No. 2014BAI09B03.

Disclosure: All authors have declared no conflicts of interest.

651P Prospective observation: Clinicopathological features and clinical utility of plasma Epstein-Barr virus DNA load of Epstein-Barr virus-associated gastric carcinoma

M-Z. Qiu

Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: EBV associated gastric carcinomas (EBVaGC) accounts for 8-9% of all gastric cancer (GC) patients. All previous reports on EBVaGC were retrospective. The value of plasma EBV-DNA load in relation to EBVaGC is under researched.

Methods: From October 2014 to September 2017, we prospectively collected GC patients with EBER examination (N = 2,760) from Sun Yat-sen University Cancer Center. We compared the EBER status in paired biopsy and resection samples of 69 metastatic GC patients. The relationship between Helicobacter pylori (HP) infection and EBER was analyzed in 148 GC patients. Plasma EBV-DNA load was dynamic monitored in EBVaGC patients. All statistical analyses were performed using the Stata 13.0. All statistical tests were two-sided.

Results: The incidence rate of EBVaGC in China was 5.07% (140/2760). EBVaGC patients were male predominant, younger, and had better histologic differentiation, earlier Tumor-Node-Metastasis stage than EBV negative GC (EBVnGC) patients. The 3-year survival was 76.84% (95% CI: 60.48-87.27%) vs 58.18% (95% CI: 55.89-60.39%) for EBVaGC and EBVnGC patients, P = 0.0001. Hp infection rate was 16.22% (23/148). There was no significant difference between EBVaGC (14.93%) and EBVnGC (17.28%) patients, P = 0.698. The consistent rate between biopsy and surgical resection samples was 98.6% (68/69). Only one patient was EBER negative in the biopsy and positive in the resection sample. The mean concentration of plasma EBV-DNA was 155.69 copies per milliliter in EBVnGC patients and 11109.6 copies per milliliter in EBVaGC patients, P < 0.001. Positive identifications of plasma EBV-DNA was associated with unfavorable prognosis. EBV-DNA load decreased when patients got PR/SD, while it increased when disease progressed.

Conclusions: This is the largest population prospective analysis of theclinicalpathological clinicopathological features and prognostic values of EBVaGC patients. The incidence rate of EBVaGC wais around 5%. Plasma EBV-DNA is a good marker in predicting recurrence and chemotherapy response for EBVaGC patients.

Legal entity responsible for the study: Sun yat-sen University Cancer Center.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

652P Is standard adjuvant chemotherapy effective in patients with Epstein-Barr virus associated gastric cancer?

J.G. Kim[1], Y. Chae[2], J.H. Baek[3], B.W. Kang[1]

[1]Oncology, Kyungpook National University Hospital, Daegu, Republic of Korea, [2]Oncology, Kyungpook National University Medical Center, Daegu, Republic of Korea, [3]Oncology, Ulsan University Hospital, Ulsan, Republic of Korea

Background: Based on a comprehensive molecular characterization of gastric cancer, Epstein-Barr virus (EBV)-associated gastric cancer (EBVaGC) can be classified as one of the four subtypes of gastric cancer (GC). Several studies have shown significantly better prognosis of EBVaGC compared with EBV-negative GC (EBVnGC). However, no published study has yet investigated the clinical significance of standard adjuvant chemotherapy in patients with resected EBVaGC. Accordingly, the present study analyzed the prognostic differences between EBVaGC and EBVnGC, and their survival impacts on standard adjuvant chemotherapy.

Methods: This study retrospectively reviewed 773 patients with gastric cancer who underwent surgical resection at Kyungpook National University Chilgok Hospital, between January 2011 and December 2017. The patients were enrolled according to the following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III according to the seventh edition of the UICC/AJCC for the stomach, and 4) postoperative adjuvant chemotherapy.

Results: Among 276 eligible patients, 59 (21.4%) and 217 patients (78.6%) were determined as EBVaGC and EBVnGC, respectively. One hundred twenty-nine (46.7%) patients were classified as stage II and 147 (53.3%) were as stage III. As for adjuvant chemotherapy, 87 patients (31.5%) received capecitabine and oxaliplatin (XELOX), while 189 (68.5%) received S-1, respectively. With a median follow-up duration of 21.3 months (2.4-89.0), the estimated 3-year disease-free survival (DFS) and overall survival (OS) rates were 74.8% and 83.0%, respectively. In a univariate analysis and multivariate analysis using a Cox proportional hazard model, EBV-positivity was not significantly associated with disease-free survival (p = 0.630) for all patients and XELOX or S-1 group.

Conclusions: In conclusion, EBV-positivity was not found to be associated with prognosis in patients with curatively respective gastric cancer who received standard adjuvant chemotherapy. Accordingly, the standard adjuvant chemotherapy can be used for patients with EBVaGC.

Legal entity responsible for the study: Jong Gwang Kim.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

653P PD-L1 expression and T-cell inflamed gene expression profile (GEP) in Korean and US patients (pts) with advanced gastric cancer (GC)

S.Y. Rha[1], G.Y. Ku[2], H.S. Kim[3], H.C. Chung[1], F.G. Amlashi[4], D.M. Maru[5], C. Fein[2], L. Tang[6], M.J. Savage[7], W. Zhou[7], T. Wu[7], S.A. Peter[7], D.P. Kelsen[8], J.A. Ajani[4]

[1]Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3]Medical Oncology and Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, [4]Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [5]Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [7]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [8]Medical Oncology, Merck & Co., Inc., New York, NY, USA

Background: PD-L1 expression and GEP have been associated with response to anti–PD-1/PD-L1 therapy. We studied PD-L1 expression and GEP in pts receiving standard therapy for GC in South Korea and the US in an observational study.

Methods: Tumor samples were collected from 2003-2017 from the Yonsei Cancer Center (South Korea), MD Anderson Cancer Center (US), and Memorial Sloan Kettering Cancer Center (US). PD-L1 expression was assessed by PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies); PD-L1+ was defined as combined positive score (CPS) ≥1. GEP was analyzed only in Korean pts. GEP score was derived from an 18-gene signature measured using extracted tumor RNA analyzed by NanoString nCounter platform. High/low GEP was based on a cutoff of –0.318. PD-L1 expression was analyzed using chi-squared and multiple logistic regression; survival was estimated using the Kaplan-Meier method, log-rank test, and Cox proportional hazards models.

Results: 574 tumor samples (73% biopsy, 27% surgical resection) from pts with GC (median [range] age 61 [21-90] years) were analyzed. Of the 574 pts, 49% (277/567) had stage IV disease; 43% (249/574) had operable disease (half of whom received adjuvant chemotherapy), and 57% (325/574) had inoperable disease (74% received chemotherapy, 18% received chemoradiation). The prevalence of PD-L1+ expression was 67% overall, 69% in Korean pts, 66% in US pts, 68% in biopsy samples, and 67% in surgical resection samples. Greater PD-L1+ expression was seen in older (≥65 years) vs younger pts (P = 0.011) and in pts with inoperable vs operable disease (P < 0.0001). PD-L1 expression was not associated with overall survival (OS) (log-rank test P = 0.25). 85% (243/286) of Korean pts had high GEP. High GEP was associated with tumor grade (P < 0.001) and clinical stage (P < 0.0001). High GEP may be associated with longer OS (adjusted hazard ratio 0.46 [95% CI 0.32-0.66]). GEP was mildly correlated with PD-L1 CPS (Spearman r = 0.24 [P < 0.0001]).

Conclusions: PD-L1 expression was similar in Korean and US pts with GC and in biopsy and surgical resection samples. GEP was associated with OS while PD-L1 expression was not. Further investigation of GEP with anti–PD-1/PD-L1 therapy is warranted.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Sarita S. Shaevitz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: S.Y. Rha: Advisory board member: Eli Lilly, MSD, Celltrion, Ipsen; Speakers' bureau: Eli Lilly; Institution research funding: MSD, BMS. G.Y. Ku: Advisory board member: Merck & Co., Inc., Eli Lilly, AstraZeneca; Institution research funding:

Merck & Co. Inc., BMS, Arog Pharmaceuticals, AstraZeneca. H.C. Chung: Advisory board member: Taiho, Celltrion, MSD, Eli Lilly, Quintiles, BMS, Merck-Serono; Speakers' bureau: Merck-Serono, Lilly, Foundation Medicine; Institution research funding: Lilly, GSK, MSD, Merck-Serono, BMS-Ono, Taiho. C. Fein: Employee of Novant Health; Travel expenses, accommodations: Aduro Biotech. M.J. Savage, W. Zhou, S.A. Peter: Employee, Stock owner: Merck & Co., Inc. T. Wu: Employee of Merck & Co., Inc. at the time the analysis was conducted for this abstract. J.A. Ajani: Institution research funding: BMS, Merck & Co., Inc., Taiho, DeltaFly, Gilead. All other authors have declared no conflicts of interest.

654P Relationship between immune related molecules and chemosensitivity and prognosis in gastric cancer

T. Hagi, Y. Kurokawa, T. Hashimoto, Y. Miyazaki, T. Takahashi, K. Tanaka, T. Makino, M. Yamasaki, K. Nakajima, M. Mori, Y. Doki

Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Japan

Background: Microsatellite instability (MSI), mainly caused by dysfunction of mutL homolog 1 (MLH1), was classified as one of distinctive molecular subtype of gastric cancer. MSI was also reported to be associated with high PD-L1 expression and high Immunoscore (IS), a density analysis of tumor-infiltrating lymphocytes. This study aimed to investigate the association between MLH1, PD-L1 expression, and IS and chemosensitivity and prognosis in gastric cancer.

Methods: A total of 271 patients who underwent gastrectomy (R0/1) for gastric cancer between 2008 and 2016 in our institution were retrospectively analyzed. Immunohistochemistry was performed to evaluate MLH1 and PD-L1 expression. IS was evaluated by the density of CD3+ and CD8+ lymphocytes in the center and invasive margin of tumor and classified into two groups; IS-High or IS-Low. The relationship between these markers and the pathological effect of neoadjuvant chemotherapy (NAC) was examined in patients with NAC, and recurrence-free survival (RFS) was compared separately with and without NAC.

Results: Low MLH1, high PD-L1 expression, and IS-High was observed in 29 (11%), 70 (26%), and 114 (42%) patients, respectively. Low MLH1 expression was significantly associated with high PD-L1 expression ($P = 0.006$) and IS-high ($P = 0.04$). In patients with NAC ($n = 114$), low MLH1 expression was significantly associated with low chemosensitivity (lower proportion of pathological effect Grade≥1b, $P = 0.006$), although PD-L1 expression and IS were not associated with chemosensitivity ($P = 0.99$, $P = 0.08$). In patients without NAC ($n = 157$), low MLH1 expression and IS-High were significantly associated with better RFS ($P = 0.02$, $P < 0.001$), however not associated in patients with NAC ($P = 0.70$, $P = 0.07$). While, PD-L1 expression was not associated with RFS in both patients with and without NAC ($P = 0.20$, $P = 0.51$). Multivariate analysis revealed that high MLH1 expression and IS-low were one of the independent risk factors for RFS (HR: 2.9 [1.3-6.9] $P = 0.014$, HR:1.9 [1.2-3.0] $P < 0.001$).

Conclusions: Although low MLH1 expression and IS-high may be associated with better prognosis, low MLH1 expression may be also associated with low chemosensitivity.

Legal entity responsible for the study: Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

655P Prognostic significance of lymphocyte-activation gene-3 expression in chemoradiotherapy-naïve esophageal and gastric adenocarcinoma

C. Siesing, M.C. Svensson, C. Hedner, B. Nodin, D. Borg, K. Jirstrom

Department of Clinical Sciences, Oncology and Pathology, Lund University, Faculty of Medicine, Lund, Sweden

Background: Neoadjuvant and/or adjuvant treatment has led to an improved survival in patients with resectable gastroesophageal adenocarcinoma (GEAC). Nevertheless, survival rates remain poor and, hence, there is a great need to identify novel treatment strategies and relevant complementary diagnostics. Immunotherapies targeting the PD-1/PD-L1 checkpoints have shown promising results, but simultaneous inhibition of other fundamental checkpoints, such as lymphocyte-activation gene-3 (LAG-3), may further improve clinical outcome. The expression and prognostic significance of LAG-3 in GEAC has however not yet been described. Herein, we examined the expression of LAG-3 in tumour-infiltrating immune cells (TIC) in chemoradiotherapy-naïve GEAC and paired lymph node metastases, with particular reference to its relationship with PD-1 and PD-L1 expression, mismatch repair (MMR) status, and survival.

Methods: Immunohistochemical LAG-3 expression was analysed in tissue microarrays with 165 primary tumours and 72 paired lymph node metastases from a retrospective consecutive cohort of patients with chemoradiotherapy-naïve resected GEAC. LAG-3 expression was denoted in categories of negative (0), low (1-10) and high (>10). PD-1, PD-L1 expression and MMR status had been previously analysed.

Results: The distribution of LAG-3 expression in primary tumours was 55.8% negative, 28.5% low, and 15.8% high. The corresponding figures in lymph node metastases were 48.6% negative, 37.5% low, and 13.9% high. LAG-3 expression did not differ by tumour location. Positive LAG-3 expression in primary tumours was an independent factor for prolonged overall survival in the entire cohort (HR = 0.64, 95% CI 0.43-0.96), and in gastric cancer (HR = 0.35, 95% CI 0.17-0.74). LAG-3 expression in primary tumours was significantly associated with PD-L1 expression in both tumour cells and TIC, and with PD-1 expression in TIC, but not with MMR status.

Conclusions: LAG-3 is expressed in a considerable proportion of GEAC, with a similar distribution in primary tumours and lymph node metastases. Positive LAG-3 expression is an independent favourable prognostic factor, particularly in gastric cancer.

Legal entity responsible for the study: Lund University.

Funding: The Swedish Research Council, The Swedish Cancer Society, University Hospital Research Grant, Mrs Berta Kamprad Foundation, Swedish Government Grant for Clinical Research (ALF).

Disclosure: All authors have declared no conflicts of interest.

656P Diagnosis of invasion depth in resectable advanced gastric cancer for neoadjuvant chemotherapy: An exploratory analysis of JCOG1302A

Y. Sato[1], J. Mizusawa[1], K. Nakamura[1], T. Fukagawa[2], H. Katai[3], S. Haruta[4], M. Yamada[5], M. Takagi[6], S. Tamura[7], T. Yoshimura[8], T. Inada[9], N. Hirabayashi[10], I. Wada[11], Y. Kodera[12], M. Tokunaga[13], T. Yoshikawa[3], N. Boku[14], T. Sano[15], M. Sasako[16], M. Terashima[17]

[1]JCOG Data Center/ Operations Office, National Cancer Center, Tokyo, Japan, [2]Department of Surgery, Teikyo University Hospital, Tokyo, Japan, [3]Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan, [5]Department of Surgery, Gifu Municipal Hospital, Gifu, Japan, [6]Department of Gastroenterological Surgery, Shizuoka General Hospital, Shizuoka, Japan, [7]Surgery Division, Yao Municipal Hospital, Osaka, Japan, [8]Department of Digestive Surgery, Tenri Hospital, Nara, Japan, [9]Department of Surgery, Tochigi Cancer Center, Tochigi, Japan, [10]Department of Surgery, Hiroshima City Asa Hospital, Hiroshima, Japan, [11]Department of Surgery, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan, [12]Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, [13]Gastric Surgery Division, National Cancer Center Hospital East, Chiba, Japan, [14]Gastrointesitnal Medical Onclogy, National Cancer Center Hospital, Tokyo, Japan, [15]Department of Gastroenterological Surgery, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [16]Department of Surgery, Yodogawa Chrisitan Hospital, Osaka, Hyogo, Japan, [17]Department of Gastric Surgery, Shizuoka Cancer Center, Shizuoka, Japan

Background: Neoadjuvant chemotherapy (NAC) has been increasingly used for gastric cancer. JCOG1302A investigated whether cT3-4/ N1-3 was a suitable criterion for NAC minimizing the contamination of pStage I. In that study, 77.2% of tumors diagnosed as cT3-4 by a combination of endoscopy and computed tomography (CT) were pT3-4. The role of endoscopic ultrasonography (EUS) or additional options in diagnosis of invasion depth was unclear.

Methods: Using data of JCOG1302A, we evaluated accuracy of endoscopic or CT diagnosis of cT3-4 to detect pT3-4, by comparing positive predictive value (PPV), negative predictive value (NPV), and kappa index (KI) between conventional endoscopy (CE) with and without EUS, CT of 5 mm and 1 mm slice, and CT with and without foaming agent (FA).

Results: Data from 1232 patients enrolled in 53 institutions were analyzed (Table). Overall, there is no remarkable difference in any comparison. More specifically, PPV and KI were slightly higher in CE alone rather than in CE combined with EUS. Although NPV was higher in 1 mm slice CT and CT with FA, PPV was higher in 5 mm slice CT and CT without FA. Table 1 Comparison of PPV, NPV, and KI between CE alone and CE combined with EUS, between 5 mm slice CT and 1 mm slice CT, and between CT without FA and CT with FA.

Table: 656P

	CE alone (n = 1232)	CE combined with EUS (n = 91)
PPV	79.2% (76.2-81.9)	73.7% (60.3-84.5)
NPV	59.2% (54.3-63.9)	58.8% (40.7-75.4)
KI	0.38 (0.33-0.44)	0.32 (0.12-0.52)
	5 mm slice CT (n = 1042)	1 mm slice CT (n = 255)
PPV	77.8% (74.6-80.7)	75.5% (68.9-81.4)
NPV	62.9% (57.1-68.5)	71.2% (57.9-82.2)
KI	0.38 (0.32-0.44)	0.39 (0.28-0.51)
	CT without FA (n = 840)	CT with FA (n = 368)
PPV	78.6% (75.1-81.8)	75.1% (69.5-80.1)
NPV	60.9% (54.4-67.3)	69.7% (59.7-78.5)
KI	0.38 (0.31-0.44)	0.40 (0.30-0.50)

95%CIs are shown in brackets

Conclusions: Additional options such as EUS, 1 mm slice CT, or FA in CT may not improve diagnostic accuracy of invasion depth in resectable advanced gastric cancer.

Legal entity responsible for the study: Japanese Clinical Oncology Group.

Funding: National Cancer Center Research and Development Fund (23-A-16, 23-A-19 and 26-A-4) from the Ministry of Health, National Cancer Center Research and Development Fund from the Ministry of Health, Labour and Welfare.

Disclosure: Y. Sato, J. Mizusawa: Grants: Ministry of Health, Labour and Welfare, Japan, Japan Agency for Medical Research and Development (AMED). K. Nakamura: Grants: Ministry of Health, Labour and Welfare, Japan, Japan Agency for Medical Research and Development (AMED); Fees: Bayer Pharma, Chugai Pharmaceutical. All other authors have declared no conflicts of interest.

657P Can preoperative diagnosis select therapeutic target of neoadjuvant chemotherapy for gastric cancer?

K. Hara[1], T. Hayashi[2], Y. Shimoda[2], M. Nakazono[2], S. Nagasawa[2], Y. Kumazu[2], T. Yamada[2], Y. Rino[3], M. Masuda[3], T. Ogata[2], T. Oshima[2], T. Yoshikawa[4]

[1]Gastroenterological Surgery, Kanagawa Cancer Center, Yokohama, Japan, [2]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, [3]Surgery, Yokohama City University, Yokohama, Japan, [4]Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan

Background: Precise clinical staging by diagnostic imaging is essential for determination of initial treatment for gastric cancer. Indeed, cT3 and T4 diseases with lymph node metastasis (T3-4/N+) were candidate of neoadjuvant chemotherapy (NAC) followed by gastrectomy, defined as cStageIII in 8th edition of AJCC/UICC TNM classification. However, pathological T3-4/N+ diseases could contain some cases that were underestimated as cStage I/II and excluded from target of NAC. This study aims to examine the accuracy of preoperative diagnosis and the prognosis from each cStage in pathological T3-4/N+ gastric cancers.

Methods: The study analyzed gastric cancer patients who received gastrectomy and diagnosed as pathological T3-4/N+ deseases between Jun 2000 and Jun 2012 at Kanagawa Cancer Center. The clinical and pathological data were analyzed retrospectively. Patients who received preoperative chemotherapy were excluded. The proportion of each cStage was investigated based on the 8th edition of AJCC/UICC, and 5-year overall survival rate (5yOS) for each cStage was calculated using the Kaplan-Meier method.

Results: In total, 337 patients were diagnosed as pathological T3-4/N+ diseases and included in this study. In clinical staging, 48 patients (14.2%) were diagnosed as cStageI, 10 patients (3.0%) as cStageIIA, 109 patients (32.3%) as cStageIIB, 159 patients (47.2%) as cStageIII, 6 patients (1.8%) as cStageIVA, and 5 patients (1.5%) as cStageIVB. 5yOS stratified by cStage was 77.0% in cStageI, 90.0% in cStageIIA, 52.2% in cStageIIB, 49.0% in cStageIII, and 0% in cStageIVA/IVB. Furthermore, survival curve of cStageIIB and cStageIII were approximately overlapped.

Conclusions: Among pathological T3-4/N+ diseases, the underestimation as cStageI and cStageIIA was acceptable, because of relative low frequency and good prognosis without NAC. Meanwhile, the underestimation as cStageIIB could not be ignored, because patients diagnosed as cStageIIB occupied one third of pathological T3-4/N+ disease and had poor prognosis comparable to cStageIII. We need to consider underestimation of preoperative diagnosis, when we determine target of NAC for advanced gastric cancer.

Legal entity responsible for the study: Kentaro Hara.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

658P Patient reported outcomes (PRO) results from phase II MONO and FAST zolbetuximab (IMAB362) trials in patients with advanced CLDN18.2+ gastric and gastroesophageal junction adenocarcinoma (GA/GEJA)

R. Morlock[1], M.R. Krukas-Hampel[2], Ö. Türeci[3]

[1]HEOR, Astellas Pharma Global Development, Inc., Northbrook, IL, USA, [2]Advisory Analytics, IQVIA Global Consulting Services, New York, NY, USA, [3]CI3- Cluster of Individualized Immune Intervention, Formerly Ganymed Pharmaceuticals GmbH, Mainz, Germany

Background: The single-arm MONO trial (NCT01197885) assessed IMAB362 (600 mg/m^2) monotherapy as salvage therapy in GA/GEJA patients and showed a 30% disease control rate. The FAST trial (NCT01630083) assessed IMAB362 (loading dose 800 mg/m^2 then 600 mg/m^2) combination therapy as 1st line therapy (IMAB362+EOX followed by single agent IMAB362 maintenance until disease progression [DP]) vs EOX alone in GA/GEJA patients. IMAB362+EOX significantly prolonged progression-free and overall survival. We describe the MONO and FAST PRO results.

Methods: EORTC QLQ-C30 and STO22 were collected at baseline, end of IMAB362 treatment (EOT), and every 8 wks post-EOT in MONO; and at baseline, Cycle 5, EOX EOT, and post-EOT every 12 wks until DP in FAST. Both studies used mixed model repeated measures (MMRM) assuming missing at random to assess HRQoL changes from baseline. The proportion of MONO patients per minimally clinically important difference (MCID) category (deterioration, no change, improvement) was evaluated at EOT; in FAST, time to HRQoL deterioration (TTD) based on MCID thresholds was assessed using Kaplan-Meier estimates and Cox models.

Results: Patients in MONO (n = 40) had stable scores in all STO22 domains but deteriorated in C30 functional (role, cognitive and physical) and symptom scales (fatigue, insomnia, pain, nausea/vomiting and appetite loss). MONO treatment responders (n = 9) showed less deterioration in C30 scales. Most patients stayed stable or had clinically meaningful improvement in HRQoL. In FAST (EOX n = 74, IMAB362+EOX n = 68), a significant difference in change from baseline was only seen for the nausea/vomiting symptom scale (P=.01) favoring EOX. IMAB362+EOX delayed TTD for global health status, trouble belching, eating restrictions, feeling tense, pain interference, acid indigestion/burning, shortness of breath and HRQoL vs EOX (all P<.05). Patients remaining on IMAB362 alone post EOX EOT generally showed better HRQoL and physical functioning than EOX alone.

Conclusions: For patients with advanced CLDN18.2 expressing GA/GEJA, IMAB362 maintained HRQoL and delayed TTD in both monotherapy and combination chemotherapy settings.

Clinical trial identification: NCT01197885 and NCT01630083.

Legal entity responsible for the study: Astellas Pharma, Inc.

Funding: Astellas Pharma, Inc.

Disclosure: R. Morlock: Employee: Astellas; Personal fees: Abbot Medical Optics, Ironwood, Genetech. M.R. Krukas-Hampel: Employee: IQVIA, contracted to do this analysis by Astellas. Ö. Türeci: Stock option owner, ex-shareholder, co-founder, CEO: Ganymed AG; Consultancy fee: Astellas; Several patent families are pending, issued, or licensed. Those relevant to this work have been acquired by Astellas.

659P Avelumab (anti–PD-L1) in Japanese patients with advanced gastric or gastroesophageal junction cancer (GC/GEJC): Updated results from the phase Ib JAVELIN solid tumour JPN trial

T. Doi[1], S. Iwasa[2], K. Muro[3], T. Satoh[4], S. Hironaka[5], T. Esaki[6], T. Nishina[7], H. Hara[8], N. Machida[9], Y. Komatsu[10], Y. Shimada[11], S. Otsu[12], S. Shimizu[13], V. Chand[14], M. Watanabe[15]

[1]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [2]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan, [4]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Hospital, Osaka, Japan, [5]Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan, [6]Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan, [7]Department of Gastrointestinal Medical Oncology, Shikoku Cancer Center, Matsuyama, Japan, [8]Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan, [9]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [10]Cancer Center, Hokkaido University Hospital, Sapporo, Hokkaido, Japan, [11]Clinical Oncology, Kochi Health Sciences Center, Kochi, Japan, [12]Department of Medical Oncology and Hematology, Oita University Hospital, Oita, Japan, [13]Biostatistics, Merck Serono Co., Ltd, Tokyo, Japan, [14]Clinical Development, EMD Serono, Inc, Billerica, MA, USA, [15]Clinical Development, Merck Serono Co., Ltd, Tokyo, Japan

Background: Avelumab, a human anti–PD-L1 IgG1 monoclonal antibody that can induce innate effector function against tumor cells in preclinical models, is an approved treatment for metastatic Merkel cell carcinoma in various countries and platinum-treated advanced urothelial carcinoma in the US and Canada. We report updated results from the dose-expansion part of a phase 1b trial of avelumab in Japanese patients (pts) with advanced GC/GEJC (NCT01943461).

Methods: Pts had stage IV GC/GEJC adenocarcinoma and progression after 1 or 2 prior lines of chemotherapy including a platinum and fluoropyrimidine agent (initially enrolled pts) or progression after platinum/fluoropyrimidine followed by a taxane or irinotecan (later pts). Pts received avelumab 10 mg/kg Q2W by IV infusion until confirmed progression, unacceptable toxicity or withdrawal. PD-L1 expression was assessed using the Dako PD-L1 IHC 73-10 assay (≥1% tumor cell cutoff).

Results: At data cutoff on Aug 10, 2016, 40 pts had received avelumab (median treatment duration 2.7 mo; range 0.5–21.4). 21 pts (52.5%) had received ≥3 prior lines of therapy for advanced disease. The objective response rate (ORR) was 10.0% (95% CI 2.8–23.7), including complete response in 1 pt and partial response in 3 pts. 17 pts had stable disease as best response and the disease control rate was 52.5%. Median progression-free survival was 2.5 mo (95% CI 1.4–2.8). Median overall survival (OS) was 9.1 mo (95% CI 7.2–11.2) and the 12-mo OS rate was 31.0% (95% CI 15.6–47.8). In evaluable pts with PD-L1 + (n = 11) or PD-L1 − (n = 27) tumors, ORR was 27.3% and 3.7%, respectively. Treatment-related adverse events (TRAEs) of any grade occurred in 32 pts (80.0%), including infusion-related reaction (27.5%; all grade 1/2), pruritus (15.0%), pyrexia (12.5%) and rash (10.0%) in ≥ 10% of pts. Grade 3 TRAEs occurred in 3 pts (7.5%; ALT increase, anemia and hyponatremia); no pt had a grade ≥4 TRAE. 5 pts had an immune-related AE (all grade 1/2); the most common were pruritus (n = 3) and maculopapular rash (n = 2).

Conclusions: Avelumab showed acceptable safety and clinical activity in Japanese pts with advanced GC/GEJC progressed after chemotherapy.

Clinical trial identification: EMR 100070-002 (NCT01943461).

Editorial acknowledgement: Medical writing support was provided by Clinical Thinking Inc, Hamilton, NJ, USA.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany and Pfizer.

Disclosure: T. Doi: Consultancy (Includes expert testimony): Lilly, Japan Chugai Pharma, Kyowa, Hakko, Kirin, MSD, Daiichi Sankyo, Amgen, Sumitomo, Dainippon, Taiho Pharmaceutical; Research funding: Taiho Pharmaceutical, Novartis, Merck Serono, Astellas Pharma, MSD, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Lilly, Japan Sumitomo Group, Chugai Pharma, Kyowa, Hakko, Kirin, Daiichi Sankyo, Celgene, Bristol-Myers Squibb, Abbvie, Quintiles. S. Iwasa: Honoraria: Chugai, Takeda; Research funding for institution: Otsuka, Taiho, Chugai, AstraZeneca, Novartis, Sanofi, Ono, Eli Lilly, Merck Serono, Daiichi-Sankyo, Nano Carrier, Teijin Pharma, Dainippon-Sumitomo, Astellas, Bayer, Abbvie, Eisai. K. Muro: Honoraria: Chugai, Taiho, Merck Serono, Yakult, Takeda. T. Satoh: Honoraria: Merck-Serono, Bristol-Myers Squibb, Chugai Pharmaceutical; Consulting or advisory role: Chugai Pharmaceutical, Eli Lilly, Merck Serono, Bristol-Myers Squibb; Research funding: Chugai Pharmaceutical, Yakult Honsha. S. Hironaka: Honoraria: Taiho, Yakult Honsha, Takeda, Novartis; Consulting or advisory role: Eli Lilly, Yakult Honsha. T. Esaki: Research funding: Merck Serono. T. Nishina: Honoraria: Merck Serono. H. Hara: Honoraria: Chugai Pharma; Taiho Pharmaceutical, Merck Serono, Yakult Honsha, Lilly, Ono Pharmaceutical, Takeda; Consulting or Advisory role: Ono Pharmaceutical, Chugai Pharma, Merck Serono, MSD; Research Funding for institution: AstraZeneca, Chugai Pharma, Merck Serono, MSD, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda, Boehringer Ingelheim, Dainippon Sumitomo Pharma, Daiichi Sankyo, Lilly, Pfizer, LSK Biopharma, Eisai, Incyte. Y. Komatsu: Honoraria: Novartis, Pfizer, Bayer; Speakers' bureau: Taiho, Lilly, Chugai, Merck, Novartis, Pfizer, Bayer; Research funding: Taiho, Lilly, MSD, Ono, Novartis, Bayer, Chugai, Yakult. S. Shimizu: Employee: Merck Serono Co, Ltd. V. Chand: Employee: EMD Serono Research & Development Institute, Inc; Stock Shareholder: Bristol-Meyers Squibb M. Watanabe: Employee: Merck Serono Co., Ltd. All other authors have declared no conflicts of interest.

660P Safety and efficacy of a DKK1 inhibitor (DKN-01) in combination with pembrolizumab (P) in patients (Pts) with advanced gastroesophageal (GE) malignancies

S.J. Klempner[1], J. Bendell[2], V. Meucci Villaflor[3], L. Tenner[4], S. Stein[5], C.A. Sirard[6], W. Newman[7], M. Kagey[7], K. Schlienger[8], J. Strickler[9]

[1]Medical Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA, [2]GI Oncology Research, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [3]Medical Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [4]Medical Oncology, University of Texas Health Science Center, San Antonio, TX, USA, [5]Medical Oncology, Yale School of Medicine, New Haven, CT, USA, [6]Medical Oncology, Leap Therapeutics, Inc., Cambridge, MA, USA, [7]Research, Leap Therapeutics, Inc., Cambridge, MA, USA, [8]Oncology, Merck & Co, Kenilworth, NJ, USA, [9]Medical Oncology, Duke University Medical Center, Durham, NC, USA

Background: Dickkopf-1 (DKK1) is a modulator of the Wnt and PI3K/AKT signaling pathways and contributes to an immunosuppressive tumor microenvironment by activating MDSCs and Tregs. DKN-01 (D), an mAb against DKK1, acts on innate immune cells, and in preclinical studies demonstrates upregulation of both PD-L1 and IFNγ-related chemokines, suggesting a role for immune checkpoint combination. Anti-PD-1 plus DKN-01 shows additive antitumor effects in the B16 syngeneic mouse model; clinical studies are underway. GE cancers commonly overexpress DKK1 and harbor Wnt pathway alterations.

Methods: Phase 1b study to evaluate dose, safety and efficacy of D (150 mg or 300 mg on Days 1 & 15) plus P (200 mg on Day 1) of each 21-day cycle in pts with advanced GE cancer. Safety, efficacy, and correlative analyses (cytokines, PBMC immunophenotyping, tumor genomics and intra-tumoral DKK1/PD-L1) are ongoing.

Results: Pts enrolled in 2 cohorts: D (150 mg [n = 2] or 300 mg [n = 11]) + P. All 13 pts had adenocarcinomas (4 pts: EC, 6 pts: GEJ, 3 pts: GC). Three pts (23%) were refractory to prior checkpoint inhibitor, and only 1 pt was known to be PD-L1+ at study entry. No DLTs or treatment related SAEs were observed. Most TEAE were Grade 1/2 and commonly gastrointestinal disorders. ≥Grade 3 TEAE included hyponatremia & anorexia (each 2 pts), lymphopenia, transfusion reaction, GI bleed, abdominal pain, dehydration, weight loss, thrombotic event & weakness (each 1 pt); only lymphopenia felt related to D. Among 9 evaluable patients there was one confirmed PR, SD in 5 pts (including one IO-refractory pt with minor response) and PD in 3 pts. The 6-week disease control rate was 75%; 6 pts remain on therapy. Most PR/SD pts have had downward trend of peripheral MDSC; more evident in pt with PR. Complete cohort details and correlative work will be presented.

Conclusions: Preliminary results demonstrate that D + P is well tolerated with no new safety signals and shows encouraging early efficacy signals in advanced GE cancer. A subset of pts with features typically associated with lower response to single agent anti-PD-1 therapy (KRAS amp, PD-L1 neg, and MSS) exhibited prolonged clinical benefit and warrant further study. Expansion to confirm efficacy is ongoing.

Clinical trial identification: NCT02013154.

Legal entity responsible for the study: Leap Therapeutics, Inc.

Funding: Leap Therapeutics, Inc.

Disclosure: S.J. Klempner: Consultant/advisory: Lilly, Astellas; Research funding (institutional): Leap, Merck, Incyte. J. Bendell: Gilead, Genentech, BMS, Five Prime, Lilly, Merck, MedImmune, Celgene, EMD Serono, Taiho, Macrogenics, GSK, Novartis, OncoMed, Leap, TG Therapeutics, AstraZeneca, BI, Daiichi Sankyo, Bayer, Incyte, Apexigen, Roche, Koltan, SynDevRx, Forty Seven, Abbvie, StemCentrix, Array, Onyx, Sanofi, Takeda, Abbott, Eisai, Celldex, Agios, ARMO, CytoMx, Nektar, ARMO, Boston Biomedical, Ipsen, Merrimack, Novartis, Tarveda, Tyrogenex, Oncogenex, Marshall Edwards, Pieris, Mersana, Calithera, Blueprint, Gritstone, Evelo, FORMA, Forty Seven, EMD Serono, Merus. V. Meucci Villaflor: Advisory board: Takeda, Genentech. S. Stein: Advisory board: Genentech/Roche, Merck. C.A. Sirard, W. Newman, M. Kagey: Employee: Leap Therapeutics, Inc. including compensation, stock options and travel award. K. Schlienger: Employee: Merck & Co, USA with compensation, stock option and travel award. J. Strickler: Research support: Leap Therapeutics. All other authors have declared no conflicts of interest.

661P Updated results from a phase I trial of M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with pretreated recurrent or refractory gastric cancer

Y-J. Bang[1], T. Doi[2], S. Kondo[3], H.C. Chung[4], K. Muro[5], I. Dussault[6], C. Helwig[7], M. Osada[8], Y-K. Kang[9]

[1]Internal Medicine (Medical Oncology), Seoul National University Hospital, Seoul, Republic of Korea, [2]Medical Oncology, National Cancer Center Hospital East, Chiba, Japan, [3]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [4]Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea, [5]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan, [6]Clinical Biomarkers, Immuno-Oncology, EMD Serono, Billerica, MA, USA, [7]Biostatistics, Merck KGaA, Darmstadt, Germany, [8]Medical Oncology, Merck Serono, Tokyo, Japan, [9]Medical Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Objective response rates (ORRs) in patients (pts) with gastric cancer (GC) treated with anti–PD-(L)1 antibodies range from 11.2% (PD-L1 unselected) to 15.5% (PD-L1+) for second line therapy. Inhibiting the transforming growth factor β (TGF-β) pathway, which plays a key role in tumor immunosuppression, may enhance the response to anti–PD-L1 treatment. We report results for M7824, an innovative first-in-class bifunctional fusion protein composed of a monoclonal antibody against PD-L1 fused with the extracellular domain of TGF-β receptor II (a TGF-β "trap") in pts with GC.

Methods: Pts in Asia with recurrent GC or gastroesophageal junction adenocarcinoma for whom standard therapy does not exist or has failed were enrolled in this expansion cohort of the ongoing, phase 1, open-label trial NCT02699515 and received M7824 1200 mg q2w until disease progression, unacceptable toxicity, or trial withdrawal. The primary objective is to assess safety/tolerability; secondary objectives include assessment of best overall response (BOR) per RECIST v1.1.

Results: As of February 15, 2018, 31 heavily pretreated pts with advanced GC (74.2% received ≥3 prior therapies) received M7824 for a median duration of 10.1 (range, 2-52) wks; 4 pts remained on treatment. 6 pts (19.4%) had grade 3 treatment-related adverse events (TRAEs): anemia (2), diarrhea (1), abnormal hepatic function (1) and rash (2). No grade 4 TRAEs occurred. 1 Grade 5 AE of death occurred after 5 doses with suspected rupture of pre-existing thoracic aortic aneurysm as per investigator's assessment. 7 pts had a confirmed objective response based on investigator-assessed BOR (ORR, 22.6%; DCR, 38.7%). There were 5 partial responses (2.4, 3.6+, 4.1+, 8.3+, and 9.7+ mo) and 2 complete responses (0.3+ and 9.0 mo). The initial assessment of PD-L1 tumor expression (22C3 assay) does not hint towards predictivity for ORR.

Conclusions: M7824 monotherapy had a manageable safety profile in heavily pretreated Asian pts (74% ≥3 prior therapies) with GC. Early signs of clinical efficacy, with an ORR of 22.6% and long lasting responses, are encouraging. Updated data will be presented.

Clinical trial identification: NCT02699515.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: Y-J. Bang: Consultancy (Includes expert testimony): AstraZeneca, Novartis, Genentech/Roche, MSD, Pfizer, Bayer, BMS, Eli Lilly, Merck Serano, FivePrime, Taiho, Ono, ADC Therapeutics, GreenCross, Samyang Biopharm; Research funding (institution): AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serono, Bayer, GSK, BMS, Pfizer, Eli Lilly, Boeringer-Ingelheim, MacroGenics, Boston Biomedical, FivePrime, CKD Pharma, Ono, Otsuka, Taiho, Takeda, BeiGene, Hanmi, Green Cross, Curis, Daiichi Sankyo, Astellas. T. Doi: Consultancy (Includes expert testimony): Lilly Japan, Chugai Pharma, Kyowa Hakko Kirin, MSD, Daiichi Sankyo, Amgen, Sumitomo Dainippon, Taiho Pharmaceutical; Research funding: Taiho Pharmaceutical, Novartis, Merck Serono, Astellas Pharma, MSD, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Lilly Japan, Sumitomo Group, Chugai Pharma, Kyowa Hakko Kirin, Daiichi Sankyo, Celgene, Bristol-Myers Squibb, Abbvie, Quintiles. S. Kondo: Research funding: MSD, Bayer, ASLAN, Pfizer, AZ, Lilly. H.C. Chung: Consultancy (Includes expert testimony): Taiho, Celltrion, MSD, Lilly, Quintiles, BMS, MerckSerono; Research funding: Lilly, GSK, MSD, MerckSerono, BMS/Ono, Taiho; Speakers bureau MerckSerono, Lilly, Foundation Medicine. I. Dussault:

Employee: EMD Serono C. Helwig: Employee, Equity ownership: Merck KGaA, Germany. M. Osada: Employee: Merck Serono, Japan. All other authors have declared no conflicts of interest.

662P Biomarker-guided enrichment of the antitumor activity of margetuximab (M) plus pembrolizumab (P) in patients with advanced HER2+ gastric adenocarcinoma (GEA)

D.V.T. Catenacci[1], H. Park[2], H.E. Uronis[3], Y-K. Kang[4], M. Ng[5], P. Gold[6], J. Lacy[7], P.C. Enzinger[8], S. Park[9], K-W. Lee[10], J. Yen[11], J. Odegaard[12], A. Franovic[13], J. Baughman[14], J. Muth[15], A. Wynter-Horton[16], T. Wu[17], J. Wigginton[18], J.K. Davidson-Moncada[19], Y-J. Bang[20]

[1]Medicine, The University of Chicago Medical Centre, Chicago, IL, USA, [2]Oncology, Washington University, St. Louis, MO, USA, [3]Department of Medicine, Duke University Medical Center, Durham, NC, USA, [4]Division of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Songpa-gu, Republic of Korea, [5]Division of Medical Oncology, National Cancer Centre (NCC), Singapore, [6]GI Oncology, Swedish Medical Center, Seattle, WA, USA, [7]Medical Oncology, Yale School of Medicine, New Haven, CT, USA, [8]Gastrointestinal Cancer Center, Dana-Farber Cancer Institute, Boston, MA, USA, [9]Hematology-Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [10]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea, [11]Bioinformatics, Guardant Health, Redwood City, CA, USA, [12]Guardant Health, Redwood City, CA, USA, [13]Medical Oncology, Guardant Health, Redwood City, CA, USA, [14]Clinical Development, MacroGenics, Inc., Brisbane, CA, USA, [15]Research, MacroGenics, Inc., Rockville, MD, USA, [16]Clinical Operations, MacroGenics, Inc., Rockville, MD, USA, [17]Biostatistics, MacroGenics, Inc., Rockville, MD, USA, [18]Clinical, MacroGenics, Inc., Rockville, NY, USA, [19]Clinical Development, MacroGenics, Inc., Rockville, NY, USA, [20]Internal Medicine (Medical Oncology), Seoul National University Hospital, Seoul, Republic of Korea

Background: Trastuzumab (T) + chemo is standard 1st line therapy (tx) for HER2+ GEA patients (pts). Pts typically progress in 6-8 months, with loss of HER2 positivity in 40% of treated pts. No anti-HER2 agents are approved in the post-T setting. We report the results of M, an anti-HER2 monoclonal antibody Fc-optimized for antibody-dependent cellular cytotoxicity, + P in HER2+ GEA pts and describe potential strategies for biomarker-guided response enrichment based on ERBB2 amplification and/or PD-L1 expression.

Methods: HER2+, PD-L1-unselected, 2nd line GEA pts post T progression received M (15 mg/kg Q3) + P (200 mg Q3). Safety, objective response rate (ORR), median overall and progression-free survival (mOS, mPFS), disease control rate (DCR), circulating-tumor DNA (ctDNA), and tumor PD-L1 expression were assessed.

Results: At data cutoff, 60 GEA pts were dosed in cohort expansion; 16.7% had treatment-related adverse events $\geq$ Grade 3. Overall, 21.6% had objective response (OR), 10 confirmed and 3 unconfirmed. DCR was 55% and mOS was 15.6 mos (95% CI: 7.26, NR). In GC pts, OR occurred in 10 of 34 (29.4%), mPFS was 4.24 mos (95% CI: 1.68, 5.62), and mOS not reached. Notably, only 31 of 51 (61%) of pts with baseline ctDNA testing showed ERBB2-amplification; 21 of 30 (70%) of pts with fresh tumor biopsy were HER2 3+ by IHC (80% concordance). Tumors were PD-L1+ positive in 13 of 28 (46%) pts tested, with higher rates in pts with GC. The presence of ERBB2 amplification by ctDNA and tumor PD-L1 expression by IHC were both associated with increased probability of OR: 33.3% v. 10.5% ($p = 0.0948$) and 43.8% v. 16.7% ($p = 0.0769$), respectively. ORR was 5 of 8 (62.5%) in ERBB2 amplified/PD-L1+ pts. In pts with activating HER2 mutations DCR was 11/15 (73%), indicating ADCC.

Conclusions: Consistent with prior tissue-based reports, many GEA pts progressing on T have lost ERBB2 amp. ERBB2 status by ctDNA NGS post-T could help identify patients more likely to respond to M+P, particularly in PD-L1+ pts. Our results suggest that M+P is well tolerated and has encouraging preliminary activity in 2nd line HER2+ GEA. Biomarker selection may further enrich for responding pts, advancing a potential chemo-free regimen in this population.

Clinical trial identification: NCT02689284.

Legal entity responsible for the study: MacroGenics, Inc.

Funding: MacroGenics, Inc.

Disclosure: D.V.T. Catenacci: Honoraria: Merck, BMS, Lilly, Genentech/Roche, Amgen, Taiho, Guardant Health, Foundation Medicine; Research funding: Genentech/Roche. H.E. Uronis: Consulting, Advisory role: Bristol-Myers Squibb; Research funding: Genentech/Roche, Bristol-Myers Squibb, Advaxis, MacroGenics, Merck. Y-K. Kang: Consulting, Advisory role: Lily/ImClone, Taiho Pharmaceutical, Ono Pharmaceutical, Roche/Genentech, Novartis; Research funding: LSK Biopharma. M. Ng: Consulting, Advisory role: MSD Oncology, Bristol-Myers Squibb; Honoraria: Taiho Pharmaceutical; Research funding: ASLAN Pharmaceuticals. J. Lacy: Advisory board: Celgene. P.C. Enzinger: Consultant: Astellis, Celgene, FivePrime, Lilly, Loxo, Merck, Taiho. K-W. Lee: Research funding: AstraZeneca/Medimmune, Green Cross Corp, MSD, Ono Pharmaceutical, Merck KGaA, Five Prime Therapeutics, MacroGenics, ASLAN Pharmaceuticals, LSK BioPharma, Array BioPharma, Pharmacyclics, Pfizer. J. Yen, A. Franovic: Employee: Guardant Health. J. Odegaard: Employee, Stock holder: Guardant Health. J. Baughman: Employee: MacroGenics, Inc. J. Muth, T. Wu, A. Wynter-Horton: Employee, Stock ownership: MacroGenics, Inc. J. Wigginton, J.K. Davidson-Moncada: Employee, Leadership, Stock and other ownership interests: MacroGenics. Y-J. Bang: Consulting, Advisory role: Samyang; Research funding: AstraZeneca/Medimmune, Novartis, Genentech/Roche, MSD, Merck/Serano, Bayer, GlaxoxSmithKline, Bristol-Myers Squibb, Pfizer, Lilly, Boehringer Ingelheim, MacroGenics, Boston Miomedical, kFive Prime Therapeutics, Chong Kun Dang Pharmaceutical, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda, BeiGene, Curis, Green Cross Corp. All other authors have declared no conflicts of interest.

663P HER2 alterations is associated with higher tumor mutation burden in gastric cancer

B. Wei[1], Z. Li[2], Q. Han[3], X. Xing[4], Y. Hao[5], J. Zhou[6], Y. Zhang[7], S. Cai[7], Y. Gu[8]

[1]Department of Gastrointestinal Surgery, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China, [2]Department of Gastrointestinal Surgery, Beijing Cancer Hospital, Beijing, China, [3]Department of Oncology, The General Hospital of People's Liberation Army (301 Hospital), Beijing, China, [4]Department of Hematology and Breast Cancer, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shengyang, China, [5]Department of General Surgery, Southwest Hospital, Chongqing, China, [6]Gastrointestinal Surgery, Peking University People's Hospital, Beijing, China, [7]The Medical Department, 3D Medicines Co., Ltd, Shanghai, China, [8]Department of Oncology, Jiangsu Province Hospital, Nanjing, China

Background: Immunotherapy has been proven to be effective in gastric cancer (GC) patients. But the efficacy of immunotherapy for HER2 positive GC has not been defined. Tumor mutation burden (TMB) has been considered as predictive biomarkers of immunotherapy. However, the association between HER2 alterations and TMB in GC is still unclear. We therefore analyzed the associated between HER2 alterations and TMB in Chinese patients with GC.

Methods: Genomic profiling of DNA from fresh or FFPE tumor tissue of 163 Chinese GC was performed using next-generation sequencing on 381 cancer associated genes in 3D Medicines laboratory. Whole-exome sequencing and Genomic Identification of Significant Targets in Cancer (GISTIC) data of 435 GC from The Cancer Genome Altas (TCGA) were also analyzed to evaluate the association between HER2 alterations with TMB. TMB was defined as number of somatic non-synonymous mutations in coding region. HER2 amplification in TCGA was defined as "2" derived from the copy-number analysis algorithms GISTIC.

Results: HER2 alterations including amplification, missense and fusion were present in 11.0% (18/163) of Chinese cohort and 17.0% (74/435) of TCGA cohort. 5.5% (9/163) of Chinese cohort and 14.3% (62/435) of TCGA cohort harbored HER2 amplification. Higher TMB level was observed in patients carrying any HER2 alterations ($P = 0.004$) in Chinese cohort, but the association was not found in TCGA cohort ($P = 0.379$). Prognosis analysis was also performed on patients in TCGA cohort. HER2 status was not an independent risk factors affecting disease free survival (HR, 1.007; 95%CI 0.60-1.69; $P = 0.979$) or overall survival (HR, 0.828; 95%CI 0.56-1.24; $P = 0.357$). Higher TMB level was associated with significantly better disease free survival (median, 43.04 vs. 25.53 months; HR, 0.685; 95%CI 0.47-1.00; $P = 0.048$) and a borderline improvement in overall survival (median, 42.51 vs. 25.69 months; HR, 0.75; 95%CI 0.56-1.02; $P = 0.070$).

Conclusions: HER2 alterations are associated with higher TMB in Chinese GC patients, but not in patients from TCGA. Chinese GC patients may exhibit distinct characteristics. Further studies are warranted to evaluate the efficacy of immunotherapy in GC patients with HER2 alterations.

Legal entity responsible for the study: Yanhong Gu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

664P Phase I/II study of single agent MCLA-128, a full length IgG1 bispecific antibody targeting the HER3 pathway: Overall safety at the recommended phase II dose (R2PD) and preliminary activity in HER2+ metastatic gastric/gastroesophageal junction cancer (GC/GEJ)

M. Alsina[1], A. Varga[2], A. Amatu[3], J.H.M. Schellens[4], P.O. Witteveen[5], V. Boni[6], V. Moreno[7], K. Bol[8], A. Lourbakos[8], M. Magin Ferrer[9], E. Wasserman[10]

[1]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [2]DITEP, Gustave Roussy, Villejuif, France, [3]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, [4]Clinical Pharmacology & Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [5]Hoofd Medische Oncologie, UMC - University Medical Center Utrecht, Utrecht, Netherlands, [6]Medical Oncology, START Madrid-CIOCC HM Hospital Sanchinarro, Madrid, Spain, [7]Medical Oncology-Start Madrid-FJD, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [8]Clinical Pharmacology, Merus NV, Utrecht, Netherlands, [9]Clinical Research, Merus NV, Utrecht, Netherlands, [10]Medical Oncology, Merus NV, Utrecht, Netherlands

Background: MCLA-128 is a novel bispecific antibody targeting HER2 and HER3 receptors with enhanced antibody-dependent cell-mediated cytotoxicity. No DLT was seen during dose escalation and the R2PD was 750 mg q3w. We report safety across solid tumor expansion indications, and efficacy in metastatic GC/GEJ patients (pts).

Methods: Safety, PK, immunogenicity and biomarkers were evaluated in heavily pretreated advanced metastatic cancer pts treated with MCLA-128, 750 mg q3w, 2-hr IV. Response (RECIST 1.1) and clinical benefit rate (CBR; CR + PR + SD $\geq$ 12 wks) were assessed in HER2-positive GC/GEJ pts who had progressed on trastuzumab.

Results: As of 15 Feb 2018, 100 pts were enrolled in the expansion cohorts, 97 of whom were treated. Mean age was 58 ± 11 years, M/F: 26/74, ECOG PS 0/1: 36/63 (1 missing). Pts received a median of 2 MCLA-128 cycles (range 1 - 27). Common related AEs were infusion-related reactions (19%), diarrhea (17%), asthenia/fatigue (15%), nausea (6%), and decreased appetite (5%). Four (4%) pts had suspected related grade 3-4 AEs. No clinically significant LVEF decline (>10% from baseline and LVEF <50%) was seen. Mean T1/2 was ~100 hr (n = 89). Steady state serum concentrations of MCLA-128 were achieved after 2 cycles. As of 25 Mar 2018, 25 GC/GEJ pts were evaluable for response, with a median 3 metastatic sites (range 1-6), and progression on 1-2 prior anti-HER2 agents. They received a median of 2 MCLA-128 cycles (range 1-17). 1 pt had a confirmed CR (8+ cy), 9 pts had SD (sustained: 4, 5, 6, 12, 17 cy). CBR was 24% (6/25 pts). Based on central analysis variable HER2 levels were observed by HER2 IHC, and HER2 amplification was confirmed by FISH in all CBR patients. 4 of the 6 CBR pts had HER2 IHC 3+.

Conclusions: MCLA-128 is very well tolerated with mainly grade 1/2 AEs. Promising single agent antitumor activity was seen in heavily pretreated GC/GEJ pts progressing on anti-HER2 therapy. Further clinical exploration of MCLA-128 in GC/GEJ pts is warranted.

Clinical trial identification: EudraCT: 2014-003277-42.

Editorial acknowledgement: Dr Sarah MacKenzie, Oncology Therapeutic Development.

Legal entity responsible for the study: Merus NV.

Funding: Merus NV.

Disclosure: M. Alsina, A. Varga, A. Amatu, J.H.M. Schellens, P.O. Witteveen, V. Boni, V. Moreno: Institution participates in corporate-sponsored research (Merus NV). K. Bol, A. Lourbakos, M. Magin Ferrer, E. Wasserman: Employee: Merus NV.

665P NRF2 activation via PI3K/AKT/mTOR/RPS6 causes resistance to anti-HER2 agents among HER2 amplified gastric cancer

V. Gambardella[1], F. Gimeno-Valiente[1], N. Tarazona[2], T. Fleitas Kanonnikoff[1], P. Tolosa[1], M. Belda Moscardò[3], B. Garcia-Mico[1], M. Huerta[1], S. Roselló[2], D. Roda[1], A. Cervantes[2], J. Castillo[2]

[1]Medical Oncology, Biomedical Research Institute INCLIVA, Valencia, Spain, [2]Medical Oncology, Hospital Clinico Universitario de Valencia. INCLIVA. CIBERONC Spain, Valencia, Spain, [3]Biobanco INCLIVAPT 17/0015/0049 B.000768, Biomedical Research Institute INCLIVA, Valencia, Spain

Background: Personalized treatment for gastric cancer (GC) represents a big challenge. HER2 is an important driver in 7-34% of cases, playing a relevant role in cell growth and survival. Trastuzumab (T), when combined with chemotherapy, improves survival. No further anti HER2 drugs demonstrated clinical benefit. Resistance to treatment is a serious problem.

Methods: OE 19 and NCI N87, HER2+ GC cell lines, were treated with increasing doses of Lapatinib (L) and T to obtain resistant clones. These were isolated and characterized by performing mutational analysis by Sequenom MassArray and Western blot (WB) to evaluate protein expression. Genome-wide expression profile was conducted. Inhibition of the altered pathways was performed with specific drugs and siRNA to verify if those alterations were responsible for resistance. In vivoexperiment was performed to corroborate the obtained results. A retrospective cohort of HER2 amplified patients treated with T was also analysed. Clinical characteristics and outcomes were collected. An immunohistochemistry (IHC) analysis to evaluate the altered pathway detected in preclinical models was conducted.

Results: L and T resistant clones were obtained. Protein expression underlined the activation of PI3K pathway and of its downstream effector RPS6 protein. Data obtained by microarray were analysed, identifying a large number of genes regulated by NFR2, a transcriptional regulator involved in oxidative stress, detoxification, and drug resistance. NRF2 expression was detected by WB and immunofluorescence. Cells were treated with GSK048 (G), a dual PI3K/TORCH1/2 inhibitor, showing a decrease in cell growth. siRNA of both RPS6 and NRF2 confirmed the decrease of proliferation and when treatment with antiHER2 was administered, sensitivity was restored. Interestingly after inhibiting PI3K pathway NRF2 expression decreases. In xenografts L and G were tested. G reduced both the expression of pRPS6 and NRF2. Patients with high IHC expression of pRPS6 treated with T, experienced worse outcome, suggesting that hyperactivation of the PI3K pathway may make antiHER2 treatment less effective.

Conclusions: Activation of NRF2 via PI3K seems to be consistently related to anti HER2 resistance in HER2 amplified GC.

Legal entity responsible for the study: INCLIVA Biomedical Research Institute.

Funding: INCLIVA Biomedical Research Institute.

Disclosure: All authors have declared no conflicts of interest.

666P Discordance between HER2 expression status in primary tumor and matched malignant ascites in gastric adenocarcinoma

Y. Yang[1], H. Kim[1], S-M. Son[2], H.S. Han[3]

[1]Department of Internal Medicine, Chungbuk National University Hospital, Cheongju-si, Republic of Korea, [2]Department of Pathology, Chungbuk National University Hospital, Cheongju-si, Republic of Korea, [3]Department of Internal Medicine, Chungbuk National University, College of Medicine, Cheongju-si, Republic of Korea

Background: Test for the human epidermal growth factor receptor 2 (HER2) expression is an essential step to select gastric cancer patients for HER2 molecular targeted therapy. Peritoneal carcinomatosis with ascites is the most common manifestation of gastric cancer metastases, prevalence upto 40% in previous reports. The aim of this study is to compare the HER2 expression status in primary gastric adenocarcinoma and paired cell block of malignant ascites.

Methods: Forty-five patients with evaluable tissue samples of both primary gastric lesion and ascites cell block were enrolled. HER2 expression status was evaluated by immunohistochemistry (IHC) in primary tumor and in paired cell blocks of ascites which was confirmed by the qualified pathologist.

Results: HER2 expression was detected in 16 patients (35.6%) from primary gastric adenocarcinoma tissue and in 10 (22.2%) from ascites cell block. HER2 overexpression defined by IHC 3+ was observed in 2 (4.4%) and 3(6.7%) of primary lesion and ascites samples, respectively. However the HER2 status of primary tumor and ascites cell block showed discordance in all of those patients with HER2 overexpression. Patients with HER2 overexpression in primary gastric tissue showed HER2 negativity in ascites cell block, and vise versa. Of the 14 patients whom with two or more serial ascites samples, the HER2 IHC score differences between the samples were observed in five patients (35.7%).

Conclusions: Incidence of HER2 overexpression was slightly lower than previous reports in primary gastric tumor and metastatic ascites samples in this study. Discordances of HER2 expression status between the primary gastric adenocarcinoma and ascites cell block or between serially sampled ascites were observed in a significant proportion of the patients (20%). HER2 testing from both primary tumor and ascites cell block and from serial ascites sample could increase the sensitivity of HER2 overexpression detection, and assist to select adequate patients for HER2 molecular targeted therapy.

Legal entity responsible for the study: Chungbuk National University Hospital.

Funding: Chungbuk National University Hospital.

Disclosure: All authors have declared no conflicts of interest.

667P A phase II study of trastuzumab with S-1 plus oxaliplatin for HER2-positive advanced gastric cancer (HIGHSOX)

K. Chin[1], A. Takashima[2], K. Minashi[3], S. Kadowaki[4], T. Nishina[5], T.E. Nakajima[6], K. Amagai[7], N. Machida[8], M. Gotoh[9], K. Taku[10], N. Ishizuka[11], D. Takahari[1]

[1]Department of Gastroenterology, Cancer Institute Hospital of JFCR, Tokyo, Japan, [2]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [3]Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan, [4]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [5]Department of Gastroenterology, Shikoku Cancer Center, Matsuyama, Japan, [6]Department of Clinical Oncology, St Marianna University School of Medicine, Kawasaki City, Japan, [7]Division of Gastroenterology, Ibaraki Prefectural Central Hospital, Kasama, Japan, [8]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [9]Cancer Chemotherapy Center, Osaka Medical College, Takatsuki, Japan, [10]Department of Medical Oncology, Shizuoka General Hospital, Shizuoka, Japan, [11]Clinical Trial Planning and Management, Cancer Institute Hospital of JFCR, Tokyo, Japan

Background: Trastuzumab with cisplatin and fluoropyrimidines(FUs) improved the overall survival of patients with human epidermal growth factor receptor type 2 (HER2)-positive advanced gastric cancer (AGC). S-1 plus oxaliplatin (SOX) is a one of the standard regimen for HER2-negative AGC especially in Japan. However, to date, few studies have evaluated the efficacy and safety of trastuzumab combined with SOX in patients with HER2-positive AGC.

Methods: This is the multi-central, phase II study that is conducted in 10 Japanese institutions. Patients with HER2-positive AGC received S-1 (80mg/m^2) twice a day orally on days 1–14, oxaliplatin (130mg/m^2) intravenously on day 1, and trastuzumab (course 1, 8mg /kg; course 2-, 6mg/kg) intravenously on day 1 of a 21-day cycle. The primary end point was confirmed response rate (cRR); secondary end points included overall survival (OS), progression-free survival(PFS), and adverse events.The sample size was determined to be 75cases based on a hypothesis of threshold RR of 50% and an expected RR of 65%, 90% power, with an alpha value of 0.1 (one-sided) using the binomial test.

Results: From June 2015 to January 2018, a total of 78 patients were screened, of whom 75 were enrolled and eligible. The median age was 64 years. ECOG PS(0/1);57/18, unresectable/recurrence; 66/9, Gastric/EGJ; 64/11, pathology(tub1/tub2/por/sig); 13/33/24/5, metastatic sites(LNs/liver/peritoneum/lung/bone/others); 40/35/20/9/3/8. The proportion of IHC 3+ was 73.3%. In the full analysis set of 75 patients as of March 2018, cRR was 65.2% (95% confidence interval (CI).52.4–76.5); n = 66: excluding unconfirmed 9 cases; and the disease control rate was 89.4% (95% CI.79.4-95.6). Median OS,

PFS, were estimated as 20.6 (95% CI.14.8–30.6) and 9.4(95% CI.7.4-14.7) months, respectively. Major grade 3 or 4 adverse events included sensory neuropathy (14.7%), neutropenia (9.3%), diarrhea (6.7%), and anemia (6.7%). There were no treatment-related deaths.

Conclusions: Trastuzumab in combination with SOX showed promising activity with well-tolerated toxicities in patients with HER2-positive AGC as well as other platinum and FUs. Final analysis based on confirmed response will be reported at the conference.

Clinical trial identification: UMIN000017602,18/5/2015.

Legal entity responsible for the study: The authors.

Funding: Japanese Foundation for Multidisciplinary Treatment of Cancer.

Disclosure: A. Takashima: Grants: Gilead Sciences, Takeda Pharmaceutical Company; Personal fees: Takeda Pharmaceutical Company, Taiho Pharmaceutical Co., Ltd, Merck, Chugai Pharmaceutical Company P, Sanofi K.K., outside the submitted work. S. Kadowaki: Grants: Boehringer Ingelheim, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Eli Lilly Japan. T. Nishina: Grants, Honoraria: Taiho Pharmaceutical, Chugai Pharmaceutical. T.E. Nakajima: Personal financial interests: Eli Lilly, Sanofi, Chugai, Sawai, Bayer, Bristol, Taiho, Merck, Ono, Takeda, Mochida, MSD; Institutional financial interests: Ono, Taiho, A2 Health Care, JCRO, Daiichi-Sankyo, Mediscience Planning. D. Takahari: Honoraria: Taiho Pharmaceutical, Eli Lilly Japan, Chugai Pharmaceutical, Yakult Honsha. All other authors have declared no conflicts of interest.

668P Updated analysis of a phase II study of SOX plus trastuzumab for the patients with HER2 positive advanced or recurrent gastric cancer: KSCC/HGCSG/CCOG/PerSeUS1501B

S. Yuki[1], K. Shinozaki[2], T. Kashiwada[3], T. Kusumoto[4], M. Iwatsuki[5], H. Satake[6], S. Tokunaga[7], Y. Emi[8], A. Makiyama[9], Y. Kawamoto[1], Y. Komatsu[10], M. Shimokawa[11], H. Saeki[12], E. Oki[12], H. Baba[5], Y. Maehara[12]

[1]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [2]Department of Medical Oncology, Hiroshima Prefectural Hospital, Hiroshima, Japan, [3]Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan, [4]Department of Gastroenterological Surgery / Clinical Research Institute Cancer Research Division, National Kyushu Medical Center, Fukuoka, Japan, [5]Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan, [6]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [7]Medical Information Center, Kyushu University Hospital, Fukuoka, Japan, [8]Department of Surgery, Saiseikai Fukuoka General Hospital, Fukuoka, Japan, [9]Department of Hematology / Oncology, Japan Community Healthcare Organization Kyushu Hospital, Kita-Kyusyu, Japan, [10]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [11]Clinical Research Institute, Cancer Biostatistics Laboratory, National Kyushu Cancer Center, Fukuoka, Japan, [12]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Background: Trastuzumab (T-mab) combined with cisplatin and fluoropyrimidines is the standard first line treatment for the patients with HER2-positive advanced gastric cancer (AGC). We conducted first phase II trial to assess the efficacy and safety of T-mab combined with S-1 and oxaliplatin (HER-SOX130) for HER2-positive AGC or recurrent gastric cancer.

Methods: Patients with IHC 3+ or IHC 2+/FISH positive received 80 mg/m^2 (80-120 mg/body) S-1 per day orally on days 1–14, 130 mg/m^2 oxaliplatin intravenously on day 1, and T-mab (8-mg/kg loading dose and 6 mg/kg thereafter) intravenously on day 1 of a 21-day cycle until one of the criteria for withdrawal of the study treatment occurred. The primary end-point was the response rate (RR). The secondary end-points were adverse events, progression-free survival (PFS), overall survival (OS), time-to-treatment failure (TTF), duration of treatment, time to failure of strategy (TFS) and dose intensity. Adverse events were recorded based on the CTCAE Ver.4.0.

Results: 42 patients were enrolled from June 2015 to May 2016. Efficacy and safety analyses were conducted in the full analysis set of 39 patients. The data cut off specific to the survival status was February 19, 2018. The proportion of patients with IHC 3+ was 87%. The incidence of grade 3 or 4 adverse events (>10%) were platelet count decreased (17.9%), anorexia (17.9%), neutrophil count decreased (12.8%), anemia (10.3%), and hyponatremia (10.3%). The confirmed RR assessed by the independent review committee was 82.1%(32/39) (95%C.I.: 67.3–91.0), and the disease control rate was 87.2%(34/39) (95%C.I.: 73.3–94.4). 9 cases underwent curative surgery after HER-SOX130. Median PFS, TTF and OS was 7.0 (95%C.I.: 5.5–14.1), 5.7 (95%C.I.: 4.6–7.0) and 27.7 (95%C.I.: 15.6–) months, respectively.

Conclusions: HER-SOX130 demonstrates promising response and survival with avourable safety profile. HER-SOX130 should be considered for the patients with HER2-positive AGC.

Clinical trial identification: UMIN000017552, 2015/05/29.

Legal entity responsible for the study: Kyushu Study group of Clinical Cancer.

Funding: Kyushu Study group of Clinical Cancer.

Disclosure: S. Yuki, K. Shinozaki, Y. Maehara: Honoraria: Yakult Honsha. Y. Komatsu: Research funding: Yakult Honsha. H. Baba: Donation Yakult Honsha. All other authors have declared no conflicts of interest.

669P Differences in outcome according to chemotherapy backbone and maintenance treatment in HER2 positive metastatic gastric cancer (GC) or gastroesophageal junction (GEJ)

N. Martinez Lago[1], S. Candamio Folgar[2], C. Grande Ventura[3], M. Salgado Fernandez[4], J. De la Camara Gomez[5], J.C. Méndez Méndez[6], D. Arias Ron[4], F. Vazquez[7], M. Reboredo Lopez[1], Y. Vidal Ínsua[2], B. Graña Suarez[1], M. Jorge Fernandez[3], M.E. Brozos Vazquez[8], M.L. Pellon Augusto[5], J. Prato Varela[1], P. Gonzalez Villarroel[3], A. Fernandez Montes[9]

[1]Medical Oncology, Hospital Universitario a Coruna, A Coruna, Spain, [2]Medical Oncology Department, University Clinical Hospital of Santiago de Compostela, Santiago de Compostela, Spain, [3]Medical Oncology, Hospital Universitario Alvaro Cunqueiro, Vigo, Spain, [4]Medical Oncology Department, Complejo Hospitalario de Ourense, Ourense, Spain, [5]Medical Oncology Department, Complexo Hospitalario Universitario de Ferrol, Ferrol, Spain, [6]Medical Oncology Department, Centro Oncológico de Galicia, A Coruña, Spain, [7]Medical Oncology Department, Complejo Hospitalario Universitario de Santiago de Compostela SERGAS, Santiago de Compostela, Spain, [8]Medical Oncology, Complexo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain, [9]Medical Oncology, Complexo Hospitalario Universitario de Ourense, Ourense, Spain

Background: Although the TOGA study used cisplatin plus capecitabine (XP) or fluorouracil (FP), oxaliplatin schedules (CAPOX or FOLFOX) are commonly used. There is also a discrepancy in the no. of cycles and the maintenance treatment with trastuzumab (T).

Methods: We conducted an observational, retrospective, multicentric study of patients with metastatic HER2 GC or GEJ treated at 6 spanish hospitals belonging to Galician Research Group on Digestive Tumors (GITuD). Demographic, clinic and pathological data were retrospectively collected and correlated with overall survival (OS) and progression free survival (PFS).

Results: 91 pts treated between May 2010 to January 2018 were recorded. Median age was 68 years (range 38-84 years), 74.7% were male, 39.6% GEJ location, 82.9% intestinal Lauren subtype, 64.5% well-moderate differentiated, 82.4% synchronous disease and 24.2% primary tumor resection. Median of metastatic locations was 2 (range 1-4). Chemotherapy backbone: FP 4.7%, XP 21.2%, CAPOX 37.6%, FOLFOX 36.5%. With a median follow up of 45.6 months, 85 pts were evaluable for efficacy. Median OS was 14.2 months (CI 95% 10.3-18.0 months) and median first line PFS was 8.9 months (CI 95% 7.7-10.1 months). Overall response rate 57.6% and disease control rate 78.8%. Median cycles of induction treatment were 6 (range 1-18). No PFS differences were found according to the platinum ($p = 0.579$) or fluropirimidine used ($p = 0.955$). Of 47 non-progressive patients after 6 months the majority received maintenance treatment for a median of 6.5 cycles (range2-77) with T +/- fluoropirimidine (21 and 16 pts) while 10 discontinued treatment. Post-induction PFS favors those who continued treatment with a PFS of 7.6 vs 5.0 months ($p = 0.033$), without differences between schemas ($p = 0.890$)). Primary tumor surgery (HR 0.380; $p = 0.010$), neutrophil to lymphocyte ratio < 5 (HR 0.461; $p = 0.008$), platelet to lymphocyte ratio <200 (HR 0.557; $p = 0.030$) were associated with prolonged OS.

Conclusions: Maintenance treatment with T has a benefit in terms of PFS even in patients who received T during induction. The practice of continuing the fluoropirimidine during maintenance doesńt appear to add any PFS benefit in our series.

Legal entity responsible for the study: Galician Research Group on Digestive Tumors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

670P Phase II study of S-1 and oxaliplatin as neo-adjuvant chemotherapy for locally advanced gastric and esophago-gastric cancer (KSCC1601)

K. Kobayashi[1], M. Iwatsuki[2], H. Orita[3], S. Hidaka[4], T. Arigami[5], T. Kusumoto[6], H. Satake[7], E. Oki[8], K. Satoshi[9], K. Tobimatsu[10], M. Shimokawa[11], H. Saeki[8], A. Makiyama[12], Y. Kakeji[13], S. Natsugoe[14], H. Baba[2], S. Eguchi[1], Y. Maehara[8]

[1]Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan, [3]Department of Surgery, Nakatsu Municipal Hospital, Nakatsu, Japan, [4]Division of Surgical Oncology, Department of Translational Medical Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, [5]Kagoshima University, Department of Onco-Biological Surgery, Kagoshima, Japan, [6]Department of Gastroenterological Surgery / Clinical Research Institute Cancer Research Division, National Kyushu Medical Center, Fukuoka, Japan, [7]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [8]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [9]Department of Surgery, Oita prefectural Hospital, Oita, Japan, [10]Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, [11]Clinical Research Institute, Cancer Biostatistics Laboratory, National Kyushu Cancer Center, Fukuoka, Japan, [12]Department of Hematology/Oncology, Japan Community Healthcare Organization Kyushu Hospital, Fukuoka, Japan, [13]Division of Gastrointestinal Surgery, Department of Surgery, Graduate School of Medicine, Kobe University, Kobe, Japan, [14]Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University, Kagoshima, Japan

Background: Neoadjuvant chemotherapy is an accepted treatment method to improve the survival for advanced gastric cancer in worldwide. This phase II study, KSCC1601, aimed to investigate efficacy and safety of S-1 and Oxaliplatin for locally advanced gastric (LAGC) and esophago-gastric cancer (EGC).

Methods: Patients received oral S-1 40-60 mg twice daily on days 1 to 14 every 3 weeks plus intravenous oxaliplatin 130 mg/m^2 on day 1 every 3 weeks for 3 courses, followed by gastrectomy with D2 lymphadenectomy. The primary endpoint was pathological response rate (pRR) according to the proportion of necrosis in the tumor: grade 0, no necrosis; grade 1a, < 1/3 necrosis; grade 1b, > 1/3 or < 2/3 necrosis; grade 2, > 2/3 or < all necrosis; and grade 3, all parts of the tumors affected by necrosis. A sample size of 46 was set according to one-sided significance level of 0.05 and power of 80% based on an exact binomial distribution, and assuming the null hypothesis of a 30% pRR and an alternative hypothesis of a 50% pRR. The incidence of anastomosis leakage in EGC was the main secondary endpoint. Other secondary endpoints were R0 resection rate, overall survival, relapse free survival and safety.

Results: Between 2016 April and 2017 July, 47 patients (24 EGC, 23 LAGC) were enrolled in this study. All patients were eligible for analysis. 42 patients (89.4%:95%CI 76.9-96.5) underwent surgery, and curative resection was performed in 41 patients. The rate of protocol treatment completeness was 42 patients (89.4%:95%CI 76.9-96.5%). pRR, the primary endpoint (grade 1b to 3), was 25 cases (59.5%:90%CI 45.7-72.3%) of primary lesions. The main toxicities of neoadjuvant chemotherapy were grade 3/4 thrombocytopenia (10.6%), neutropenia (6.4%), anemia (4.3%), grade 3/4 anorexia (12.8%). The number of anastomosis leakage so as to 20 EGC according to the Clavien–Dindo classification was 2 for grade IIIa, 2 for grade IIIb, and 1 for grade IV (25.0%:90%CI 10.4-45.6%). Survival data will be updated in further investigation.

Conclusions: The S-1 and oxaliplatin was well tolerated and is promising as a preoperative chemotherapy regimen for patients with LAGC and EGC.

Clinical trial identification: UMIN000021061.

Legal entity responsible for the study: KSCC.

Funding: Yakult Honsha Co., Ltd., Cres Kyushu.

Disclosure: All authors have declared no conflicts of interest.

671P A multicenter phase II trial of perioperative capecitabine plus oxaliplatin for clinical stage III gastric cancer (OGSG1601)

R. Kawabata[1], T. Terazawa[2], J. Matsuyama[3], S. Endo[4], O. Shiraishi[5], S. Fujita[6], Y. Akamaru[7], H. Taniguchi[8], M. Tatsumi[9], M. Gotoh[2], S-W. Lee[10], Y. Kurokawa[11], T. Shimokawa[12], D. Sakai[13], T. Kato[14], K. Fujitani[15], T. Satoh[16]

[1]Surgery, Osaka Rosai Hospital, Sakai, Osaka Perfecture, Japan, [2]Cancer Chemotherapy Center, Osaka Medical College, Takatsuki, Japan, [3]Surgery, Yao Municipal Hospital, Yao, Japan, [4]Surgery, Higashiosaka City General Hospital, Higashiosaka, Japan, [5]Surgery, Kindai University, Osakasayama, Japan, [6]Surgery, NTT West Osaka Hospital, Osaka, Japan, [7]Surgery, Ikeda Municippal Hospital, Ikeda, Japan, [8]Surgery, Minoh City, Japan, [9]Surgery, Hoshigaoka Medical Center, Hirakata, Japan, [10]General and Gastroenterological Surgery, Osaka Medical College, Takatsuki, Japan, [11]Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan, [12]Clinical Study Support Center, Wakayama Medical University, Wakayama, Japan, [13]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan, [14]Colorectal Surgery, National Hospital Organization Osaka National Hospital, Osaka, Hyogo, Japan, [15]Surgery, Osaka General Medical Center, Osaka, Japan, [16]Surgery, Osaka University Graduate School of Medicine, Suita, Japan

Background: D2 gastrectomy followed by postoperative S-1 is the standard therapy for the patients (pts) with stage III gastric cancer (GC) in East Asia, but 40% of the pts develop a recurrence. We hypothesize that the perioperative capecitabine and oxaliplatin (CapeOx) might improve survival for clinical stage III GC.

Methods: In this phase II trial, the eligibility criteria included pathologically confirmed clinical SS/SE N1-3 M0 GC according to Japanese Classification of GC (JCGC) 3rd English Edition. Perioperative CapeOx consisted of three cycles of CapeOx (capecitabine; 2,000 mg/m^2 for 14 days, oxaliplatin; 130 mg/m^2 day 1) every 3 weeks as neoadjuvant chemotherapy (CT), followed by five cycles of adjuvant CapeOx after the D2 gastrectomy. The primary endpoint was the pathological response rate (pRR) according to JCGC (≥ Grade 1b). The planned sample size was 34 pts calculated on the hypothesis that the expected pRR was 65% and the threshold was 40%, with one-sided alpha of 0.05 and power of 90%.

Results: Thirty-seven pts were enrolled from Apr. 2016 to May. 2017, and fully evaluated for efficacy and toxicity. R0 and R1 resection were achieved in 29 and three pts, respectively. One pt underwent R2 resection, and four pts could not undergo surgical resection. Sixteen pts underwent total gastrectomy, and 17 pts underwent distal gastrectomy. The pRR was 54.1% (one-sided p = 0.058, 95% CI: 36.9-70.5). The relative dose intensity (RDI) of Capecitabine and Oxaliplatin were 90.7% and 92.0%, respectively. Twenty-seven pts received adjuvant therapy, and the RDI of capecitabine and Oxaliplatin were 80.9% and 63.4%, respectively. Grade 3/4 toxicities of neoadjuvant CT included neutropenia (8%), thrombocytopenia (8%), and anorexia (8%). Grade 3/4 toxicities of adjuvant CT included neutropenia (27%), diarrhea (8%), and anorexia (3%). Grade IIIa surgical complications included intraabdominal abscess (3%), bowel obstruction (3%), and anastomotic leakage (3%).

Conclusions: This phase II trial of perioperative CapeOx showed favorable antitumor activity with an acceptable safety profile for stage III GC, although pRR as primary endpoint did not meet the prespecified threshold.

Clinical trial identification: UMIN000021641.

Legal entity responsible for the study: Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG).

Funding: Yakult Honsha Co., Ltd.

Disclosure: D. Sakai: Belongs to a donated fund laboratory: Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Ltd. T. Satoh: Honoraria, Consulting fee: Eli Lilly, Chugai, Merck Serono; Research funding (institution): Sanofi, Yakult Honsha, Chugai, Ono. All other authors have declared no conflicts of interest.

672P Comparison of preoperative neoadjuvant chemotherapy (SOX) with different courses of treatment on the patients with advanced gastric cancer

X. Wang

General Surgery, Chinese PLA General Hospital, Beijing, China

Background: Objective: To analyze the safety and efficacy of different periods of preoperative adjuvant chemotherapy (SOX) regimen in the treatment of advanced gastric cancer.

Methods: From June 1 2010 to June 1 2017, 120 patients aged from 25 to 80 with clinical stage IIA-IIIC gastric cancer received neoadjuvant chemotherapy with S-1 and oxaliplatin and gastrectomy in Chinese PLA General Hospital. Patients were randomly assigned to two groups with different length of treatment in preoperative neoadjuvant chemotherapy. There were 60 patients in the group with 3 periods preoperative neoadjuvant chemotherapy of treatment, and 60 patients in the group with 5 periods preoperative neoadjuvant chemotherapy of treatment. An ambispective cohort study was conducted. We compared short-term surgical outcomes between the two groups.

Results: There was no significant difference in clinical pathological features between the two groups. However, the five-cycle group had less operative time (229 minutes vs 240 minutes, P = 0.031) and less intraoperative blood loss (158 ml vs. 201 ml, P = 0.006). The short-term prognosis was similar in both groups. The R0 resection rate was higher in the 5-cycle group, especially in stage III subgroup.

Conclusions: The longer preoperative chemotherapy in neoadjuvant chemotherapy, the better the effect of the neoadjuvant chemotherapy in patients with advanced gastric cancer, so we can try to use more preoperative neoadjuvant chemotherapy.

Legal entity responsible for the study: Chinese PLA general hospital.

Funding: Chinese national nature science foundation and Beijing's NOVO programme.

Disclosure: The author has declared no conflicts of interest.

673P Phase II trial of neoadjuvant therapy using apatinib plus SOX regimen in locally advanced gastric cancer: Updated results

Y. Zheng, X. Yang, H. Shi, Z. Yang, C. Yan, Z. Ni, M. Li, B.K. Sah, W. Liu, W. Xu, X. Yao, Z. Zhu, M. Yan, Z. Zhu, C. Li

Department of Gastrointestinal Surgery, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Institute of Digestive Surgery, Shanghai Key Laboratory of Gastric Neoplasms, Shanghai, China

Background: Locally advanced gastric cancer (LAGC) has a poor prognosis. Neoadjuvant chemotherapy can reduce tumor loading, degrade staging and increase possibility of complete resection, thus prolonging the survival of LAGC patients (pts). We conducted a phase II trial to assess the feasibility of SOX regimen in combination with apatinib (an anti-angiogenic agent) as neoadjuvant therapy in LAGC.

Methods: This study recruited untreated LAGC pts with pathologically and/or cytologically confirmed adenocarcinoma. Treatment included three 21-day cycles of apatinib (oral, 500 mg qd; discontinued in the last cycle), S-1 (oral, 40-60 mg, bid, day 1-day 14) and oxaliplatin (iv, 130 mg/m^2, day 1), followed by radical surgery after 4 weeks. The primary outcome was neoadjuvant therapy related toxicity, and the secondary outcomes included tumor response, R0 resection rate, postoperative pathological evaluation and surgical morbidity. The target sample size was 30 pts.

Results: From Dec 2016 to Apr 2018, 30 eligible pts were enrolled. 70% was males. The median age was 60 years (range 43–73 years). At the cut-off date for data analysis (24th Apr, 2018), 24 pts completed the three cycles of neoadjuvant therapy. One complete response, 17 partial response, 5 stable disease and 1 progressive disease (PD) were achieved, yielding an objective response rate of 75.0% and disease control rate of 95.8%. 23 pts received radical surgery except the one who had PD, and all achieved R0 resection. Of the 23 pts receiving surgery, the first 18 pts had completed the postoperative pathological analysis, and the median tumor regression was 85%. Among the pts who had received at least one dose of the preoperative treatment, the incidence of adverse events (AEs) and grade 3/4 AEs were 96.4% and 32.1%, respectively. The main grade 3/4 AEs included hypertension, leukopenia, diarrhea and oral mucositis (all 7.1%). In regard to surgical morbidity, 6 (26.1%) experienced fever, 1 (4.3%) had a duodenal stump fistula, and 1 (4.3%) had incision fat necrosis. No surgical mortality occurred.

Conclusions: Three-weekly neoadjuvant therapy with apatinib plus SOX followed by radical surgery for LAGC showed acceptable toxicity and promising efficacy.

Clinical trial identification: Chinese Clinical Trial Registry (ChiCTR-OPC-16010061).

Legal entity responsible for the study: Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Institute of Digestive Surgery, Shanghai Key Laboratory of Gastric Neoplasms.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

674P The efficacy and safety of (neo)adjuvant therapy for gastric cancer: A network meta-analysis

T. van den Ende[1], E. Ter Veer[1], M. Machiels[2], R.M.A. Mali[1], F.A. Abe Nijenhuis[1], L.D. Waal[1], M. Laarman[1], S.S. Gisbertz[3], M.C.C.M. Hulshof[2], M.G.H. van Oijen[1], H.W.M. van Laarhoven[1]

[1]Medical Oncology, Academic Medical Center (AMC), Amsterdam, Netherlands, [2]Radiotherapy, Academic Medical Center (AMC), Amsterdam, Netherlands, [3]Surgery, Academic Medical Center (AMC), Amsterdam, Netherlands

Background: Alternatives in treatment-strategies exist for resectable gastric cancer treated with curative intent including: perioperative chemotherapy, adjuvant chemoradiotherapy and adjuvant chemotherapy. Our aims were (1) to assess the benefit of perioperative, neoadjuvant and adjuvant treatment-strategies and (2) to determine the optimal adjuvant regimen for gastric cancer treated with curative intent.

Methods: PubMed, EMBASE, CENTRAL, and ASCO/ESMO conferences were searched up to August 2017 for randomized controlled trials on curative treatment for resectable gastric cancer. We performed two network-meta-analyses (NMA). NMA-1 compared perioperative, neoadjuvant and adjuvant strategies only if there was a direct comparison. NMA-2 compared different adjuvant regimens with chemotherapy or chemoradiotherapy, after curative resection. Overall-survival (OS) and disease-free-survival (DFS) were analyzed using random-effects NMA on the hazard ratio (HR)-scale and calculated as combined HRs and 95% credible intervals (95%CrIs).

Results: NMA-1 consisted of 9 direct comparisons between strategies for OS (14 studies, n = 4,187 patients). NMA-2 consisted of 16 direct comparisons between adjuvant chemotherapy/chemoradiotherapy regimens for OS (37 studies, n = 10,761) and 14 for DFS (30 studies, n = 9,714 patients). Compared to taxane-containing-perioperative-chemotherapy, surgery-alone (HR = 0.58, 95%CrI = 0.38-0.91) and perioperative-chemotherapy (HR = 0.79, 95%CrI = 0.58-1.15) were inferior in OS. Compared to surgery-alone neoadjuvant chemotherapy was non-significant (HR = 1.00, 95%CrI = 0.67-1.47). After curative-resection, the doublet oxaliplatin-fluoropyrimidine (for one-year) was the most efficacious adjuvant regimen in OS (HR = 0.47, 95%CrI = 0.28-0.80). The addition of radiotherapy to chemotherapy did not improve OS and DFS.

Conclusions: For resectable gastric cancer treated with curative intent, (1) taxane-containing perioperative-chemotherapy is the preferred treatment strategy; and (2) adjuvant oxaliplatin-fluoropyrimidine is the optimal regimen after curative resection.

Legal entity responsible for the study: Academic Medical Center.

Funding: Has not received any funding.

Disclosure: S.S. Gisbertz: Consultant: Medtronic; Unrestricted research grant: Olympus. M.G.H. van Oijen: Unrestricted research grants: Bayer, Lilly, Merck Serono, Nordice, Roche. H.W.M. van Laarhoven: Consultant: Philips, Celgene, Lilly, Nordic; Unrestricted research funding: Philips, Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Roche. All other authors have declared no conflicts of interest.

675P Irinotecan, oxaliplatin, 5-fluorouracil/leucovorin (FOLFIRINOX) as first-line therapy in advanced HER2-negative gastric or gastroesophageal adenocarcinoma (G/GEA)

E. Obarevich, N. Besova, E. Trusilova, V. Gorbunova

Chemotherapy Department, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation

Background: G/GEA is relatively chemosensitive, but triplet chemotherapy (CT) regimens with docetaxel have the most efficacy with overall response rate (ORR) 37-58%, median progression free survival (MPFS) 5.2-9.7 mo, median overall survival 9.2-18.8 mo. Irinotecan is active drug for the 1st line CT of G/GEA patients (pts). FOLFIRINOX regimen have shown promising activity in other GI cancers (pancreatic, colorectal). The aim of our study was to evaluate efficacy and tolerability of mFOLFIRINOX in G/GEA.

Methods: G/GEA patients (pts) received 9 cycles of irinotecan 180mg/m^2+oxaliplatin 85mg/m^2+leucovorin 200mg/m^2+5-fluorouracil 250mg/m^2 bolus followed by 2200mg/m^{2}x48h (mFOLFIRINOX) on d1 every 2 weeks without subsequent maintenance therapy. Primary G-CSF prophylaxis was not provided.

Results: 108 CT-naïve pts with G/GEA were included from Jan 2012 to Oct 2015 (48 female, 60 male). ECOG 0/1/2/3/4 were 41/51/7/1% pts. ORR was 52,8%, SD–39,8%, PD–5,6%. MPFS and MOS were 7,83 mo and 16,8 mo, respectively. The main toxicities Grade(gr) ≥3 in pts included neutropenia–47,2%, febrile neutropenia–5,6%, diarrhea–5,6%; we noted else thrombocytopenia gr 1-2 - 29,6%, asthenia gr 1-3 - 87%, hepatotoxicity - 25%/gr 3–0,9%, neurotoxicity–15,7%/gr–1,9%. 31(28,7%) pts received G-CSF on 8,5% cycles. There were no deaths and treatment discontinuation due to toxicity. After the complete regression of distant metastases 11 pts were operated (D2 gastrectomy). For these pts MPFS was18,47 mo, MOS–29,33 mo.

Conclusions: mFOLFIRINOX showed remarkable ORR, PFS and OS in patients with advanced gastroesophageal or gastric adenocarcinoma in the fist-line setting. This regimen may be one more reasonable therapeutic option for these pts. We recommend mFOLFIRINOX for Phase III clinical trial compared with FLOT regimen.

Legal entity responsible for the study: Besova N.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

676P Efficacy and safety for apatinib combined with oxaliplatin and S1 in initially treated metastatic gastric cancer: A single-center observational study

J. Peng, L. Peng, H. Wu, K. Wu, W. Chen, C. Xie, J. Xu, X. Zhang, D. Chen, S. Cai, Y. He

Gastrointestinal Surgery Center, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Currently, S-1 combined with oxaliplatin (SOX) is widely used in the first-line treatment of advanced gastric cancer in China. Apatinib has demonstrated encouraging anti-cancer activity in gastric cancer within both in vitro and in vivo models. We evaluated the efficacy and safety of apatinib combined with SOX in initially treated patients with metastatic gastric cancer.

Methods: In this single arm study, patients with unresectable metastatic gastric adenocarcinoma was enrolled to received chemotherapy with apatinib (500mg, once daily) and SOX regimen. Oxaliplatin was administered at a dose of 130 mg/m^2 on day 1, and S-1 (40–60 mg depending on patient's body surface area) was given orally twice daily for 2 consecutive weeks followed by a 1-week rest. The primary end point was response rates, Secondary endpoints were safety, median progression-free survival and median overall survival.

Results: Thirty-one eligible patients were enrolled between January 2016 and September 2017. Two patients achieved a complete response and 19 patients had partial response. The objective response rates was 67.7%. Seven patients had stable disease and the disease control rates was 90.3%. Disease progression was seen in 3 cases (9.7%). Progression-free survival was 5.9 months (95% confidence interval: 3.2–12.6) and median overall survival was 13.6 months (95% confidence interval: 7.3–22.1). The most common grade 3 to 4 hematologic adverse events (AE) were leucopenia (12.9%), neutropenia (38.7%), thrombocytopenia (6.5%) and anaemia (25.8%), nonhematologic AE were nausea (12.9%), anorexia (32.3%), hand-foot syndrome (6.5%), hypertension (9.7%) and proteinuria (3.2%). No treatment-related death was documented during the drug administration.

Conclusions: Apatinib plus SOX is effective for initially treated metastatic gastric cancer with more favorable safety.

Editorial acknowledgement: Approved by the hospital ethics committee of the first affiliated hospital of Sun Yat-sen University (SYU).

Legal entity responsible for the study: Peng Jianjun.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

677P Afatinib in combination with cisplatin and 5-fluorouracil (5-FU) as first line treatment in inoperable gastric and gastro-esophageal junction (GEJ) cancer: A phase II study by the Hellenic Cooperative Oncology Group

T. Makatsoris, E. Samantas, K. Manousou, V. Karavasilis, G. Aravantinos, D. Tryfonopoulos, A. Psyrri, D.G. Pectasides, E. Pazarli, C. Petraki, A. Tsipoura, I.G. Kaklamanos, G. Fountzilas, G. Pentheroudakis

Data Office, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece

Background: Inoperable gastric and GEJ cancer is usually treated with platinum- and fluoropyrimidine-based combination chemotherapy. Targeting of the epidermal growth factor family of receptors has been unsuccessful except in the case of HER2 targeting with trastuzumab. Afatinib, has shown activity in preclinical models of gastric cancer and has been combined with cisplatin and 5-FU in phase I studies.

Methods: Patients (pts) were treated with the combination of cisplatin (75 mg/m^2 ; day 1), 5-FU (750 mg/m^2; continuous infusion days 1-4) and afatinib (40 mg/day; week1: days 3-5, weeks 2, 3: days 1-5), in an effort to optimize therapy efficacy and tolerability. Primary endpoint was the objective response rate (ORR) in the intention to treat (ITT) and the per-protocol (PP) population. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety profile.

Results: Among the 55 pts (median age 64; range 20-77) enrolled (ITT), the ORR was 34.5% (44.2% in PP pts; N = 43). After a median follow-up of 33.3 months, median PFS and OS were 5 (95% CI 4-6; 49 relapses) and 9.3 (95% CI 6.7-11.5; 43 deaths) months, respectively. Median relative dose intensities administered were 0.97 for 5-FU, 0.96 for cisplatin and 0.94 for afatinib. Grade 3/4 adverse events (AEs) occurred in 34 pts (61.8%) and 9 pts (16.4%), respectively. Most common grade 3/4 AEs were

neutropenia (27.3%), anemia (12.7%), hypokalemia (10.9%), diarrhea (5.4%), infections (5.4%). Acneiform rash grade 1/2 was noted in 20% of pts, while there were 4 (7.3%) thromboembolic events (grade 1-3). There were no treatment related deaths. Pts with GEJ cancers had worse OS than pts with gastric cancer ($p = 0.03$).

Conclusions: The combination of afatinib with cisplatin / 5-FU in pts with inoperable gastric / GEJ cancer has modest activity, however afatinib weekend breaks optimized the compliance and tolerability of the combination. Identification of predictive biomarkers could potentially help in further evaluation of the role of afatinib in gastric / GEJ cancer.

Clinical trial identification: NCT01743365 (December 6, 2012).

Legal entity responsible for the study: Hellenic Cooperative Oncology Group.

Funding: Hellenic Cooperative Oncology Group.

Disclosure: All authors have declared no conflicts of interest.

678P Treatment patterns and changes in quality of life during first-line palliative chemotherapy in Korean patients with advanced gastric cancer

K-W. Lee[1], J.W. Kim[1], J.G. Kim[2], B.W. Kang[3], I.J. Chung[4], Y.S. Hong[5], T-Y. Kim[6], K.H. Lee[7], D.Y. Zang[8], Y.H. Ko[9], E-K. Song[10], J.H. Baek[11], D. Koo[3], S.Y. Oh[12], H. Cho[13]

[1]Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [2]Department of Oncology/Hematology, Kyungpook National University School of Medicine, Daegu, Republic of Korea, [3]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea, [4]Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun, Jeonnam, Republic of Korea, [5]Medical Oncology, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Republic of Korea, [6]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [7]Yeungnam University College of Medicine, Department of Internal Medicine, Daegu, Republic of Korea, [8]Division of Hematology and Oncology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea, [9]Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Republic of Korea, [10]Medical Oncology, Chonbuk National University Medical School, Jeonju, Republic of Korea, [11]Department of Internal Medicine, Ulsan University Hospital, Ulsan, Republic of Korea, [12]Oncology & Hematology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea, [13]Medical Department of Genzyme, Sanofi Korea, Seoul, Republic of Korea

Background: The purpose of this study was to evaluate chemotherapy patterns and changes in quality of life (QOL) during first-line palliative chemotherapy for Korean patients with unresectable or metastatic/recurrent gastric cancer (GC).

Methods: This was a non-interventional, multi-center, prospective, observational study of 527 patients in Korea. QOL assessments were conducted using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ)-C30 and QLQ-STO22 every 3 months over a 12-month period during first-line palliative chemotherapy. The specific chemotherapy regimens were selected by individual clinicians.

Results: Most patients (93.2%) received combination chemotherapy (mainly fluoropyrimidine plus platinum) as their first-line palliative chemotherapy. The median progression-free survival and overall survival were 8.2 and 14.8 months, respectively. Overall, 'a little' changes (differences of 5-10 points from baseline) were observed in some of the functioning or symptom scales; none of the QOL scales showed either 'moderate' or 'very much' change (i.e., $\geq$11 point difference from baseline). When examining the best change in each QOL domain from baseline, scales related to some aspects of functioning, global health status/QOL, and most symptoms revealed significant improvements ($p < 0.05$). Throughout the course of first-line palliative chemotherapy, most patients' QOL was maintained to a similar degree, regardless of their actual response to chemotherapy.

Conclusions: This observational study provides important information on the chemotherapy patterns and QOL changes in Korean patients with advanced GC. Overall, first-line palliative chemotherapy was found to maintain QOL, and most parameters showed an improvement compared with the baseline at some point during the course.

Legal entity responsible for the study: Keun-Wook Lee.

Funding: Sanofi-Aventis Korea Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

679P Meta-analysis of biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer

K. Nishikawa[1], W. Koizumi[2], A. Tsuburaya[3], T. Yamanaka[4], S. Morita[5], K. Fujitani[6], Y. Akamaru[7], K. Shimada[8], H. Hosaka[9], N. Nakayama[10], Y. Miyashita[11], T. Tsujinaka[12], J. Sakamoto[13]

[1]Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [2]Gastroenterology, Kitasato University School of Medicine, Kanagawa, Japan, [3]Surgery, Tsuboi Cancer Center Hospital, Koriyama, Japan, [4]Biostatistics, Yokohama City University Hospital, Yokohama, Japan, [5]Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [6]Surgery, Osaka General Medical Center, Osaka, Japan, [7]Surgery, Ikeda Municippal Hospital, Ikeda, Japan, [8]Internal Medicine, Showa University Kouto-Toyosu Hospital, Tokyo, Japan, [9]Gastroenterology, Gunma Prefectural Cancer Center, Ohta, Japan, [10]Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan, [11]Data Center, Epidemiological & Clinical Research Information Network, Okazaki, Japan, [12]Surgery, Kaizuka City Hospital, Kaizuka, Japan, [13]Surgery, Tokai Central Hospital, Kakamigahara, Japan

Background: Biweekly CPT-11 plus CDDP (BIRIP) and CPT-11 alone are both expectable options for treating advanced gastric cancer (AGC) in second-line setting. Recently, two randomized phase III trials (TCOG GI-0801 and ECRIN TRICS) employing the same regimens have been reported. Both trials did not demonstrate the survival benefit of BIRIP due to underpowered. Therefore, we conducted a meta-analysis to compare the efficacy and safety of these two regimens in patients who have been enrolled in these two randomized trials.

Methods: Individual patient–level data from these two trials were collected for this study. In these two trials, patients with metastatic or recurrent gastric cancer refractory to S-1-based chemotherapy were randomly allocated to BIRIP (CPT-11, 60 mg/m^2; CDDP, 30 mg/m^2, q2w) or CPT-11 (150 mg/m^2, q2w). Overall survivals (OS) and progression-free survival (PFS) were described using Kaplan-Meier methods. Tumor responses were evaluated using RECIST ver. 1.0. Adverse events were evaluated using CTCAE ver. 3.0.

Results: Cumulative data from eligible 290 patients from these two trials were evaluated. OS were 12.3 (95% confidence interval [CI]: 10.5–14.1) in BIRIP group and 11.3 (95% CI: 10.0–13.2) months in CPT-11 group (hazard ratio 0.87; 95% CI: 0.68–1.12, $P = 0.272$). PFS was significantly longer in BIRIP group (4.3months [95% CI: 3.5–5.1]) than in CPT-11 group (3.3months [2.9–4.1]; HR 0.77; 95% CI: 0.61–0.98, $P = 0.035$). The response rate was 20.5% [95% CI: 13.3–27.7] in BIRIP group and 16.0% [95% CI: 9.6–22.4] in CPT-11 group ($P = 0.361$). The disease control rate was significantly better in BIRIP group (72.1% [95% CI: 64.2–80.1]) than in CPT-11 group (59.2% [95% CI: 50.6–67.8]) ($P = 0.032$). The incidences of grade 3 or worse adverse events did not differ between the two groups, for example neutropenia (35.9% vs. 32.4%) and elevation of serum creatinine (0.7% vs. 0.7%). The incidences of anemia (16.6% vs. 10.3%) was higher for BIRIP than for CPT-11. But diarrhea (1.4% versus 4.1%) was more common in CPT-11 group.

Conclusions: BIRIP significantly prolonged PFS as compared with CPT-11 alone and was tolerated as second-line treatment for AGC, but did not demonstrate the survival benefit.

Clinical trial identification: UMIN 000025367.

Legal entity responsible for the study: The non-profit organization Epidemiological & Clinical Research Information Network (ECRIN).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

680P A phase III study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer who failed in first-line therapy (KCSG ST10-01)

K-W. Lee[1], C.H. Maeng[2], T-Y. Kim[3], D.Y. Zang[4], Y.H. Kim[5], I.G. Hwang[6], S.C. Oh[7], J.S. Chung[8], H.S. Song[9], J.W. Kim[1], S.J. Jeong[10], J.Y. Cho[11]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea, [2]Medical Oncology, Kyung Hee University Hospital, Seoul, Republic of Korea, [3]Seoul National University Hospital, Department of Internal Medicine, Seoul, Republic of Korea, [4]Division of Hematology and Oncology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea, [5]Division of Oncology/Hematology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea, [6]Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea, [7]Division of Hematology/Oncology, Internal Medicine Department, Korea University Guro Hospital, College of Medicine, Korea University, Seoul, Republic of Korea, [8]Department of Internal Medicine, Hemato-Oncology, Pusan National University Hospital, College of Medicine Pusan National University, Busan, Republic of Korea, [9]Section of Hemato-Oncology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Republic of Korea, [10]Statistics Support Department, Medical Science Research Institute, Kyung Hee University Hospital, Seoul, Republic of Korea, [11]Department of Medical Oncology, Division of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Background: Although emerging treatments have been introduced to patients with metastatic or recurrent gastric cancer (MRGC) as second-line therapy, paclitaxel or irinotecan are still viable options. This phase III study compared the efficacy and safety of

paclitaxel versus irinotecan in patients with MRGC who failed to first-line chemotherapy.

Methods: Patients were randomized to receive either paclitaxel (70 mg/m^2; days 1, 8, 15, every 4 weeks) or irinotecan (150 mg/m^2 biweekly). The primary endpoint was progression-free survival (PFS).

Results: This study was stopped early due to low accrual rate. A total of 112 patients were enrolled, of which 54 were allocated to paclitaxel, and 58 to irinotecan. Median PFS of paclitaxel or irinotecan group were 3.5 and 2.1 months, respectively [hazard ratio (HR) 1.27; 95% confidence interval (CI), 0.86-1.88; p = 0.234]. Non-inferiority of irinotecan to paclitaxel was not proven according to the predefined upper margin of non-inferiority (1.32). Median overall survival (OS) was 8.6 months in the paclitaxel group, and 7.0 months in the irinotecan group (HR, 1.39; 95% CI, 0.91-2.11; p = 0.126). There was no difference in response rate (p = 0.783) between paclitaxel (15.8%) and irinotecan (13.6%). Among toxicities of ≥ grade 3, neutropenia (11.5%) was the most common toxicity, followed by peripheral neuropathy (7.7%) in the paclitaxel group, and neutropenia (34.5%) followed by nausea, vomiting and anemia (8.6%, respectively) in the irinotecan group.

Conclusions: Although paclitaxel showed numerically longer PFS and OS compared with irinotecan, this was statistically insignificant. Both irinotecan and paclitaxel are valid second-line treatment options in MRGC.

Editorial acknowledgement: This study was partly funded by Boryung Pharmaceutical and CJ HealthCare Corp. The research was supported in part by the Korean Cancer Study Group (KCSG) and KCSG data center (Study Number: KCSG ST10-01).

Legal entity responsible for the study: Korean Cancer Study Group (KCSG).

Funding: Boryung Pharmaceutical, CJ HealthCare Corp.

Disclosure: All authors have declared no conflicts of interest.

681P Impact of adding ramucirumab to paclitaxel in patients with advanced gastric cancer according to the level of ascites: A multicenter retrospective study

T. Masuishi[1], S. Kadowaki[1], H. Hirano[2], S. Kawai[3], T. Yamada[4], T. Moriwaki[4], N. Machida[3], N. Boku[2], K. Muro[5]

[1]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [2]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [3]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [4]Division of Gastroenterology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [5]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Background: Adding ramucirumab (Ram) to paclitaxel (PTX) improved the overall survival (OS) in patients with advanced gastric cancer (AGC) in the RAINBOW trial, which excluded patients with high levels of ascites.

Methods: This retrospective study included patients with AGC who received PTX alone or PTX+Ram as a 2nd-line treatment from Nov. 2013 to Nov. 2016. Selection criteria were ECOG PS of 0–2, refractory or intolerant to fluoropyrimidines, and no prior use of taxane or Ram. The level of ascites was classified as low (no or limited to either the pelvic cavity or upper abdomen) or high (extended from the pelvic cavity to the upper abdomen). An adjusted HR (aHR) for progression-free survival (PFS) and OS was calculated by a multivariate Cox model that contained variables with p < 0.05 in the univariate analysis to reduce imbalance between both treatments.

Results: Among 305 patients, 201 (PTX/PTX+Ram, 115/86) and 104 patients (PTX/PTX+Ram, 63/41) were classified into the low and high ascites groups, respectively. There were no significant differences in the baseline characteristics between PTX and PTX+Ram in either group, excepting the proportion of patients with PS of 2 (PTX/PTX+Ram, 18/9% and 24/10% in the low and high groups, respectively) and high ALP levels (PTX/PTX+Ram, 36/23% in the low group). The median PFS in PTX/PTX+Ram was 3.0/5.2 months (m) (HR 0.56, 95%CI 0.42–0.75, p < 0.0001; aHR 0.59, 95%CI 0.44–0.79, p = 0.0004) in the low group and 2.2/3.5 m (HR 0.61, 95%CI 0.40–0.92, p = 0.02; aHR 0.57, 95%CI 0.42–0.77, p = 0.0003) in the high group, and the median OS was 6.9/10.6 m (HR 0.67, 95%CI 0.48–0.93, p = 0.02; aHR 0.69, 95%CI 0.49–0.97, p = 0.03) in the low group and 4.8/6.2 m (HR 0.57, 95%CI 0.37–0.88, p = 0.01; aHR 0.64, 95%CI 0.40–0.99, p = 0.046) in the high group. The incidence of febrile neutropenia was not different between PTX (3%) and PTX+Ram (3%) in the low group but was higher in PTX+Ram (12%) than in PTX (3%) in the high group.

Conclusions: Our study suggests that adding Ram to PTX may prolong survival in patients with AGC, regardless of the level of ascites. However, there is a risk of febrile neutropenia when administering PTX+Ram to patients with a high level of ascites.

Legal entity responsible for the study: Shigenori Kadowaki.

Funding: Has not received any funding.

Disclosure: T. Masuishi, N. Boku, K. Muro: Honoraria: Lilly S. Kadowaki: Research funding: Lilly. All other authors have declared no conflicts of interest.

682P Identification of patients who benefit from apatinib in advanced gastric cancer: Data derived from a real-world study

J. Feng[1], B. Shen[1], H. Jiang[2], L. Wang[3], J. Qian[4], Y. Shu[5], P. Chen[6], G. Mao[7], B. Liu[8], X. Zhang[9], C. Liu[10], J. Wu[11], X. Li[12], W. Cai[13], W. Shen[14], Q. Wang[15], J. He[16], D. Hua[17], Z. Zhang[18], Y. Zhang[19]

[1]Department of Oncology, Jiangsu Cancer Hospital, Nanjing, China, [2]Department of Oncology, Changzhou No.2 People's Hospital, Changzhou, China, [3]Department of Oncology, Bayi Hospital of People's Liberation Army, Nanjing, China, [4]Department of Oncology, Suzhou Municipal Hospital, Suzhou, China, [5]Department of Oncology, Jiangsu Province Hospital, Nanjing, China, [6]Department of Oncology, Yancheng City No.1 People's Hospital, Yancheng, China, [7]Department of Oncology, Affiliated Hospital of Nantong University, Nantong, China, [8]Department of Oncology, Nanjing Drum Tower Hospital, Nanjing, China, [9]Department of Oncology, Northern Jiangsu People's Hospital, Yangzhou, China, [10]Department of Oncology, Wuxi People's Hospital, Wuxi, China, [11]Department of Oncology, The First People's Hospital of Changzhou, Changzhou, China, [12]Department of Oncology, Affiliated Hospital of Jiangsu University, Zhenjiang, China, [13]Department of Oncology, The First People's Hospital of Wujiang, Wujiang, China, [14]Department of Oncology, The First People's Hospital of Kunshan, Kunshan, China, [15]Department of Oncology, Jiangyin People's Hospital, Jiangyin, China, [16]Department of Oncology, Huai'an First People's Hospital, Huai'an, China, [17]Department of Oncology, Affiliated Hospital, Jiangnan University, Wuxi, China, [18]Department of Oncology, Changshu No.2 People's Hospital, Changshu, China, [19]Department of Oncology, Jiangning People's Hospital, Nanjing, China

Background: A prospective, multicenter, non-intervention registered study of apatinib is being conducted in advanced gastric cancer patients (pts). The result of interim analysis on efficacy and safety was released in ESMO 2017 Congress (695P). Herein, we mainly aimed to identify pts who benefit from apatinib treatment.

Methods: Pts with advanced or metastatic adenocarcinoma of stomach or gastro-esophageal junction who received apatinib administration were included in this real world study. The subgroup analyses were stratified by numbers of metastatic sites, ECOG PS, dosage of apatinib, and occurrence of adverse events (AEs).

Results: As of January 2018, data on 321 pts were available for final analysis. The median progression free survival (mPFS) and median overall survival (mOS) were 4.0 mos and 8.2 mos, respectively. 239 pts (74.5%) reported AEs. Main AEs were proteinuria (17.1%), hypertension (15.9%), and hand-foot syndrome (8.7%). As in table, the mPFS and mOS of pts with ≤2 metastatic sites were longer than those of pts with >2 metastatic sites (mPFS: p = 0.0087, mOS: p = 0.0006). For pts with ECOG PS 0, 1, and ≥2, the differences among groups were significant (mPFS, p < 0.001; mOS, p = 0.0316). Among different dose groups, dose ≥500 mg got longer mPFS (p < 0.001) and mOS (p = 0.0059). What's more, pts who reported proteinuria, hypertension, hand-foot syndrome, or leukopenia had longer mPFS (ps < 0.05) and mOS (ps < 0.05) compared with those who didn't.

Table: 682P Prognostic factors associated with apatinib treatment

		n	mPFS, mos	p	mOS, mos	p
Metastatic site	≤2	199	5.0	0.0087	9.1	0.0006
	>2	67	4.0		6.6	
ECOG PS	0	80	5.7	<0.001	8.7	0.0316
	1	168	4.3		8.2	
	≥2	73	3.0		6.6	
Dosage, mg	250	111	3.4	<0.001	7.7	0.0059
	500	187	4.5		9.5	
	>500	23	5.0		11.8	
Proteinuria	No	266	3.6	0.0003	8.0	0.0035
	Yes	55	5.6		9.2	
Hypertension	No	270	3.6	<0.001	8.0	0.0212
	Yes	51	6.0		8.8	
Hand-foot syndrome	No	293	3.8	0.0015	8.0	<0.001
	Yes	28	6.2		11.3	
Leukopenia	No	261	3.5	<0.001	7.7	<0.001
	Yes	60	7.3		9.6	

Conclusions: The real world study confirms that apatinib is safe and effective for advanced gastric cancer pts. Factors associated with better prognosis were ≤2 metastatic sites, ECOG PS 0/1, dose ≥500 mg, and occurrence of proteinuria, hypertension, hand-foot syndrome, or leukopenia.

Clinical trial identification: ChiCTR-OPN-15006601, release date June 11, 2015.

Legal entity responsible for the study: Jiangsu Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

683P A real world study of apatinib treatment in gastric cancer: Current status and clinical benefit

G. Sun[1], D. Li[2], Z. Ning[3], Y. He[4], J. Chang[5], F. Zhang[6], C. Jiang[7], Y. Cheng[8], L. Xia[9], B. Hu[10], C. Yu[5], Z. Wang[11], D. Wang[12], G. Wang[13], Y. Zhao[14], J. Wang[15], H. Liang[16], M. Xiong[5], W. Peng[1], H. Qian[17]

[1]Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [2]Department of General Surgery, Lu'an People's Hospital, Lu'an, China, [3]Department of Gastrointestinal Surgery, Anhui Provincial People's Hospital, Hefei, China, [4]Department of Oncology, Anhui Provincial People's Hospital, Hefei, China, [5]Department of Gastrointestinal Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [6]Department of Oncology, Maanshan Municipal People's Hospital, Maanshan, China, [7]Department of Gastrointestinal Surgery, The First Affiliated Tumor Hospital of Bengbu Medical College, Bengbu, China, [8]Department of General Surgery, The Second Hospital of Anhui Medical University, Hefei, China, [9]Department of Oncology, Anhui Provincial Hospital of Traditional Chinese Medicine, Hefei, China, [10]Department of Oncology, Anhui Provincial Hospital, Hefei, China, [11]Department of Oncology, The First Affiliated Tumor Hospital of Bengbu Medical College, Bengbu, China, [12]Department of Gastrointestinal Surgery, Wanbei Coal-electricity Group General Hospital, Suzhou, China, [13]Department of Gastrointestinal Surgery, Tongling People's Hospital, Tongling, China, [14]Department of Gastrointestinal Surgery, Lu'an People's Hospital, Lu'an, China, [15]Department of Oncology, The PLA Navy Anqing Hospial, Anqing, China, [16]Department of Radiotherapy, Lu'an People's Hospital, Lu'an, China, [17]Department of Oncology, Fuyang Cancer Hospital, Fuyang, China

Background: Apatinib, a small molecule VEGFR TKI, has been approved in the treatment of advanced or metastatic gastric cancer (GC) in China. We performed a real world study to observe the current status, efficacy and safety of apatinib treatment in clinical practice, and preliminarily define patients (pts) who could benefit from apatinib.

Methods: From September 2017, pts (age ≥18 yrs) with pathologically or histologically diagnosed GC who were given apatinib treatment met the inclusion criteria. The target sample size is 1000.

Results: As of April 2018, 651 pts from 37 centers were eligible. There are 491 (75.4%) males and 160 (24.6%) females. The median age was 62.5 yrs. The majority pts were at stage IV (399, 61.3%), had prior surgery (370, 56.8%) and chemotherapy (341, 52.4%). Pts with ECOG PS 0–2 were 520 (79.9%), and ECOG PS 1 was most common (403, 61.9%). Metastases were detected in 370 (56.8%) pts, which mainly were hepatic and pulmonary metastases. Pts received apatinib monotherapy or in combination with chemotherapy. The dose of apatinib in most pts (70.0%) was 500 mg qd. Apatinib was used in perioperative treatment for 269 (41.3%) pts. 382 (58.7%) pts with unresectable locally advanced, recurrent, or metastatic disease received apatinib as different lines of systemic therapy; among whom, 284 pts were evaluable for response, and 113 pts obtained complete clinical efficacy and safety assessment. 12 achieved partial response, 79 had stable disease and 22 got progressive disease. Thus, the objective response rate (ORR) and disease control rate (DCR) were 10.6% and 80.5%. 78.8% pts reported adverse events (AEs). The incidence of grade 3-4 AEs was 22.1%. Main apatinib-related AEs were hypertension (20.3%), and hand-foot syndrome (26.5%). There were tendencies showed that prognostic factors related with higher ORR were lines of apatinib (≤2, 11.3%; >2, 9.5%) and duration of medication (< 90 days, 7.1%; 90-120 days, 6.7%; >120 days, 11.9%).

Conclusions: In the real world, GC pts receiving apatinib therapy are mainly elderly men, stage IV, and ECOG PS 1. Apatinib is confirmed to be effective and safe for GC pts. Further analysis is needed to identify pts who obtain benefits from apatinib treatment.

Clinical trial identification: NCT03333967.

Legal entity responsible for the study: The First Affiliated Hospital of Anhui Medical University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

684P An exploratory study of intraperitoneal paclitaxel combined with mFOLFOX6 for peritoneal disseminated gastric cancer patients with inadequate oral intake

S. Kadowaki[1], H. Ishigami[2], K. Muro[3], S. Yoshida[4], Y. Hirono[5], T. Tomita[6], H. Yabusaki[7], T. Kusumoto[8], M. Ota[9], Y. Kodera[10], Y. Tsuji[11], A. Hidemura[12], O. Hachiya[13], K. Oba[14], J. Kitayama[15]

[1]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [2]Department of Chemotherapy, The University of Tokyo, Tokyo, Japan, [3]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [4]Department of Gastroenterology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan, [5]Department of Gastroenterological Surgery, University of Fukui, Yoshida-gun, Japan, [6]Department of Gastroenterology, Hyogo College of Medicine, Nishinomiya, Japan, [7]Department of Gastroenterological Surgery, Niigata Cancer Center Hospital, Niigata, Japan, [8]Department of Gastroenterological Surgery/Clinical Research Institute Cancer Research Division, National Kyushu Medical Center, Fukuoka, Japan, [9]Department of Gastroenterological Surgery, National Kyushu Cancer Center, Fukuoka, Japan, [10]Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, [11]Department of Medical Oncology, Tonan Hospital, Sapporo, Japan, [12]Department of Surgery, Kantorosai Hospital, Kawasaki, Japan, [13]Department of Gastroenterological, General, Breast and Thyroid Surgery, Yamagata University, Yamagata, Japan, [14]Interfaculty Initiative in Information Studies, The University of Tokyo, Tokyo, Japan, [15]Support Center for Clinical Investigation, Jichi Medical University, Shimotsuke, Japan

Background: Oral fluoropyrimidine plus platinum is a standard treatment for advanced gastric cancer but cannot be applied to peritoneal disseminated patients with inadequate oral intake. mFOLFOX6 has been reported to be tolerable and active for this population. In addition, we have reported the safety and efficacy of intraperitoneal (IP) paclitaxel (PTX) combined with S-1 based regimens in clinical trials. Therefore, we conducted a multicenter, exploratory study of IP PTX combined with mFOLFOX6 for peritoneal disseminated patients with inadequate oral intake.

Methods: Eligibility criteria included: pathologically proven gastric adenocarcinoma; peritoneal metastasis; no or short term (<1 month) previous chemotherapy without progression; inadequate oral intake; and age between 20–80 years. mFOLFOX6 was administered at the standard doses on days 1 and 15, and IP PTX was administered at 20 mg/m^2 on days 1, 8 and 15 every 4 weeks. The primary endpoint was 1-year overall survival (OS) rate. Secondary endpoints were progression-free survival (PFS), time to treatment failure (TTF), response rate, negative conversion rate on peritoneal cytology and safety.

Results: Among 36 patients enrolled from January 2016 to April 2017, 34 receiving at least one dose of protocol treatment were evaluated in terms of efficacy and safety. Sixteen patients had malignant ascites. The median number of courses was 6 (range 1–17). The 1-year OS rate was 55.9% (95% confidence interval [CI], 37.9%–72.8%). The median PFS was 7.5 months (95% CI, 5.1–12.5 months). The median TTF was 5.6 months (95% CI, 4.4–7.7 months). The best overall response was stable disease in all three patients with target lesions. The negative conversion rate on peritoneal cytology was 73.1% (95% CI, 52.2%–88.4%). Major grade 3 or 4 adverse events included neutropenia, elevation of alanine aminotransferase and aspartate aminotransferase, febrile neutropenia, sensory neuropathy, and diarrhea. There were no treatment-related deaths.

Conclusions: mFOLFOX6 plus IP PTX is well tolerated and active in gastric cancer patients with peritoneal metastasis and inadequate oral intake.

Clinical trial identification: UMIN000019206; release date: 1/Jan/2016.

Legal entity responsible for the study: The University of Tokyo.

Funding: Japan Agency for Medical Research and Development.

Disclosure: S. Kadowaki: Grants: Boehringer Ingelheim, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Eli Lilly Japan. H. Ishigami: Honoraria:Taiho Pharmaceutical; Research funding: Taiho Pharmaceutical, Chugai Pharma. K. Muro: Research funding: MSD, Daiichi Sankyo, Ono Pharmaceutical, Kyowa Hakko Kirin, Shionogi, Gilead Sciences, Eli Lilly Japan, Takeda Pharmaceutical, Taiho Pharmaceutical, Chugai Pharmaceutical, Merck Serono, Yakult Honsha; Honoraria: Chugai Pharmaceutical, Takeda Pharmaceutical, Eli Lilly, Merck Serono, Taiho Pharmaceutical, Yakult Honsha. Y. Kodera: Honoraria: Olympus, Chugai Pharma, Eli Lilly, Johnson & Johnson, Ajinomoto, Takeda, Yakult Honsha, Taiho Pharmaceutical, Otsuka, Kaken Pharmaceutical, Ono Pharmaceutical, Asahi Kasei, Covidien/Medtronic, MSD K.K; Research funding: Chugai Pharma, Daiichi Sankyo, Bristol-Myers Squibb Japan, Otsuka, Taiho Pharmaceutical, Abbott Japan, Abbvie. Y. Tsuji: Honoraria: Merck Serono, Eli Lilly Japan, Chugai, Taiho, Ono, Daiichi Sankyo, Yakult Honsha, Eisai, Medicon outside the submitted work. J. Kitayama: Funding: Taiho Pharma Co. Limit., Chugai Pharma Co. Limit., Merck-Serono Co. Limit., Eli Lilly Co. Limit. All other authors have declared no conflicts of interest.

685P Relation of overall survival, progression free survival, post progression survival and response rate in four randomized Japanese phase III trials comparing various combinations of S-1 therapy for first-line treatment of advanced gastric cancer

M. Takeuchi[1], W. Ichikawa[2], K. Shitara[3], Y. Sunakawa[4], K. Oba[5], W. Koizumi[6], Y. Sakata[7], H. Furukawa[8], M. Takeuchi[9], M. Fujii[10]

[1]Faculty of Environment and Information Studies, Keio University, Fujisawa, Japan, [2]Medical Oncology, Showa University Fujigaoka Hospital, Yokohama, Japan, [3]Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [4]Clinical Oncology, St.Marianna University School of Medicine, Kanagawa, Japan, [5]Biostatistics, The University of Tokyo School of Public Health, Tokyo, Japan, [6]Gastroenterology, Kitasato University School of Medicine, Sagamihara, Minami-li, Sagamihara, Japan, [7]Misawa City Hospital, Misawa, Aomori, Japan, [8]Department of Surgery, Kindai University Faculty, Osaka-Sayama, Japan, [9]Clinical Medicine (Biostatistics), Kitasato University, Tokyo, Japan, [10]Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan

Background: S-1 is a commonly used agent in first line therapy of advanced gastric cancer in Japan. Several randomised studies compared S-1 monotherapy and various S-1 combination for gastric cancer. However, there has been no analysis of the relation of overall survival (OS), progression free survival (PFS), post progression survival (PPS) and response rate (RR) in gastric cancer trials.

Methods: Data from four randomized Japanese Phase III trials (START, SPIRITS, GC0301/TOP-002, G-SOX) were combined to evaluate the relation of OS, PFS, PPS and RR. The correlation between OS and PFS and OS and PPS was evaluated. OS, PFS and PPS was also evaluated for each of the RECIST categories and responders were defined as patients with complete response (CR) or partial response (PR).

Results: A total of 1911 patient data was available for analysis. 424 patients had either missing or not available RECIST data and were excluded leaving 1487 patients for analysis of which 678 patients were defined as responders (22 CR and 656 PR). 1276 patient data was used for the analysis of PPS. The correlation of OS and PFS was moderate with a Spearman's correlation coefficient of 0.611. The correlation of OS and PPS was strong with a Spearman's correlation coefficient of 0.8705. As the RECIST categories worsened, OS, PFS, PPS shortened. The median OS for the responders and non-responders (530.5 days, 272 days p-value<0.005) the median PFS for responders and non-responders (207 days, 82.5 days p-value<0.005) and the median PPS for responders was significantly longer than non-responders (316 days, 179 days p-value<0.005).

Conclusions: Although there are limitations, the analysis shows positive linear correlation between OS and PFS as well as OS and PPS. Patients in better RECIST categories have longer time to OS, PFS and PPS. From the correlation observed, response rate may be a surrogate endpoint to OS, PFS and PPS. Formal validation of the surrogacy of response rate to OS, PFS, and PPS in gastric cancer patients will be analyzed and presented using joint modeling of the survival data.

Clinical trial identification: UMIN000019519.

Legal entity responsible for the study: Japan Clinical Cancer Research Organization (JACCRO).

Funding: Japan Clinical Cancer Research Organization (JACCRO).

Disclosure: M. Takeuchi: Travel grants: Taiho Pharmaceutical; Consulting fees: AnGes. W. Ichikawa: Research funding: Takeda, Taiho Pharmaceutical, Chugai Pharma; Honoraria: Merck Serono, Taiho Pharmaceutical, Chugai Pharma, Takeda. K. Shitara: Funding: Chugai Pharma, Daiichi Sankyo, Eli Lilly Japan, Taiho Pharmaceutical, MSD, Ono Pharmaceutical. Y. Sunakawa: Honoraria: Merck Serono, Yakult Honsha, Takeda, Chugai Pharma, Taiho Pharmaceutical. Y. Sakata: Honoraria Taiho Pharmaceutical M. Takeuchi: Consulting fees: Hisamitsu Pharmaceutical, Kowa, Shionogi Pharma, Abbvie, Astellas. M. Fujii: Travel grants: Japan Clinical Cancer Research Organization. All other authors have declared no conflicts of interest.

686P Immune gene expression profiling (GEP) of resected gastric adenocarcinomas (GAs) to identify biomarkers associated with immune checkpoint inhibitor (ICPI) response in early stage disease

J. Chao[1], H. Yin[2], J. Lee[3], S.J. Klempner[4], R. Pillai[2]

[1]Department of Medical Oncology and Therapeutics, City of Hope, Duarte, CA, USA, [2]Department of Pathology, City of Hope, Duarte, CA, USA, [3]Medicine, Samsung Medical Center, Seoul, Republic of Korea, [4]Medical Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA

Background: Clinical trials of ICPIs in early stage GA are ongoing. Nanostring (NS) GEP allows for simultaneous interrogation of a wide range of genes involved in immune signaling. We conducted a retrospective analysis of resected GAs to gain insight on the immune landscape in this setting.

Methods: We profiled 45 archival GAs treated with upfront surgery (pT2N0 to pT4N3 AJCC7) using a 770-gene immune profiling panel on the NS platform. Clinicopathologic data were abstracted and overall survival (OS) was analyzed using Kaplan-Meier methods.

Results: The majority of patients (44/45) had ≥ stage II disease. NS GEP demonstrated 4 distinct molecular signatures, A-D. Group D exhibited the greatest downregulation of pro-inflammatory genes relative to the other 3. Grouping was not correlated to tumor location, Lauren histology, or stage. When applying an analogous 18 gene T-cell inflamed signature from the KEYNOTE-059 trial, 10/45 GAs matched this signature, indicative of higher likelihood of response to single agent ICPI. OS did not differ between T-cell inflamed vs. non-T-cell inflamed (Table). Comparing signatures associated with greatest (B+C) vs. least (A+D) CD8+ T-cell gene expression as a surrogate for T-cell infiltration, OS favored groups B+C. We also observed a 4 gene (MS4A1, CD19, BLK, TNFRSF17) B-cell signature significantly favored high vs. low expressors for OS.

Table: 686P

NS GEP (n)	Median OS (mo)	Log-rank Test
T-cell inflammed (10)	Not reached (NR)	p = .52
Non-T-cell inflamed (35)	59.9	
Group B+C (24)	NR	p = .07
Group A+D (21)	33.0	
High B score (23)	NR	p = .02
Low B score (22)	33.0	

Conclusions: This data supports ongoing trials of ICPIs in early stage GA. ICPIs alone are unlikely to be sufficient for the majority of patients, necessitating biomarkers to guide addition of ICPIs to current multimodality approaches. Subsets of GAs were quantifiable by NS GEP to exhibit pre-existing CD8+ T-cell infiltration or B-cell signaling and more favorable prognosis. This suggests ICPIs alone or chemotherapy de-escalation strategies should be explored. Tumor-immune cell immunohistochemistry and MSI data will be presented.

Legal entity responsible for the study: City of Hope.

Funding: NIH.

Disclosure: J. Chao: Research funding: Merck, Novonco Therapeutics; Consulting, Advisory roles: Lilly, Five Prime Therapeutics, Boston Biomedical, Merck; Speakers' bureau: Merck. S.J. Klempner: Research funding: Leap Therapeutics; Consulting, Advisory roles: Lilly, Boston Biomedical, Astellas Pharma; Speakers' bureau: Foundation Medicine. R. Pillai: Consulting, Advisory roles: Qiagen. All other authors have declared no conflicts of interest.

687P Significant prognostic markers related to lymphocytes in gastric cancer

T. Hashimoto, Y. Kurokawa, T. Takahashi, Y. Miyazaki, K. Tanaka, T. Makino, M. Yamasaki, K. Nakajima, M. Mori, Y. Doki

Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

Background: There is growing consensus that host immunity, of which lymphocytes are well-known as an indicator, plays important roles against the development of malignancy. Based on this concept, many studies reported the prognostic value of preoperative markers related to lymphocytes. This study aimed to investigate the prognostic value of pre- and postoperative lymphocyte counts and representative markers related to lymphocytes in predicting overall survival (OS) in patients with gastric cancer.

Methods: A total of 177 consecutive patients who underwent curative gastrectomy for pStage II or III gastric cancer from 2010 to 2014 were enrolled. We evaluated pre- and postoperative lymphocytes and representative markers including neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR), and prognostic nutrition index (PNI). The optimal cutoff values of them were determined using the receiver operating characteristic (ROC) curve analysis. Prognostic value of them were analyzed using both Kaplan-Meier and multivariate Cox regression methods.

Results: Elevated pre- and postoperative lymphocytes, especially postoperative lymphocytes tended to be associated with better OS when classified into three groups [5-year OS: 46.2% in low-group (<1000), 62.5% in middle-group (1000-2000), and 80.9% in high-group (≥2000)]. ROC analysis revealed a higher predictive power for recurrence with the postoperative markers compared with preoperative ones. Postoperative lymphocyte (>1400), NLR (<2.3), LMR (>2.8), PLR (<150), and PNI (>47.0) were significantly associated with better OS ($P < 0.001$, $P < 0.001$, $P = 0.007$, $P = 0.001$, and $P < 0.001$, respectively). Of these markers, postoperative PNI (>47.0) was most associated with better OS on each pStage ($P = 0.003$ on pStage II, and $P = 0.070$ on pStage III). Multivariate analysis revealed that postoperative PNI (>47.0) and pN(-) were independent prognostic factors for OS.

Conclusions: Postoperative markers related to lymphocytes could have higher predictive power compared with preoperative ones, and postoperative PNI may be a better predictor of OS in patients with gastric cancer.

Legal entity responsible for the study: The Supporting Center for Clinical Research and Education (SCCRE).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

688P Correlation between clinic-pathological features, MSI, PD-L1 and survival in resectable gastric cancer: Looking for prognostic biomarkers

M. Ratti[1], N. Valeri[2], J.C. Hahne[2], A. Lampis[2], M. Ghidini[1], G. Tomasello[1], G. Tanzi[1], L. Toppo[1], C. Pizzo[1], B. Donida[1], C. Senti[1], M. Salati[3], M. Trombatore[1], M. Fassan[4], R. Passalacqua[1]

[1]Oncology, Istituti Ospitalieri di Cremona, Cremona, Italy, [2]Medicine, The Royal Marsden NHS Foundation Trust in Chelsea, London, UK, [3]Oncology, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [4]Medicine, University of Padova, Padua, Italy

Background: The identification of prognostic biomarkers (PB) for gastric cancer (GC) patient selection is compelling to improve survival outcomes. Microsatellite instability (MSI) is related with a positive prognostic effect in resected GC, whereas perioperative chemotherapy (CT) is detrimental. In metastatic MSI GC, immunotherapy (IT) with anti-PD1/PDL-1 drugs has shown promising results. Nevertheless, in early stages (ES), data on the relation between MSI, clinic-pathological (CP) features, PDL-1 expression and overall survival (OS) remain sparse, especially in Western population. In this study, the prognostic role of MSI status, CP features and PDL-1 status in a large cohort of Italian GC patients (pts) was examined.

Methods: CP data of 148 consecutive stage I-III GC pts resected in Cremona Institute between 2010 and 2014 (mostly chemo and/or radio-naive) were collected. MSI analysis was performed on tissue samples for all cases by polymerase chain reaction. PDL-1 expression, evaluated by immunohistochemistry, was assessed in MSI group. Differences between subgroups were evaluated with Chi-square test; Kaplan-Meier method and Long Rank test were used to calculate OS.

Results: Female sex ($p = 0.012$), earlier TNM stages ($p = 0.011$) and lower nodal involvement ($p = 0.029$) significantly correlated with MSI status. MSI is significantly associated with prolonged survival ($p < 0.001$), with an advantage of 28.6 months in OS compared to the microsatellite stable (MSS) group. Most MSI pts (71%) expressed PDL-1. Although not statistically significant, MSI pts without PD-L1 expression showed a better trend in OS compared with MSI GC pts expressing PDL-1 and with MSS group.

Table: 688P Main CP differences between MSS and MSI groups and survival outcomes

	MSS 110 (79.7%)	MSI 38 (25.7%)	p
SEX M F	77 (70) 33 (30)	18 (47.4) 20 (52.6)	0.012
STAGE (TNM)	19 (17.3) 26 (23.6)	13 (34.2) 13 (34.2)	0.011
I II III	65 (31.6)	12 (31.6)	
NODAL METASTASES NO YES	26 (23.6) 84 (76.4)	16 (42.1) 22 (57.6)	0.029
OS (months)	16.1	44.7	<0.001

Conclusions: MSI is an independent PB in GC and identifies a subset of pts with better OS and specific CP characteristics, including high expression of PDL-1. MSI could be a promising biomarker to select pts for CT vs IT in ES of GC.

Legal entity responsible for the study: ASST Cremona.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

689P Neutrophil-lymphocyte ratio (NLR) as an important prognostic factor for paclitaxel as a second line chemotherapy in advanced gastric cancer (AGC): Results from phase III DREAM study

M-H. Ryu[1], J.H. Kim[2], S.C. Oh[3], S. Park[4], J.G. Kim[5], J.W. Kim[6], S-H. Cho[7], K-E. Yoon[8], Y-K. Kang[9]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Internal Medicine, Asan Medical Center, Seoul, Republic of Korea, [3]Division of Hematology/Oncology, Internal Medicine Department, Korea University Guro Hospital, College of Medicine, Korea University, Seoul, Republic of Korea, [4]Hematology-Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [5]Department of Oncology, Kyungpook National University Medical Center, Daegeu, Republic of Korea, [6]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea, [7]Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea, [8]Clinical Trial Team, Daehwa Pharmaceutical, Co., Ltd., Seoul, Republic of Korea, [9]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Songpa-gu, Republic of Korea

Background: Paclitaxel is the most commonly used second-line chemotherapy in AGC. Recently, the DREAM phase 3 study (NCT01839773) have demonstrated that the efficacy and safety of DHP107, an oral paclitaxel, is comparable to those of intravenous (i.v.) paclitaxel. This post-hoc analysis was conducted to evaluate whether NLR is related with the treatment outcomes for both oral and i.v. paclitaxel.

Methods: In the DREAM study, pts were randomized 1:1 to DHP107 (200 mg/m^2 orally twice daily on days 1, 8, 15, every 4 weeks) or i.v. paclitaxel (175 mg/m^2 on day 1, every 3 weeks). High vs low NLR was defined by the baseline median. With comparable efficacy between two arms in the original DREAM study, all the patients ($n = 236$) enrolled in the DREAM study were included in this post-hoc analysis for NLR.

Results: Median age was 59 years (range, 27–83) and 185 pts (78.4%) were male. The median for NLR was 2.08. Thirty-four (28.8%) out of the 118 pts with low NLR (<2.08) achieved a complete or partial response, while 17 (14.4%) out of the 118 pts with high NLR (>2.08) showed responses ($p = 0.007$). With a median follow up duration of 10.8 months (range, 0.4-27.8) in surviving pts, median progression-free survival (PFS) was 4.1 months (95% confidence interval [CI], 2.8-4.3) with low NLR and 1.6 months (95% CI, 1.4-2.5) with high NLR ($p = 0.0012$); and median overall survival (OS) was 12.0 months (95% confidence interval [CI], 9.7-14.5) with low NLR and 7.1 months (95% CI, 5.4-9.1) with high NLR ($p = 0.0004$). With a multivariate analysis including important clinical factors, low NLR remained an independent factor for better PFS (HR 0.66, 95% CI 0.49-0.89, $p = 0.0065$) and OS (HR 0.57, 95% CI 0.42-0.78, $p = 0.0005$).

Conclusions: The current study demonstrates that low NLR is correlated with better treatment outcomes for both oral and intravenous paclitaxel as a second-line chemotherapy in AGC.

Clinical trial identification: NCT01839773.

Legal entity responsible for the study: Daehwa Pharmaceutical, Co., Ltd.

Funding: Daehwa Pharmaceutical, Co., Ltd.

Disclosure: Y-K. Kang: Consultant: Ono, BMS, Taiho, Roche, Lilly, Blueprint, Taiho, Daehwa, LSK Biopharma. All other authors have declared no conflicts of interest.

690P Combination versus single-agent as palliative chemotherapy for gastric cancer: Significance of age and platelet-to-lymphocyte ratio

M.S. Ahn, Y.W. Choi, H. Lee, S.Y. Kang, J-H. Choi

Hematology-Oncology, Ajou University School of Medicine, Suwon, Republic of Korea

Background: Although combination chemotherapy (CC) is generally recommended in recurrent or metastatic gastric cancer, the results of randomized trials are conflicting.

Methods: A retrospective review was conducted on 687 patients who received palliative chemotherapy for recurrent ($n = 304$) or primary metastatic ($n = 383$) gastric cancer. We compared the overall survival (OS) between CC and single-agent chemotherapy (SC) among these patients, while analyzing clinicopathological characteristics affecting outcome including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

Results: While 521 (75.8%) patients underwent CC, SC was more frequently performed in old age (≥70) (57.6%) and ECOG performance status (PS) 2/ 3 (65.8%) patients ($p < 0.0001$, both). The median OS of patients who received CC was significantly longer than that of patients who received SC (11 vs. 8 months, $p < 0.0001$). Although patients with CC showed better OS in the majority of subgroups, no difference in OS between CC and SC was observed in patients with old age ($p = 0.599$), ECOG PS 2/3 ($p = 0.821$), signet ring cell histology ($p = 0.40$), palliative surgical resection ($p = 0.407$), and high PLR ($P = 0.137$), with a significant interaction between age and type of the regimen (CC vs. SC) ($p = 0.011$). Multivariate analysis revealed that palliative resection and ≥2nd line chemotherapy were independently associated with favorable OS ($p < 0.0001$, both), whereas ECOG PS 2/3 ($p = 0.004$), poorly differentiated and signet ring cell histology ($p = 0.02$, $p < 0.0001$), peritoneal metastasis ($p = 0.045$), high NLR ($P = 0.001$), and high PLR ($P = 0.028$) were independent prognostic factors of poor OS. In patients who underwent palliative resection before chemotherapy, there was a significant interaction between PLR and type of the regimen ($p = 0.017$), without significant difference in OS between CC and SC in patients with high PLR ($p = 0.306$).

Conclusions: Although CC is the standard of care in recurrent or metastatic gastric cancer, SC can be considered as a reasonable option in certain subgroups, such as elderly patients or those with high PLR after palliative resection.

Legal entity responsible for the study: Department of Hematology-Oncology, Ajou University School of Medicine.

Funding: Samyang Biopharmaceuticals Corporation.

Disclosure: All authors have declared no conflicts of interest.

691P Venous thromboembolism during preoperative chemotherapy in the CRITICS gastric cancer trial

A.E. Slagter[1], K. Sikorska[2], C. Grootscholten[3], H.W.M. van Laarhoven[4], H. Boot[5], E. Meershoek-Klein Kranenbarg[6], C.J.H. van de Velde[6], N.C. van Grieken[7], E.P.M. Jansen[1], M. Verheij[1], A. Cats[5]

[1]Radiation Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [2]Biometrics, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [3]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [4]Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [5]Gastrointestinal Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [6]Surgical Oncology, Leiden University Medical Center, Leiden, Netherlands, [7]Pathology, Vrije University Medical Center (VUMC), Amsterdam, Netherlands

Background: Venous thromboembolism (VTE) is a common complication in patients with cancer. Gastric cancer (GC) has been associated with one of the highest risks of VTE. Risk factors for VTE in GC have mainly been investigated in Asian populations and/or in metastasised setting and include: gender, age, body mass index (BMI), stage, primary tumour localisation and chemotherapy, in particular cisplatin. Limited data is available on risk factors for VTE in resectable GC in Western patients. The aim of this study was to identify risk factors for VTE during preoperative chemotherapy in resectable GC patients. In addition, we addressed the question whether VTE was a risk factor for not proceeding to surgery.

Methods: Patients with resectable GC selected from the CRITICS trial (stages Ib-IVa; American Joint Cancer Committee, sixth edition; no distant metastasis) should preoperatively be treated with 3 cycles of 3-weekly epirubicin, cisplatin/oxaliplatin and capecitabine (ECC or EOC). Inclusion criterion for this analysis was start of at least 1 chemotherapy cycle. VTE was defined as any thrombus in the venous system, excluding superficial and/or device related VTE. Risk factors of interest were fitted in a multivariable logistic regression model: age, gender, BMI, ECC/EOC and tumour localisation.

Results: A total of 781 patients were included in this analysis of whom 78 (10%) developed a VTE during the preoperative period. Results of the multivariable analysis are shown in the table. Seventy four patients with VTE proceeded to surgery (95%), compared to 666 patients (95%) without VTE (p = 0.99).

Table: 691P Multivariable analysis

Variable		No VTE (n = 703)		VTE (n = 78)		OR (95%CI)	p value
		n	%	n	%		
Age in years	<60	287	91	28	9	*	
	60-69	261	88	34	12	1.31 (0.76-2.23)	0.329
	70+	155	91	16	9	1.01 (0.53-1.94)	0.970
Gender	Male	474	91	49	9	*	
	Female	229	89	29	11	1.20 (0.72-1.98)	0.483
BMI¤	<25	368	92	33	8	*	
	25-30	246	90	28	10	1.30 (0.76-2.21)	0.342
	≥30	88	84	17	16	2.16 (1.14-4.09)	0.018
ECC/EOC	ECC	564	89	68	11	*	
	EOC	139	93	10	7	0.61 (0.30-1.22)	0.162
Tumour localisation	Distal	223	88	29	12	*	
	Middle	209	89	26	11	0.96 (0.54-1.68)	0.877
	Proximal	150	94	10	6	0.52 (0.24-1.12)	0.094
	GOJ	121	90	13	10	0.87 (0.43-1.76)	0.693

* reference; ¤ BMI unknown (n = 1); OR= Odds Ratio; CI= Confidence Interval

Conclusions: High BMI (≥30) was the only independent risk factor for developing VTE in resectable GC, preoperatively treated with ECC/EOC. Cisplatin was not identified as a significant risk factor for VTE in this cohort. A diagnosis of VTE did not influence the clinical decision to proceed to surgery.

Clinical trial identification: NCT00407186.

Legal entity responsible for the study: Netherlands Cancer Institute.

Funding: Dutch Cancer Society, Dutch Colorectal Cancer Group, and Hoffmann-La Roche.

Disclosure: All authors have declared no conflicts of interest.

692P The difference of risk factor for gastric cancer surgery between elderly and non-elderly patients

T. Hayashi[1], T. Oshima[1], K. Hara[1], Y. Shimoda[1], M. Nakazono[1], S. Nagasawa[1], Y. Kumazu[1], T. Yamada[1], Y. Rino[2], M. Masuda[2], T. Ogata[1], T. Yoshikawa[1]

[1]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, [2]Surgery, Yokohama City University, Yokohama, Japan

Background: The risk factor for gastric cancer surgery is expected to be characteristic feature of elderly in comparison to non-elderly due to decline in organ function and co-morbidities related to aging. However, the differences in the risk factors for gastric cancer surgery between elderly and non-elderly have not been evaluated. The aim of this study was to identify characteristics of risk factors of gastric cancer surgery for elderly.

Methods: This retrospective study examined 2500 patients who underwent gastrectomy with D1, D1+, D2, or D3 lymphadenectomy during 2000 to 2016 at Kanagawa Cancer Center hospital with curative intent. Patients were divided into two groups according to age, more than 75 years old (n = 406), E group; and less than 75 years old (n = 2094), Y group. Multivariate logistic regression analysis was performed to assess the independent contribution of variables to postoperative complication in each group.

Results: Mean age was 61.3 y.o. in Y group and 78.3 y.o. in E groups. Charlson Index (0/1/2) was 1523/557/14 in Y group, and 228/173/5 in E group ($p < 0.001$). ECOG-PS was (0/1/2/3) was 1918/173/2/1 in Y group, and 345/59/1/1 in E group ($p < 0.001$). Extent of the stomach resection (total/proximal/distal) was 768/37/1289 in Y group, and 149/4/253 in E group. Stage (I/II/III/IV) was 1227/323/331/213 in Y group, 225/58/86/37 in E group. Postoperative complications were observed in 267 patients (13%) in Y group and 84 patients (21%) in E group. The most frequent complication was pancreatic fistula (n = 41), followed by anastomotic leakage (n = 36) in Y group, and pneumonia (n = 20), followed by anastomotic leakage (n = 19) in E group. Multivariate analysis identified male sex (odds ratio: 1.87), and total gastrectomy (odds ratio: 1.58) as independent predictors of postoperative complications in Y group, and male sex (odds ratio: 3.01), stage IV (odds ratio: 2.54), and Charlson score > 1 (odds ratio: 1.76) in E group.

Conclusions: In elderly patients, co-morbidity more strongly affects postoperative complications compared with non-elderly patients. Co-morbidities especially in major organ function should be taken into consideration for future trials evaluating gastric cancer surgery for elderly patients.

Legal entity responsible for the study: Kanagawa Cancer Center.

Funding: Has not received any funding.

Disclosure: T. Hayashi: Personal fee, Lectual fee Chugai, Ono, MSD. T. Yoshikawa: Personal fee, Lectual fee Taiho, Chugai, Yakult, Ono, MSD. All other authors have declared no conflicts of interest.

693P Gastric cancer in young patients

M.M. Seker, A. Bahceci, T. Kacan

Medical Oncology Department, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

Background: The majority of gastric cancer-related studies include elderly patients. Studies have shown that gastric cancer carries more poor prognostic factors in younger patients.

Methods: In this study we retrospectively reviewed the results of gastric cancer patients under age 30 who had diagnosed and treated at our hospital. Statistical analysis of the study was done by the Kaplan-Meier test, Long Rank test and Cox regression analysis in the SPSS17 statistical program.

Results: 824 patients had diagnosed with gastric cancer at our clinic. Of these, 30 (3.6%) patients were under 30 years of age. 17 of them were women (56.6%) and 13 of them were men (43.4%). Of these, the results of 22 patients, 9 males and 13 females, whose data were available, had evaluated. At the time of diagnosis, 5 patients (23%) were stage 2, 6 patients (27%) were stage 3, and 11 patients (50%) had metastatic disease. R0 resection was performed in 10 patients (90.9%) and R2 resection was performed in 1 patient (9.1%). Palliative surgery had performed in 4 (36.3%) of 11 metastatic patients. The tumor was grade 1 in 5,5% of patients, grade 2 in 16,6%, grade 3 in 77,8%. The tumor was diffuse type in 83.3% of patients and intestinal type in 16.6% of patients. The median follow-up was 11 months (2-101 months). Median progression free survival (PFS) was 3 months in metastatic patients, but median PFS was not achieved in non-metastatic patients. The 1 year PFS was 58% (p = 0.001) in non-metastatic patients (Figure 1A). Median overall survival (OS) was 6 months in metastatic patients, and median OS was not achieved in non-metastatic patients (p = 0.001). The estimated OS was 67 months in non-metastatic patients (Figure 1B). Tumor grade, histopathological subtype, presence of lymphovascular and perineural invasion and chemotherapy regimens were not correlated with PFS and OS. There was no correlation between OS and serum CEA, AFP, Ca19-9 and Ca125 levels at the time of diagnosis.

Conclusions: The ratio of gastric cancer under age 30 varies between 1-2% in the literature. In our study, the ratio of patients under 30 years old was 3.6%. Although young patients have more poor prognostic criteria such as diffuse type, proximal location, high grade, and lymphovascular invasion, the survival rates were similar to the elderly patients, according to the other studies in the literature.

Legal entity responsible for the study: Cumhuriyet University Faculty of Medicine.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

694P Differences in presentation and outcomes among young and old patients with gastric cancer

M. Al Otaibi[1], J. Al Barak[2], J. Al Abbad[1], A. Akbar[3]
[1]Medical Oncology Department, Kuwait Cancer Control Centre Al Sabah Hospital, Shuwaikh, Kuwait, [2]Medical Oncology, Kuwait Cancer Control Center, Kuwait, [3]Histopathology Department, Kuwait Cancer Control Centre Al Sabah Hospital, Shuwaikh, Kuwait

Background: The worldwide incidence of gastric cancer (GC) has been increasing in young patients (YP) over the past few decades. It is unclear whether there are differences in disease characteristics and prognosis between YP and older patients (OP). This review examines the differences in presentation and outcomes between YP and OP.

Methods: A retrospective review of all cases of sporadic GC referred to the Kuwait Cancer Control Center (KCCC) between 2008 and 2016 was conducted. We collected data on patients' demographics, risk factors, disease clinicopathologic characteristics, stage at diagnosis and survival. Patients at the age of 50 years or younger at the time of diagnosis were designated as YP. Continuous variables were summarized with mean and standard deviation, or median and interquartile range (IQR) as appropriate and compared with Mann-Whitney U test. Categorical variables were described as frequencies (percent) and compared with Fisher's exact test. A level of 0.05 was defined as statistically significant.

Results: Evaluable data were available for 167 patients. 52 (31.1%) where YP. The mean age was 43.2 ($\pm$5.7) years for YP compared with 64.3 ($\pm$8.4) years for OP. In YP 63.5% were males compared to 72.2% in EG, $p = 0.28$. YP tends to present more with epigastric pain as opposed to OP who presented with GI bleed (hematemesis, melena or symptomatic anemia). There were less smokers in YP (23.1%) relative to OP (42.5%), $p = 0.009$. We found no difference with regards to family history, H. Pylori status, histological subtype, grade or stage at diagnosis. The overall survival was 78.8% for YP versus 63.5% for OP, $p = 0.051$.

Conclusions: Compared to their older counter parts, YP with GC tend to present with more epigastric pain and less likely to be smokers. No significant differences were found in disease characteristics or outcomes between YP and OP. More research is needed to further understand the raise of GC among YP.

Legal entity responsible for the study: Ministry of Health of Kuwait.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

695P Prospective observational cohort study of oesophagogastric cancer patients (POCOP): A Dutch nationwide cohort

J.J. van Kleef[1], L.V. van de Poll-Franse[2], R.H. Verhoeven[3], M. Slingerland[4], J.P. Ruurda[5], J. Heisterkamp[6], C. Rosman[7], J.W.B. de Groot[8], E.A. Kouwenhoven[9], M.A. van Dijk[10], E. de Graaf[11], T. van Voorthuizen[12], F. Daams[13], S. Lagarde[14], G.A.P. Nieuwenhuijzen[15], J. Vincent[16], M. van Berge Henegouwen[17], M.G.H. van Oijen[1], M.A.G. Sprangers[18], H.W.M. van Laarhoven[1]
[1]Department of Medical Oncology, Academic Medical Center (AMC), Amsterdam, Netherlands, [2]Department of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [3]Department of Research, Netherlands Comprehensive Cancer Organisation, Utrecht, Netherlands, [4]Department of Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [5]Department of Surgery, University Medical Center Utrecht, Utrecht, Netherlands, [6]Department of Surgery, Elisabeth-Tweesteden Hospital, Tilburg, Netherlands, [7]Department of Surgery, Radboud University Medical Center, Nijmegen, Netherlands, [8]Department of Medical Oncology, Isala Hospital, Zwolle, Netherlands, [9]Department of Surgery, HospitalGroup Twente (ZGT), Almelo, Netherlands, [10]Department of Medical Oncology, ZorgSaam Hospital, Terneuzen, Netherlands, [11]Department of Medical Oncology, Reinier de Graaf Hospital, Delft, Netherlands, [12]Department of Medical Oncology, Rijnstate Hospital, Arnhem, Netherlands, [13]Department of Surgery, VU Medical Center, Amsterdam, Netherlands, [14]Department of Surgery, Erasmus Medical Center, Rotterdam, Netherlands, [15]Department of Surgery, Catharina Cancer Institute, Catharina Hospital, Eindhoven, Netherlands, [16]Department of Medical Oncology, Elkerliek Hospital, Helmond, Netherlands, [17]Department of Surgery, Academic Medical Center, Amsterdam, Netherlands, [18]Department of Medical Psychology, Academic Medical Center (AMC), Amsterdam, Netherlands

Background: POCOP is a novel prospective scientific database including oesophagogastric cancer patients, initiated by the Dutch Upper GI Cancer Group (DUCG) to stimulate multidisciplinary research. Within POCOP treatment and diagnostic strategies as well as prognostic and predictive factors for outcome can be evaluated on a population-based level. We present the design and current proceedings.

Methods: All patients with oesophagogastric cancer in the Netherlands are eligible. Patients need to provide consent for: 1) the reuse of clinical data collected by the Netherlands Cancer Registry (NCR), 2) longitudinal collection of patient reported outcomes (PROs), receiving future information on new interventional studies (including cohort multiple randomized controlled trials (cmRCT)), and/or 3) linkage with Dutch databases e.g. the Dutch Upper GI Cancer Audit, the biobank of The Parelsnoer Institute and general practitioner databases. Funding: Dutch Cancer Society (UVA 2014-7000).

Results: Thus far, clinical data is being collected from almost all Dutch patients with oesophagogastric cancer diagnosed from 2015 onwards. Clinical data mainly consist of patient, tumour and multidisciplinary sequential treatment characteristics. The collection of longitudinal PROs started in 2016. Of all patients who gave consent ($N = 1000$), 92% also participated in the PRO-registry. PRO compliance was 87%, 67% and 46% (not accounted for death or drop-out) at diagnosis, 3 and 6 months follow-up, respectively. 81% of patients consented to receive future information on new interventional studies, including cmRCTs. Collaborations with phase II/III trials and other cohort studies were established to reduce patient burden regarding completion of PROs and trial registration burden. Obtained data is governed by the DUCG scientific committee which includes members of participating hospitals, the study team and the NCR.

Conclusions: POCOP provides real world population-based data to stimulate (inter-)national multidisciplinary research and provides the opportunity to perform novel trials within the established infrastructure. Researchers can acquire data by submitting a research proposal to the scientific committee of the DUCG (www.ducg.nl).

Legal entity responsible for the study: Dutch Upper GI Cancer Group.
Funding: Dutch Cancer Society.
Disclosure: J.W.B. de Groot: Advisory role: BMS and MSD. T. van Voorthuizen: Travel, accomodations, expenses: Ipsen, Astellas M. van Berge Henegouwen: Consulting/advisory: Olympus, Covidien; Research funding: Olympus; Travel, accomodations, expenses: Johnson&Johnson M.G.H. van Oijen: Research funding: Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Roche. H.W.M. van Laarhoven: Consultancy: Celgene, Lilly, Nordic. Research funding: Bayer, Lilly, Merck Serono, Roche. All other authors have declared no conflicts of interest.

697P A phase I, open-label, multi-center, dose-escalation study of codrituzumab, an anti-glypican-3 monoclonal antibody, in combination with atezolizumab in patients with locally advanced or metastatic hepatocellular carcinoma

A-L. Cheng[1], C-J. Yen[2], T. Okusaka[3], M. Ikeda[4], C-H. Hsu[1], S-Y. Wu[2], C. Morizane[3], Y. Hashimoto[5], K. Ueshima[6], T. Ohtomo[7], T. Tanaka[8], M. Kudo[6]
[1]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan, [2]Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, [3]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [5]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [6]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan, [7]Oncology Lifecycle Management Dept., Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, [8]Translational Clinical Research Science & Strategy Dept., Chugai Pharmaceutical Co., Ltd., Tokyo, Japan

Background: Codrituzumab (Cod) is a recombinant humanized monoclonal antibody against Glypican-3 (GPC3). GPC3 is over-expressed in hepatocellular carcinoma (HCC). Cod elicits antibody-dependent cellular cytotoxicity against human HCC cell lines and shows more potent anti-tumor activity when combined with anti-PD-L1 antibody in syngeneic mouse model. This is a phase I dose-escalation study to evaluate safety/tolerability and pharmacokinetics in combination with the anti-PD-L1 antibody, atezolizumab (Atezo) in advanced HCC patients.

Methods: This study is composed of a 3 + 3 dose-escalation part and an expansion part. Patients with advanced or metastatic HCC who had failed prior systemic therapy, GPC3 high expression, ECOG PS 0-1, Child-Pugh A-B7 were eligible. Cod given intravenously 800 or 1600 mg on Day 1, 4, then weekly from Day 8 combined with 1200 mg every 3 weeks dosing of Atezo until disease progression/toxicity. The objectives were to determine MTD of Cod and Atezo combination primarily, to assess safety, antitumor effect (RECIST 1.1) and pharmacokinetics secondarily, and to assess biomarkers exploratory.

Results: Ten patients each were enrolled in dose-escalation and expansion parts, respectively. There were 16 men/4 women, median age 58, all Asian, HBV/HCV/neither 11/4/5, ECOG 0/1 15/5. No dose limiting toxicities were observed in dose-escalation part. The most frequently observed adverse events (AEs) were pyrexia (80%), fatigue (50%), decreased appetite (30%), aspartate aminotransferase increased, lymphocyte count decreased (25%), constipation, cough, nasopharyngitis (20%). Grade 3 or higher AEs ($\geq$ 2 patients) were aspartate aminotransferase increased, lymphocyte count decreased (20%), anemia (15%), and ascites (10%). There was 1 confirmed PR, 10 SD (including 1 unconfirmed PR) among 18 evaluable patients and 6 of them had SD for more than 6 months before progression.

Conclusions: Cod + Atezo combination was well-tolerated and showed antitumor activity in this advanced, previously treated and GPC3 highly expressed HCC patients.

Clinical trial identification: JapicCTI-163325 Registered date: 22/07/2016.
Legal entity responsible for the study: Chugai Pharmaceutical Co., Ltd.
Funding: Chugai Pharmaceutical Co., Ltd.

Disclosure: T. Okusaka: Advisory board: Dainippon Sumitomo Pharma, Taiho Pharmaceutical, Zeria Pharmaceutical, Daiichi Sankyo; Research funding: Eli Lilly Japan K.K. Eisai, Novartis Pharma K.K. Yakult Honsha, Taiho Pharmaceutical, Kowa Company, Kyowa Hakko Kirin, Ono Pharmaceutical, Bayer Yakuhin, Pfizer Japan Inc. AstraZeneca K.K., Dainippon Sumitomo Pharma, Nano Carrier, Baxter Chugai Pharmaceutical, M. Ikeda: Advisory board: Bayer, Yakuhin, Eisai, Novartis Pharma, Shire, MSD; Research funding: Bayer Yakuhin, Kyowa Hakko Kirin, Yakult, Eli Lilly Japan, Ono Pharmaceutical, Eisai, AstraZeneca, Baxalta Japan Limited, Chugai Pharmaceutical, Bristol Myers Sqiibb, Merck Serono, Nano Carrier, Aslan Pharmaceuticals, Novartis Pharma, Takara Bio. C-H. Hsu: Advisory board: BMS, ONO, MSD, Merck/Sorono, Novartis, Research funding: MSD. C. Morizane: Advisory board: Yakult Honsha, Novartis, Taiho Pharmaceutical; Research funding: Pfizer, Nobelpharma, Eisai, Yakult Honsha, Ono Pharmaceutical, Taiho Pharmaceutical; Honoraria: Pfizer, Novartis, Yakult Honsha, Lilly, Nobelpharma, Fujifilm, Teijin Pharma, Taiho Pharmaceutical. Y. Hashimoto: Advisory board: Medicos Hirata. T. Ohtomo: Employee: Chugai Pharmaceutical. T. Tanaka: Stock ownership, Employee: Chugai pharmaceutical. M. Kudo: Advisory board: Eisai, Bayer, MSD, Ono, BMS; Research funding: Ono, MSD, Eisai. All other authors have declared no conflicts of interest.

698P Phase II efficacy and safety data for the MET inhibitor tepotinib in patients (pts) with sorafenib-treated advanced hepatocellular carcinoma (HCC)

T. Decaens[1], C. Barone[2], E. Assenat[3], M. Wermke[4], A. Fasolo[5], P. Merle[6], J.F. Blanc[7], V. Grando[8], R. Bruns[9], J. Straub[10], C. Zhao[11], S. Faivre[12]

[1]Institute for Advanced Biosciences, CHU de Grenoble, La Tronche, France, [2]Medical Oncology, Policlinico Universitario A. Gemelli, Rome, Italy, [3]Medical Oncology, CHU Saint Eloi, Montpellier, France, [4]University Cancer Center, University Hospital Carl-Gustav-Carus, Dresden, Germany, [5]Oncology, IRCCS San Raffaele, Milan, Italy, [6]Service d'Hépato-Gastro-Entérologie, Centre Hospitalier de la Croix Rousse, Lyon, France, [7]Hepatology and Medical Oncology, CHU Bordeaux Haut-Lévêque, Bordeaux, France, [8]Hepatology, Jean Verdier Hospital, Bondy, France, [9]Biostatistic, Merck KGaA, Darmstadt, Germany, [10]Clinical Biomarker & Companion Diagnositics, Merck KGaA, Darmstadt, Germany, [11]Clinical Research, EMD Serono Inc, Billerica, MA, USA, [12]Medical Oncology, Hopital Beaujon, Clichy, France

Background: MET is a potential therapeutic target in advanced HCC; tepotinib is a highly selective MET inhibitor. Here we report final analysis results from a single-arm multicenter phase 2 study investigating the efficacy and safety of tepotinib in pts with sorafenib-treated advanced MET+ HCC (NCT02115373).

Methods: Adults with advanced MET+ HCC, Child-Pugh Class A, Eastern Cooperative Oncology Group performance status 0–1, and ≥4 weeks of prior sorafenib therapy were eligible for treatment. MET status was assessed by immunohistochemistry (2+ or 3+) and in-situ hybridization. Pts received tepotinib at the recommended phase 2 dose (RP2D) of 500 mg once-daily. The primary endpoint was progression-free survival status at 12 weeks; secondary endpoints included safety and other efficacy parameters.

Results: 49 pts had received treatment; median (range) duration of therapy was 3.02 (0.03–16.49) months. Median (range) age was 66 (19–82) years and most patients were male (83.7%). The null hypothesis that the rate of progression-free subjects at 12 weeks is ≤ 15% has been rejected as 31/49 pts (63.3%; 90% confidence interval [CI]: 50.5, 74.7) were progression-free at 12 weeks; median PFS was 3.4 months (90% CI: 2.8, 4.2). Overall, there were 4/49 responders (8.2%; 90% CI: 2.8, 17.7; 1 complete and 3 partial responses). Median overall survival was 5.6 months (90% CI: 5.1, 8.2 months). The most common treatment-related adverse events (AEs) were peripheral edema (n = 32; 38.8%), fatigue (n = 10; 18.4%) and diarrhea (n = 16; 16.3%). 17 pts (34.7%) discontinued treatment due to AEs and 1 pt (2%) died from a treatment-related AE (hypoglycemic coma).

Conclusions: These data indicate that tepotinib has anti-tumor activity in pretreated MET+ advanced HCC and was well tolerated at the RP2D, with no new safety signals detected.

Clinical trial identification: NCT02115373.

Editorial acknowledgement: Medical writing assistance (funded by Merck KGaA, Darmstadt, Germany) was provided by Martin Quinn, PhD of Bioscript Science (Macclesfield, UK).

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: C. Barone: Advisory board membership, Fee for presentation: Merck Serono. M. Wermke: Honaries: BMS, Novartis, Roche, Bayer, Glenmark, AstraZeneca; Travel reimbursements: AstraZeneca, BMS, MSD, Novartis, Glenmark; Research funding: Novartis, Pfizer. P. Merle: Advisory board member: Bayer, Ipsen, BMS. J.F. Blanc: Advisory board member: Bayer, Lilly Oncology, BMS, Onxeo, Esai, Ipsen. R. Bruns, J. Straub: Employee: Merck KGaA. C. Zhao: Employee: EMD Serono Inc. S. Faivre: Consultant, Clinical trials grants: Blueprint, BMS, Bayer Pharma, Eli Lilly, Ipsen, Merck Serono, MSD, Novartis. All other authors have declared no conflicts of interest.

699P Real-world data on nivolumab treatment in Asian patients with advanced hepatocellular carcinoma

S.E. Yoon[1], J.Y. Hur[1], K.K. Lee[1], S.J. Lee[1], J. Lee[1], S.W. Paik[2], H.Y. Lim[1]

[1]Hematology-Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Gastroenterology, Samsung Medical Center, Seoul, Republic of Korea

Background: Nivolumab, an anti-PD-1 antibody showed durable responses and long-term survival in patients with hepatocellular carcinoma (HCC) and was approved by FDA as 2nd line treatment after sorafenib treatment in 2017. We present real-world experience with nivolumab in HCC.

Methods: We retrospectively reviewed the medical records of HCC patients who had nivolumab treatment at Samsung Medical Center. Nivolumab treatment was given every two weeks until progression or intolerable toxicity. Response evaluation was done based on RECIST v1.1.

Results: A total of 76 patients were treated with nivolumab between March 2017 and May 2018. The median age was 60 years (range; 30-83 years) and 86% were male patients. The cohorts included 56 patients with hepatitis B viral infection, 7 with hepatitis C viral infection and 19 without viral infection. Most of patients (96.0%) were ECOG performance statue 0 or 1 and patients with Child-Pugh A were 59 (77.6%). 70 patients (92.1%) had previous sorafenib therapy and 8 patients received nivolumab as 3rd or more line (10.5%). There were three patients with previous history of liver transplantation. With median follow-up duration of 15 weeks (range, 5-39), the median treatment cycle was 4 (range,1-26). 17 patients (22.4%) received standard dose of 3mg/kg, whereas 59 patients (77.6%) received less than 3mg/kg of nivolumab. Partial response was observed in 6 patients (ORR 7.9%) and they all are on nivolumab therapy for 4-13 months. Disease control rate was 39.5%. The most common adverse events (AEs) were anorexia(15.6%) and puritus(15.8%)., nausea (13.1%), liver dysfunction (21%) and fatigue(7.9%). However, these were almost grade 1 or 2 except for two cases of grade 3 liver dysfunction and grade 3 diabetes. There was no HBV reactivation observed.

Conclusions: Compared to phase I/II study of nivolumab (CheckMate 040), our real-world data showed lesser ORR and DCR. Move advanced disease status, liver dysfunction and short follow-up duration might explain it. However, nivolumab showed a manageable safety profile even in transplanted patients.

Legal entity responsible for the study: Samsung Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

700P Stemness in hepatocellular carcinoma reduced by inhibition of WEE1 expression

K.U. Park[1], M.J. Ko[2], H.M. Ryoo[3], Y-H. Lee[4]

[1]Oncology, Dongsan Medical Center Kemyung University Hospital, Daegu, Republic of Korea, [2]Department of Hematology/Oncology, Keimyung University School of Medicine, Daegu, Republic of Korea, [3]Hematology/Oncology, Daegu Catholic University, Daegu, Republic of Korea, [4]Department of Molecular Biology, Keimyung University School of Medicine, Daegu, Republic of Korea

Background: Chemotherapy targets proliferating cells, not cancer stem cells (CSCs). Targeting agents, e.g. sorafenib for hepatocellular carcinoma (HCC), do not seem to target CSCs as evidenced by frequent tumor relapse and resistance after therapy. Identification and characterization of signaling pathways and biomarkers associated with CSC biology are priorities for developing new paradigms of molecular cancer therapeutics. Increase of WEE1 kinase activity through an epigenetic regulation plays an important role in the development of HCC. However, the functional role of WEE1 in HCC progression remains to be clarified.

Methods: Human HCC cell lines were transfected with WEE1 siRNA and tested for growth inhibition, apoptotic induction, molecular changes in both RNA and protein levels, and changes in CSC phenotype using various methods such as MTS, FACS, microscopic analysis, Real-time PCR, Western blotting, sphere forming assay. To find the molecular changes in response to WEE1 knockdown, global changes in gene expression were examined using RNA sequencing.

Results: We demonstrated that WEE1 siRNA silencing caused inhibition of HCC cell growth through blockade of cell cycle progression and induction of apoptosis. The anti-proliferative effects were driven by a subset of molecular alterations including the upregulation of cdk inhibitor p21 and the downregulation of AKT1, CDK2, cyclin B1, PARP1 and GPAM which are functionally involved in control of cell cycle, apoptosis and lipid metabolism. WEE1 silencing resulted in a strong inhibition of lipogenesis and caused a marked decrease in fat accumulation. Knockdown of WEE1 dramatically reduced the portion of liver CSC population through co-downregulation of cancer stemness genes, weakened the capacity of sphere formation and cancer cell migration. Systemic delivery of a modified WEE1 siRNA encapsulated in lipid nanoparticles nhibited human HCC growth in murine xenograft models, and increased survival.

Conclusions: Our findings suggest that the epigenetic modifier WEE1 functionally involve to HCC lipid metabolism and CSC-like phenotype maintenance and that molecular targeting of WEE1 may be an effective systemic therapy for prevention of tumor recurrence via elimination of CSCs in liver tumor microenvironment.

Legal entity responsible for the study: Keon Uk Park.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

701P Analysis of single-nucleotide polymorphisms (SNPs) in the phase III RESORCE trial of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC)

K. Köchert[1], G. Meinhardt[2], J. Bruix[3], M. Teufel[4]

[1]*Clinical Statistics EU – SBU Oncology, Bayer AG, Berlin, Germany,* [2]*Clinical Development Oncology, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA,* [3]*BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBEREHD, Barcelona, Spain,* [4]*Translational Medicine Oncology, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA*

Background: Regorafenib is a multikinase inhibitor that improved overall survival (OS) and time to progression (TTP) in patients with HCC who progressed during sorafenib treatment in the phase 3 RESORCE trial. This exploratory analysis evaluated the impact of SNPs on regorafenib treatment benefit (OS and TTP) and the occurrence of hand–foot skin reaction (HFSR) in the RESORCE trial.

Methods: Genotyping of 187 SNPs was performed on whole blood DNA from 330/573 (58%) patients from RESORCE using a custom NimbleGen™ kit and sequencing libraries that were made using NimbleGen™ KAPA Hyper construction kits. The prognostic and predictive effects of the SNPs, as well as the impact on the occurrence of grade $\geq$1 HFSR, were assessed using Cox proportional hazards regression with Breslow tie handling or logistic regression, respectively. Models were adjusted for clinical covariates as determined by Akaike information criterion (AIC)-based selection and adjusted for population stratification. P values were corrected for multiple testing using Bonferroni correction and deemed significant at an adjusted $\alpha \leq 0.05$.

Results: The overall RESORCE and biomarker cohorts were generally similar for demographic variables (except the latter had a smaller proportion of Asian patients) and outcomes. None of the assessed SNPs were prognostic or predictive of OS. In contrast, 6 SNPs (positioned in the UGT1A1, VEGFC, and TIE2 genes) were prognostic for TTP; SNP rs4148323 in the UGT1A1 gene was predictive for TTP (HR 0.24, 95% CI 0.12–0.49; adjusted p = 0.012). The rs1547651 SNP in the VEGFA gene showed a significant prognostic effect on the occurrence of grade $\geq$1 HFSR (odds ratio [OR] 0.04, 95% CI 0.01–0.19; adjusted p = 0.037), while the rs114681547 SNP, also in the VEGFA gene, showed a predictive effect (OR 26.23, 95% CI 5.39–197.96; adjusted p = 0.038).

Conclusions: These exploratory results suggest that the detected SNP biomarkers may be candidates for future research to gain deeper understanding of the biological mechanisms determining clinical benefit of regorafenib treatment in HCC.

Clinical trial identification: NCT01774344.

Editorial acknowledgement: Editorial assistance in the preparation of this abstract was provided by Katrin Gudmundsdottir of SuccinctChoice Medical Communications (London, UK), with financial support from Bayer.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: K. Köchert, G. Meinhardt, M. Teufel: Stock ownership, Employee: Bayer. J. Bruix: Grants, Research support: Bayer; Advisory board: Bayer, AbbVie, Bristol-Myers Squibb, Novartis, Roche, Onxeo, Terumo, Sirtex and BTG; Consulting: Daiichi Sankyo, ArQule, Bayer, AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Lilly, Kowa, Novartis, Roche, Onxeo, Terumo, Sirtex.

702P Outcomes by baseline alpha-fetoprotein (AFP) levels in the phase III CELESTIAL trial of cabozantinib (C) versus placebo (P) in previously treated advanced hepatocellular carcinoma (HCC)

R.K. Kelley[1], A.B. El-Khoueiry[2], T. Meyer[3], L. Rimassa[4], P. Merle[5], S.L. Chan[6], A. Tran[7], F. Parnis[8], V.C. Tam[9], S. Cattan[10], D.W. Markby[11], D.O. Clary[11], A-L. Cheng[12], G.K. Abou-Alfa[13]

[1]*Oncology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA,* [2]*Medical Oncology, USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA,* [3]*Medical Oncology, Royal Free Hospital, London, UK,* [4]*Oncology, Humanitas Cancer Center, Milan, Italy,* [5]*Hepatology, Groupement Hospitalier Lyon Nord, Lyon, France,* [6]*Clinical Oncology, The Chinese University of Hong Kong, Shatin, Hong Kong, China,* [7]*Hepatology, Groupe Hospitalier L'Archet, Nice, France,* [8]*Oncology, Adelaide Cancer Centre, Adelaide University, Kurralta Park, Australia,* [9]*Medical Oncology, University of Calgary, Calgary, AB, Canada,* [10]*Diseases of the Digestive System - Hepatology, CHRU Lille, Lille, France,* [11]*Medical Affairs, Exelixis Inc., San Francisco, CA, USA,* [12]*National Taiwan University Hospital, Taipei, Taiwan,* [13]*Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Background: High baseline AFP levels are associated with poor prognosis in patients (pts) with HCC and are associated with a distinct molecular profile. C, an inhibitor of MET, VEGFR, and AXL, improved overall survival (OS) and progression-free survival (PFS) in the phase 3 CELESTIAL trial (NCT01908426). Median OS was 10.2 mo with C vs 8.0 mo with P (HR 0.76, 95% CI 0.63–0.92; p = 0.0049), and median PFS was 5.2 mo with C vs 1.9 mo with P (HR 0.44, 95% CI 0.36–0.52; p < 0.0001).

Methods: 707 pts were randomized 2:1 to receive C (60 mg qd) or P. Eligible pts had pathologic diagnosis of HCC, Child-Pugh score A, and ECOG PS $\leq$ 1. Patients must have received prior sorafenib and 1–2 prior lines of systemic therapy for HCC and must have progressed following at least one. Stratification was by disease etiology, geographic region, and extent of disease. Outcomes were analyzed by baseline AFP levels using cut-offs of 20, 200, and 400 ng/mL.

Results: Overall, 69% of pts had baseline AFP $\geq$20 ng/mL, 49% had AFP $\geq$200 ng/mL, and 41% had AFP $\geq$400 ng/mL. For pts with baseline AFP <400 ng/mL, median OS was 13.9 mo with C vs 10.3 mo with P (HR 0.81), and median PFS was 5.5 mo with C vs 1.9 mo with P (HR 0.47). For pts with baseline AFP $\geq$400 ng/mL, median OS was 8.5 mo with C vs 5.2 mo with P (HR 0.71), and median PFS was 3.9 mo with C vs 1.9 mo with P (HR 0.42). C also improved OS vs P in pts with AFP $\geq$200 ng/mL or $\geq$ 20 ng/mL, and C improved PFS irrespective of AFP levels (Table). Pts with high baseline AFP experienced high-grade transaminitis more frequently in both treatment groups; grade 3/4 elevated aspartate aminotransferase with C vs P was 8% vs 4% for AFP <400 ng/mL and 17% vs 11% for AFP $\geq$400 ng/mL.

Table: 702P

Baseline AFP, ng/mL	Patients, N		HR C vs P (95% CI)	
	C	P	OS	PFS
<20	139	77	0.97 (0.67–1.40)	0.57 (0.41–0.78)
$\geq$20	331	160	0.67 (0.54–0.84)	0.41 (0.33–0.51)
<200	242	118	0.83 (0.63–1.10)	0.52 (0.40–0.67)
$\geq$200	228	119	0.70 (0.54–0.91)	0.39 (0.30–0.50)
<400	278	136	0.81 (0.62–1.04)	0.47 (0.37–0.60)
$\geq$400	192	101	0.71 (0.54–0.94)	0.42 (0.32–0.55)

Conclusions: C improved OS and PFS vs P in patients with previously treated advanced HCC across a range of baseline AFP levels. High AFP levels were associated with a larger treatment benefit with C for both OS and PFS.

Clinical trial identification: NCT01908426.

Legal entity responsible for the study: Exelixis, Inc.

Funding: Exelixis, Inc.

Disclosure: R.K. Kelley: Consulting or advisory role: Genentech for IDMC (self), Bayer, BMS, Astra Zeneca, DebioPharm, Agios (institution); Research funding: Adaptimmune, Agios, Astra Zeneca, Bayer, Bristol Myers Squibb, Celgene, Exelixis, Eli Lilly, Medimmune, Merck, Novartis, Regeneron, Sanofi, Taiho, Target Pharma Solutions, Tekmira. A.B. El-Khoueiry: Honoraria: BMS, Bayer, Exelixis, EMD Serono, Eisai, Roche, Cytomx, Merck; Consulting or advisory role: BMS, Bayer; Research funding: Astrazeneca, Astex. T. Meyer: Consulting or advisory role: Bayer, Eisai, BMS, BTG, Ipsen; Research funding: Bayer. L. Rimassa: Consulting or advisory role: Lilly, Bayer, Sirtex Medical, Italfarmaco, Sanofi, Arqule, Baxter, Ipsen, Exelixis, Amgen; Travel accomodations expenses: Arqule, Ipsen. S.L. Chan: Consulting or advisory role: AstraZeneca, MSD; Research funding: MSD, Pfizer, Sirtex. A. Tran: Consulting or advisory role: Gilead, Abbvie, MSD; Speakers' bureau: Gilead, Abbvie, MSD; Travel, accomodations, expenses: Gilead, Abbvie, MSD. V.C. Tam: Honoraria: Celgene, Apobiologix; Travel accomodations expenses: Amgen. D.W. Markby, D.O. Clary: Employee, Stock ownership: Exelixis. A-L. Cheng: Consulting or Advisory role: Bayer, Schering Pharma, Bristol-Myers Squibb, Eisai, Merck Serono, Novartis, Ono Pharmaceutical, ONXEO; Speakers' bureau: Novartis; Research funding: Sanofi. G.K. Abou-Alfa; Self consulting: Agios, Amgen, Antengene, Aptus, Aslan, Astellas, Astra Zeneca, Bayer, BMS, Boston Scientifc, Carsgen, Celgene, Casi, Daiichi, Debio, Delcath, Eisai, Exelixis, Halozyme, Inovio, Ipsen, Merck, Onxeo, PCI Biotech, Roche, Sanofi, Servier, Sillajen, Sirtex, Yakult Immediate; Family member consulting: Celgene, CytomX, Gilead, Halozyme, Sanofi, Silenseed; Institutional research: Agios, Array, Astra Zeneca, Bayer, BMS, Casi, Celgene, Exelixis, Genentech, Incyte, Lilly, Mabvax, MedImmune, Momenta, Novartis, OncoMed Pharmaceuticals, Roche. All other authors have declared no conflicts of interest.

703P Assessment of disease burden in the phase III CELESTIAL trial of cabozantinib (C) versus placebo (P) in advanced hepatocellular carcinoma (HCC)

J.F. Blanc[1], T. Meyer[2], A-L. Cheng[3], A.B. El-Khoueiry[4], I. Cicin[5], Y. Chen[6], L. Bolondi[7], V. Dadduzio[8], A. Baron[9], Z-Z. Lin[3], J. Adriani[10], R.K. Kelly[11], G.K. Abou-Alfa[12]

[1]Service d'Hépato-Gastroentérologie et d'Oncologie Digestive, Hôpital Haut-Lévêque, Chu Bordeaux, France, [2]Oncology, Royal Free Hospital, London, UK, [3]Oncology, National Taiwan University Hospital, Taipei, Taiwan, [4]Medical Oncology, USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [5]Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Turkey, [6]Liou Ying ChiMei Hospital, Department of Medical Oncology, Tainan, Taiwan, [7]University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy, [8]Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [9]Oncology, California Pacific Medical Center, San Francisco, CA, USA, [10]Clinical Research & Development, Exelixis, Inc, San Francisco, CA, USA, [11]Medical Oncology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [12]Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: Extrahepatic spread (EHS) and macrovascular invasion (MVI) are poor prognostic factors in HCC. In the CELESTIAL trial (NCT01908426), C improved overall survival (OS) and progression-free survival (PFS) vs P in patients (pts) with previously treated advanced HCC. Median OS was 10.2 mo with C vs 8.0 mo with P (HR, 0.76; 95% CI, 0.63–0.92; P = 0.0049). Median PFS was 5.2 mo with C versus 1.9 mo with P (HR, 0.44; 95% CI, 0.36–0.52; P < 0.0001). Here, we analyze OS and PFS based on (i) EHS, (ii) MVI, and (iii) the sum of target lesion diameters (SOD) at baseline.

Methods: A total of 707 pts, stratified by disease etiology, geographic region, and the presence of EHS and/or MVI, were randomized 2:1 to receive C, 60 mg once daily (N = 470) or P (N = 237). Eligible patients had a pathologic diagnosis of HCC, Child-Pugh score A, and ECOG performance status ≤1. Pts received prior sorafenib and ≤2 lines of prior systemic therapy. Tumors were assessed every 8 weeks by investigator.

Results: In the overall population, 78% pts had EHS, 30% had MVI and 85% had EHS and/or MVI. Among pts with EHS, 50% had metastasis to the lung, 40% to lymph nodes and 17% to bones. C improved OS (HR ≤ 0.8) vs P in pts with or without MVI (Table). C also improved OS vs P in pts with EHS or high SOD. PFS was improved with C irrespective of the extent of the disease.

Table: 703P

	No. pts		Median OS, mo		OS HR (95% CI)	Median PFS, mo		PFS HR (95% CI)
	C	P	C	P		C	P	
EHS								
Yes	369	182	9.6	6.9	0.72 (0.58-0.89)	5.0	1.9	0.46 (0.37-0.56)
No	101	55	12.0	12.3	0.96 (0.63-1.46)	5.4	1.9	0.45 (0.31-0.66)
MVI								
Yes	129	81	7.6	5.3	0.75 (0.54-1.03)	3.7	1.8	0.42 (0.31-0.58)
No	339	156	12.4	9.7	0.80 (0.64-1.01)	5.5	1.9	0.48 (0.38-0.59)
SOD								
< median	231	120	12.5	10.5	0.94 (0.71-1.24)	5.5	1.9	0.48 (0.37-0.61)
≥ median	234	117	8.2	5.3	0.58 (0.45-0.76)	4.2	1.9	0.44 (0.34-0.57)

Conclusions: C generally improved OS in pt subgroups defined by extent of disease burden. The presence of MVI, EHS, or high SOD at baseline was associated with shorter OS in both treatment groups.

Clinical trial identification: NCT01908426.

Legal entity responsible for the study: Exelixis.

Funding: Exelixis, Inc.

Disclosure: J.F. Blanc: Consulting or advisory role: Bayer, SP, BMS, Ipsen. T. Meyer: Consulting or advisory role: Bayer, BTG, Ipsen; Research funding: Bayer, BTG. A-L. Cheng: Consulting or Advisory role: Bayer Schering Pharma, Bristol-Myers Squibb, Eisai, Merck. Serono, Novartis, Ono Pharmaceutical, Onxeo; Speakers' bureau: Novartis; Research funding: Sanofi. A.B. El-Khoueiry: Honoraria: BMS, Bayer, Exelixis, EMD Serono, EISAI, Roche, Cytomx, Merck. Consulting or advisory role: BMS, Bayer; Research funding: AstraZeneca, Astex. L. Bolondi: Consulting or advisory role: Bayer, BMS, Sirtex, Guerbet; Speakers bureau: Bayer, BMS, Sirtex, Bracco, Eli-Lilly, Guerbet, Meda-Pharm; Travel accommodations expenses: Bayer, BMS, Bracco, Sirtex, Guerbet, Eli-Lilly. V. Dadduzio: Travel, accommodations, expenses: Bayer, Amgen, Astellas. A. Baron: Speakers' bureau: BMS, Merck, Genentech, Lilly. J. Adriani: Employee, Stock ownership: Exelixis. R.K. Kelly: Consulting or advisory role: Genentech for IDMC (self); Bayer, BMS, AstraZeneca, DebioPharm, Agios; Research funding: Adaptimmune, Agios, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Exelixis, Eli Lilly, Medimmune, Merck, Novartis, Regeneron, Sanofi, Taiho, Target Pharma Solutions, Tekmira. G.K. Abou-Alfa: Self consulting role: Agios, Amgen, Antengene, Aptus, Aslan, Astellas, AstraZeneca, Bayer, BMS, Boston Scientifc, Carsgen, Celgene, Casi, Daiichi, Debio, Delcath, Eisai, Exelixis, Halozyme, Inovio, Ipsen, Merck, Onxeo, PCI Biotech, Roche, Sanofi, Servier, Sillajen, Sirtex, Yakult Immediate; Family member consulting: Celgene, CytomX, Gilead, Halozyme, Sanofi, Silenseed; Institutional Research; Agios, Array, AstraZeneca, Bayer, BMS, Casi, Celgene, Exelixis, Genentech, Incyte, Lilly, Mabvax, Medimmune, Momenta, Novartis, OncoMed Pharmaceuticals, Roche. All other authors have declared no conflicts of interest.

704P Outcomes by prior transarterial chemoembolization (TACE) in the phase III CELESTIAL trial of cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC)

T. Yau[1], A-L. Cheng[2], T. Meyer[3], B-Y. Ryoo[4], J-W. Park[5], H-J. Klümpen[6], H.Y. Lim[7], S. Kim[8], J. Knox[9], M. Patel[10], A.B. El-Khoueiry[11], R.K. Kelley[12], G.K. Abou-Alfa[13]

[1]Oncology, Queen Mary Hospital, Hong Kong, China, [2]National Taiwan University Hospital, Taipei, Taiwan, [3]Medical Oncology, Royal Free Hospital, London, UK, [4]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [5]Center for Liver Cancer, National Cancer Center, Goyang-si, Republic of Korea, [6]Department of Medical Oncology, Academic Medical Center, Amsterdam, Netherlands, [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [8]CHU Besançon, Besançon, France, [9]Princess Margaret Hospital, Toronto, ON, Canada, [10]Exelixis, Inc., South San Francisco, CA, USA, [11]Medical Oncology, USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [12]Division of Hematology/Oncology, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA, [13]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: Pts with HCC and localized disease commonly receive treatment with TACE but often progress and require systemic therapy. In the CELESTIAL trial (NCT01908426), C, an inhibitor of MET, VEGFR, and AXL, improved overall survival (OS) and progression-free survival (PFS) vs P in previously treated pts with advanced HCC. Median OS was 10.2 mo for C vs 8.0 mo for P (HR 0.76, 95% CI 0.63–0.92; p = 0.0049), and median PFS was 5.2 mo for C vs 1.9 mo for P (HR 0.44, 95% CI 0.36–0.52; p < 0.0001) (Abou-Alfa, JCO 2018). Here, outcomes were analyzed for pts who received prior TACE.

Methods: 707 pts were randomized 2:1 to receive C (60 mg qd) or P stratified by disease etiology, geographic region, and extent of disease. Eligible pts had pathologic diagnosis of HCC, Child-Pugh score A, and ECOG PS ≤ 1. Pts must have received prior sorafenib and could have received up to two lines of prior systemic therapy for HCC. Outcomes were analyzed by number of prior TACE treatments (0, ≥1, 1-2, ≥3).

Results: Overall, 203 (43%) pts in the C arm and 111 (47%) pts in the P arm had received prior TACE with a median of 2 and 3 treatments, respectively. For pts who received TACE, 54% received 1-2 treatments and 46% received ≥3. 61% of pts enrolled in Asia, 39% in Europe, and 37% in North America received prior TACE. For pts who received prior TACE vs no TACE, 67% vs 76% received 1 prior systemic regimen and 32% vs 23% received 2. C was associated with improved OS and PFS vs P irrespective of prior TACE treatment (Table). Median OS was 11.4 mo for C vs 8.6 mo for P in pts with prior TACE and 9.5 mo for C vs 7.2 mo for P in pts with no prior TACE. Grade 3/4 adverse events were similar for pts with and without prior TACE in both arms.

Conclusions: C improved OS and PFS compared with P in pts with previously treated advanced HCC irrespective of whether they had received prior TACE.

Table: 704P

	No Prior TACE		Prior TACE					
			≥1		1-2		≥3	
	C (N = 267)	P (N = 126)	C (N = 203)	P (N = 111)	C (N = 118)	P (N = 52)	C (N = 85)	P (N = 59)
OS HR (95% CI)	0.69 (0.54–0.90)		0.82 (0.62–1.09)		0.89 (0.59–1.37)		0.80 (0.54–1.17)	
PFS HR (95% CI)	0.43 (0.33–0.54)		0.50 (0.38–0.64)		0.58 (0.41–0.84)		0.38 (0.26–0.57)	

Clinical trial identification: NCT01908426

Legal entity responsible for the study: The authors.

Funding: Exelixis, Inc.

Disclosure: A-L. Cheng: Honoraria, Consulting, Advisory role, Speakers' bureau: Bayer, Eisai, Ono, Genentech, Novartis, BMS, Merck, MSD. T. Meyer: Consulting, Advisory role: Bayer, BTG, Ipsen; Research funding: Bayer, BTG. J-W. Park: Honararia: Bayer, BMS, Ono; Consulting, Advisory role: BMS, Ono, Bayer, Eisai, Midatech, Roche. H-J. Klümpen: Travel, accommodations and expenses to the ENETS knowledge network, sponsored by Ipsen. J. Knox: Honoraria: Novartis; Consulting or advisory role: Lilly, Merck; Research funding; AstraZeneca. M. Patel: Emplyee, Stock ownership: Exelixis, Genentech/Roche. A.B. El-Khoueiry: Honoraria: BMS, Bayer, Exelixis, EMD Serono, EISAI, Roche, Cytomx, Merck; Consulting or advisory role: BMS, Bayer; Research funding: AstraZeneca, Astex. R.K. Kelley: Consulting or advisory role: Genentech for IDMC (self), Bayer, BMS, AstraZeneca, DebioPharm, Agios; Research funding: Adaptimmune, Agios, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Exelixis, Eli Lilly, Medimmune, Merck, Novartis, Regeneron, Sanofi, Taiho, Target Pharma Solutions, Tekmira. G.K. Abou-Alfa: Self Consulting: Agios, Amgen, Antengene, Aptus, Aslan, Astellas, AstraZeneca, Bayer, BMS, Boston Scientifc, Carsgen, Celgene, Casi, Daiichi, Debio, Delcath, Eisai, Exelixis, Halozyme, Inovio, Ipsen, Merck, Onxeo, PCI Biotech, Roche, Sanofi, Servier, Sillajen, Sirtex, Yakult Immediate; Family member consulting: Celgene, CytomX, Gilead, Halozyme, Sanofi, Silenseed Institutional Research Agios, Array, AstraZeneca, Bayer, BMS, Casi, Celgene, Exelixis, Genentech, Incyte, Lilly, Mabvax, Medimmune, Momenta, Novartis, OncoMed Pharmaceuticals, Roche. All other authors have declared no conflicts of interest.

705P Clinicopathological evaluation of skin lesions (SL) in patients with hepatocellular carcinoma (HCC) treated with sorafenib

L.G.D. Fonseca[1], A. Díaz[2], V. Sapena[1], Á. Díaz-González[1], L. Boix[1], M. Sanduzzi-Zamparelli[1], C. Fuster[2], N. Llarch[1], G. Iserte[1], F. Torres[3], J. Bruix[4], M. Reig[1]

[1]BCLC Group. Liver Unit, Hospital Clínic of Barcelona. IDIBAPS. CIBERehd, Barcelona, Spain, [2]Department of Pathology, Hospital Clínic of Barcelona. IDIBAPS. CIBERehd, Barcelona, Spain, [3]Medical Statistics Core Facility, Hospital Clínic of Barcelona. IDIBAPS. CIBERehd, Barcelona, Spain, [4]BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBEREHD, Barcelona, Spain

Background: Dermatologic adverse events (DAE) are frequently experienced in patients under sorafenib. Although the majority appear as rash or hand-foot reaction, some patients may present SL requiring biopsy or local procedures that may impact in the treatment. While there are series of patients with melanoma and BRAF inhibitors presenting SL, there is no information on HCC patients with sorafenib.

Methods: We analyzed a prospective database of patients with HCC treated with sorafenib. Patients who developed biopsed SL were included and the pathology samples were reviewed.

Results: Between oct-2007 and jan-2018, 313 patients were treated with sorafenib (54.6% BCLC-C, 88.7% ECOG-PS0 and 83.6% CPA), 88 (28.1%) presented DAE in the first 60 days (eDAE) and 24 (7.7%) developed SL submitted to excisional biopsy. From the 24 patients, 33 SL were biopsied and 5 patients presented more than 1 SL. Most of the patients with SL were male (79.2%), CPA (87.5%), HCV etiology (87.5%) and 2 had liver transplantation. The median time from sorafenib initiation until SL biopsy was 8.5 months (IQR 4.4 to 18.1). SL are described in the table. Lymphocyte proliferation at the interface between the SL and dermis was noted in 61.1%. The median treatment duration (MTD) and OS in the whole cohort were 6.5 months [IQR 3.3-13.9] and 13.6 months [CI95% 12.2- 15.6], respectively. For the subgroup with SL, the MTD and OS was 12.5 [9.5 - 22.0] and 26.5 months [CI95% 17.0 - 43.9], respectively. For those with both eDEA and SL, the MTD and OS was 17.9 months [7.7-28.9] and 26.5 [22.0-51.6] respectively. There was no permanent discontinuation related to the SL.

Table: 705P SL subtypes

	n = 33 lesions (100%)
Tumor SL	22 (66.7%)
Keratoacanthomas	7 (21.2%)
Squamous cell carcinomas	5 (15.2%)
Basal cell carcinomas	3 (9.1%)
Seborrheic queratosis	3 (9.1%)
Hypertrophic keratoma	1 (3%)
Sebaceous hyperplasia	1 (3%)
Pilomatrixioma	1 (3%)
Trichilemmal cyst	1 (3%)
Non-Tumor SL	7 (21.2)
Suppurative folliculitis	2 (6.1%)
Interphase dermatitis	2 (6.1%)
Subacute spongiform dermatitis	1 (3%)
Septal panniculitis/ Erythema nodosum	1 (3%)
Lichen planus	1 (3%)
Livedo reticularis	2 (6.1%)
Thrombotic vasculopathy	1 (3%)
Epi/Hypodermic necrosis	1 (3%)

Continued

Conclusions: This is the largest series on patients with HCC and sorafenib that presented biopsed SL. Similar to other tumors treated with BRAF inhibitors, patients with HCC and sorafenib are in risk of developing SL. Interestingly, the majority presented lymphocyte proliferation. This reinforces the need to understand the immune modulation by sorafenib.

Legal entity responsible for the study: BCLC group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

706P Relationship between ethnicity and overall survival (OS) in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib (S): Results from a Canadian multi-centre HCC database

D.E. Meyers[1], R. Lee-Ying[1], M. Alghamdi[1], H-W. Sim[2], V.O. Zaborska[3], Y-J. Ko[4], T. Raycraft[3], E. Batuyong[1], W.Y. Cheung[1], H. Samawi[1], J.M. Davies[3], V.C. Tam[1]

[1]Medical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada, [2]Oncology, Princess Margaret Cancer Center, Toronto, ON, Canada, [3]Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, [4]Sunnybrook Health Sciences Centre, Odette Cancer Centre, Toronto, ON, Canada

Background: The SHARP and Asia-Pacific (AP) trials showed that S improves OS compared to placebo in advanced HCC. However, OS was worse in the AP trial, which included predominantly East Asian (EA) patients. The purpose of this study was to determine whether ethnicity affects OS in patients with advanced HCC being treated with S.

Methods: Patients who received S for the treatment of HCC between 01/01/08 and 30/06/16 in the provinces of British Columbia and Alberta, as well as Princess Margaret Cancer Centre and Sunnybrook Odette Cancer Centre in Toronto, Ontario were included. Patient demographics and clinical variables were retrospectively collected. Patients were dichotomized by ethnicity as either EA or not according to a validated list of surnames. Survival outcomes were assessed with Kaplan-Meier curves and compared with the log-rank test. A Cox-proportional hazard model was constructed with ethnicity and relevant clinical characteristics to assess their impact on survival.

Results: A total of 757 patients were included. Mean age was 64 years. 81% men, 36% East Asian, and 86% Child-Pugh (CP) A at initiation of S. Underlying cause of liver disease was 31% hepatitis B Virus (HBV) and 30% hepatitis C virus (HCV). Majority of patients had a performance status of 0 (30%) or 1 (58%). EA compared to non-EA were more likely to have HBV (68 vs 11%) and less likely to have HCV (13 vs 39%), $p < 0.01$. Median OS was 8.6 months for EAs and 9.6 months in non-EAs ($p = 0.89$). On multivariate analysis, ethnicity (HR 1.01, 95% CI 0.82 – 1.27, $p = 0.89$) was not a significant prognostic factor for OS. However, no previous localized treatment (HR 1.66 95%CI 1.39 - 1.99, $p < 0.01$), higher ECOG (HR 1.63 95% CI 1.34-1.97. $p < 0.01$), CP B at initiation of S (HR 1.72 95% CI 1.34 - 2.20, $p < 0.01$) and HBV compared to HCV (HR 1.39 95% CI 1.08-1.80, $p = 0.01$) were associated with worse survival.

Conclusions: Ethnicity does not affect OS in HCC patients treated with S. However, patients treated with S who have a history of HCV appear to have a better OS than those with HBV. Higher baseline ECOG, no previous localized treatments and CP B liver function appear to negatively affect OS.

Legal entity responsible for the study: CHORD consortium.

Funding: Department of Oncology, University of Calgary.

Disclosure: J.M. Davies: Advisory capacity: Bayer. All other authors have declared no conflicts of interest.

707P Efficacy and safety of sorafenib (SFN) in elderly patients with hepatocellular carcinoma (HCC)

L. Gomes Da Fonseca, G. Nader Marta, M.I. Braghiroli, P. M. Hoff, J. Sabbaga

Medical Oncology, ICESP - Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

Background: HCC is the second leading cause of cancer-related deaths worldwide. Sorafenib (SFN) has been the backbone of advanced HCC treatment over the past decade. Since the mean age of HCC presentation is between 50 and 60 years, data on SFN use in the elderly patients (pts) remain scarce due to underrepresentation of this population in pivotal clinical trials. Thus, the treatment of elderly HCC pts represents a

clinical challenge given the concomitance of advanced age with chronic hepatopathy, raising concerns about clinical benefit and increased toxicity in this subgroup. We analyzed a cohort of HCC pts with the aim of evaluating the efficacy and safety of SFN in this specific population.

Methods: A cohort of pts with advanced HCC treated with SFN was retrospectively evaluated. Pts were divided into 2 groups: (A) those younger than 70 years-old (y-o) and (B) those who were 70 y-o or older at the time of SFN initiation. Survival (OS) was calculated from the first day of SFN to death or last data record. Time to treatment failure (TTF) due to disease progression or toxicity was calculated from the first to the last day on SFN. TTF and OS were estimated using Kaplan-Meier and curves were compared by log-rank test.

Results: We analyzed 226 HCC pts treated with SFN from Oct-2007 to Jan-2017. Group B was comprised of 37 (16.4%) pts, median age 73.5 years (70-85), 75.7% male, 29.7% had HCV, 86.5% Child-Pugh A, 37.8% had extrahepatic spread. Reduced starting dose SFN (< 800 mg/d) was more common in Group B than in Group A (27% vs 11.8%, p = 0.026). No statistically significant differences in OS (7.9 vs 9.8 months, p = 0.534) or TTF (3.5 vs 4.3 months, p = 0.962) were detected between Groups A and B. The incidence of dermatologic adverse events (38.6% vs 34.1%, p = 0.596) and hypertension (7% vs 5%, p = 0.641) did not differ significantly between Groups A and B, respectively. Intolerance leading to SFN discontinuation occurred in 11% and 9.5% of pts in Groups A and B, respectively (p = 0.780).

Conclusions: Our findings suggest that the efficacy and the incidence of adverse events were similar in elderly HCC pts treated with SFN when compared to younger pts. Thus, age alone should not be used to determine the therapy of pts with advanced HCC being considered for SFN.

Legal entity responsible for the study: Instituto do Câncer do Estado de São Paulo.

Funding: Has not received any funding.

Disclosure: G. Nader Marta: Travel expenses: Bayer. M.I. Braghiroli: Honoraria: MSD; Research funding: Bayer. J. Sabbaga: Consulting or advisory role: Bayer, MSD; Speaker's bureau: Roche, Bayer, MSD; Travel expenses: Bayer. All other authors have declared no conflicts of interest.

708P Relationship between change in α-fetoprotein (AFP) and patient (pt) survival in hepatocellular carcinoma (HCC): A real-world electronic medical records (EMR) database study

L.M. Hess[1], Z.L. Cui[2], T. Sugihara[3], Y. Fang[3], A. Girvan[1], P.B. Abada[4]

[1]*Global Patient Outcomes and Real World Evidence, Eli Lilly and Company, Indianapolis, IN, USA,* [2]*Global Statistics, Eli Lilly and Company, Indianapolis, IN, USA,* [3]*Clinical Solutions, Syneos Health, Indianapolis, IN, USA,* [4]*Medical, Eli Lilly and Company, Indianapolis, IN, USA*

Background: Serum AFP levels are used as a diagnostic and prognostic marker for pts with HCC. Assessment of the clinical relevance of changes in AFP over time outside of clinical trials is lacking. This study was designed to explore the relationship between changes in AFP levels and overall survival (OS) in a real-world setting.

Methods: This retrospective analysis used the IMS Oncology EMR database (US patients, 12/01/2007-12/31/2014). Eligible pts were diagnosed with HCC, 18+ years old, had at ≥ 1 AFP test recorded 60 days prior to 180 days after diagnosis, and received anticancer therapy ≤180 days after diagnosis. Survival analyses were by Kaplan-Meier method. The gamma-frailty model was used to correlate AFP change utilizing previously-reported definitions of AFP change (above/below 400 ng/mL, ≥20 ng/mL, ≥7 ng/mL/month, ±20%, ±50%) and OS.

Results: A total of 907 pts met eligibility criteria (77.3% male, median 65 years of age). Of 697 pts with AFP prior to start of first-line therapy, the 453 (65%) with a baseline AFP <400 ng/mL had an OS of 4.2 months and the 244 (35%) with ≥400 ng/mL an OS of 2.9 months. An increase in AFP was associated with a decrease in OS in the 278 patients with baseline and first-line therapy (1L) AFP (Table). Of the 101 pts with an AFP test before start of second line therapy, 32.7% had AFP ≥400 ng/mL. Relationship between change in AFP and OS.

Table: 708P

Observed AFP change during 1L	N	Median OS (95% CI), months	Cross ratio	Kendalls Tau
Decrease (↓) to < 400 from ≥ 400 ng/mL	20	14.3 (4.8-30.9)	1	0
↓ ≥ 20 ng/mL	85	7.4 (5.7-11.9)	1	0
↓ ≥ 7 ng/mL/month	68	6.8 (5.0-12.7)	1	0
↓ ≥ 20%	98	11.1 (7.3-13.2)	1	0
↓ ≥ 50%	51	12.2 (7.3-18.2)	1	0
Increase (↑) to ≥ 400 from < 400 ng/mL	18	5.9 (3.6-7.4)	1.506	0.202
↑ ≥ 20 ng/mL	140	4.8 (3.7-5.5)	1.902	0.311
↑ ≥ 7 ng/mL/month	124	4.5 (3.1-5.2)	2.006	0.335
↑ ≥ 20%	141	5.2 (4.1-6.5)	1.841	0.296
↑ ≥ 50%	109	5.4 (4.5-6.9)	1.755	0.274

Conclusions: Increases and decreases in AFP during 1L, regardless of AFP change definition, were generally associated with shorter and longer OS, respectively. Conclusions are limited by the risk of immortal time and selection bias, as not all patients had multiple AFP measures recorded.

Legal entity responsible for the study: Eli Lilly and Company.

Funding: Has not received any funding.

Disclosure: L.M. Hess, Z.L. Cui, A. Girvan, P.B. Abada: Employee: Eli Lilly and Company. All other authors have declared no conflicts of interest.

709P Antiviral therapy improves outcomes after radiofrequency ablation for HBV-related hepatocellular carcinoma: A propensity score matching analysis

K. Wang, F. Shen, J. Liu, Z. Yan, J. Li, Y. Xia, L. Shi, G. Qian, Z. Lu, Y. Chen, X. Wan, M. Wu, Y. Zhang

Hepatobiliary Surgery, Eastern Hepatobiliary Surgical Hospital (EHSH), 2nd Military Medical University, Shanghai, China

Background: We intended to explore hepatitis B virus (HBV) reactivation after percutaneous radiofrequency ablation (PRFA) for HBV-related hepatocellular carcinoma (HCC) and the impact of antiviral therapy (AVT) on post-PRFA outcomes.

Methods: Data on 538 consecutive patients who underwent PRFA for HBV-related early HCC at the Eastern Hepatobiliary Surgery Hospital between 2007 and 2011 were studied. Propensity score matching (PSM) analysis was used to compare the outcomes between the study groups. Recurrence free survival (RFS) and tumor recurrence were endpoints. Post-PRFA viral reactivation, hepatitis, and patterns of tumor recurrence were also observed. Logistic regression, Kaplan-Meier method and Cox proportional regression were used during the analysis.

Results: Viral reactivation developed in 10.8% of patients who underwent PRFA. Patients with HBV reactivation had higher 1-, 3-, and 5-year tumor recurrence rates than patients without viral reactivation after PRFA (46.9%, 81.6% and 81.6% vs 36.0%, 63.5% and 65.4%, P = 0.004). AVT reduced viral reactivation rate (P < 0.001) and decreased 1-,3-,5-year tumor recurrence rate when compared with the no-AVT (30.2%, 58.6% and 61.4% vs 44.1%, 72.6% and 73.0%, P = 0.001). The local recurrence of tumor after PRFA was only associated with tumor diameter (P = 0.010), however, viral reactivation (P = 0.015) and AVT (P < 0.001) were independent risk factors of intrahepatic distant recurrence.

Conclusions: HBV could be reactivated after PRFA. Viral reactivation and AVT had opposite impact on intrahepatic distant recurrence but not local tumor progression of HCC patients after PRFA.

Legal entity responsible for the study: Feng Shen MD.

Funding: State Key Project on Infectious Diseases of China (2012ZX10002-011,016 to FS).

Disclosure: All authors have declared no conflicts of interest.

710P Practice patterns and deterioration of liver function after transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): Final analysis of OPTIMIS in Europe and Canada

J-L. Raoul[1], T. Decaens[2], K. Burak[3], J. Koskinas[4], G.E. Villadsen[5], A. Heurgue-Berlot[6], I. Bayh[7], A-L. Cheng[8], M. Kudo[9], H.C. Lee[10], K. Nakajima[11], M. Peck-Radosavljevic[12,13]

[1]Digestive Oncology, Institut de Cancérologie de l'Ouest, Nantes, France, [2]Clinique Universitaire d'Hépato-gastroentérologie, CHU Grenoble Alpes, Grenoble, France, [3]Calgary Liver Unit, Division of Gastroenterology and Hepatology, Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [4]2nd Department of Internal Medicine, Medical School of Athens, Hippokration Hospital, Athens, Greece, [5]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark, [6]Department of Hepato-Gastroenterology, Centre Hospitalier Universitaire Reims, Reims, France, [7]Bayer AG, SBU Oncology, Pharmaceuticals, Wuppertal, Germany, [8]National Taiwan University Hospital, Taipei, Taiwan, [9]Kindai University Faculty of Medicine, Osaka, Japan, [10]Asan Medical Center, Seoul, Republic of Korea, [11]Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, [12]Medical University of Vienna, Vienna, Austria, [13]Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

Background: TACE is commonly used in patients (pts) with unresectable HCC (uHCC). However, there is no global consensus on appropriate TACE use. Evaluating the risks associated with TACE is critical to ensure pt eligibility for subsequent effective therapies.

Methods: OPTIMIS is an international, prospective, non-interventional study of uHCC pts for whom the decision to treat with TACE was made prior to enrollment. Here we report practice patterns, subsequent treatments, and liver deterioration data from Europe and Canada (Eur/Can) and the global population. TACE ineligibility was defined using international and regional guidelines.

Results: Overall, 1650 enrolled pts received TACE including 497 from Eur/Can (n = 447 Eur, n = 50 Can). Of those, 40% of pts in Eur/Can and 39% globally were TACE ineligible according to guidelines (Table). After exclusion of pts with prior sorafenib use, 35% of pts in Eur/Can and 31% globally became TACE ineligible during the study (to be assessed for primary endpoint). Of those, 8% in Eur/Can and 9% globally received sorafenib immediately after TACE ineligibility. At inclusion, most pts were BCLC stage B, and the presence of extrahepatic spread and portal vein thrombosis was lower in Eur/Can vs globally (Table). In pts with available laboratory values, chronic liver function deterioration (worsening in CTCAE grade 30–90 days post TACE) after first TACE was noted in Eur/Can and the global population: ALT 19% and 19%, albumin 30% and 29%, AST 25% and 24%, bilirubin 9% and 11%, and INR 15% and 14%, respectively.

Table: 710P Disease characteristics and TACE ineligibility at inclusion

n (%)	Europe/Canada (n = 497)	Global total (Europe/Canada, Central/South America, Asia) (N = 1650)
Disease status Extrahepatic spread Portal vein thrombosis	19 (4) 15 (3)	118 (7) 123 (7)
BCLC stage B C D Missing	298 (60) 149 (30) 2 (<1) 48 (10)	1034 (63) 529 (32) 19 (1) 68 (4)
Ineligible for TACE	201 (40)	636 (39)

Conclusions: Adherence to TACE eligibility guidelines appear to be similar in Eur/Can and the global population. In the Eur/Can subgroup, chronic deterioration of liver function was observed. These results also suggest that systemic therapies are not commonly used after TACE ineligibility in Eur/Can clinical practice.

Clinical trial identification: NCT01933945.

Editorial acknowledgement: Editorial assistance in the preparation of this abstract was provided by Luke Burke of SuccinctChoice Medical Communications (London, UK), with financial support from Bayer.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: J-L. Raoul: Grants, Research support: Celgene; Advisory board: Genoscience Pharma, Bayer Schering Pharma AG, BTG plc, Bristol-Myers Squibb; Honoraria: Bayer, Merck Serono. T. Decaens: Grants, Research support: ArQule, Genoscience pharma; Advisory board: Bayer, Bristol-Myers Squibb, Ipsen; Consulting: Bayer, Bristol-Myers Squibb. K. Burak: Grants, Research support: Bayer, Lupin. J. Koskinas: Grants, Research support: Gilead Sciences, Novartis, Roche, Merck Sharp & Dohme, Bayer, Bristol-Myers Squibb, AbbVie, Janssen; Clinical trials talks: Novartis, Roche, Merck Sharp & Dohme, Bayer, Gilead Sciences, Janssen, AbbVie, Bristol-Myers Squibb. I. Bayh: Advisory board: Fresenius Medical Care Deutschland GmbH; Stock ownership, Consulting: Fresenius Medical Care Deutschland GmbH; Full-time employee: Bayer. A-L. Cheng: Advisory board: Bayer Schering Pharma, Bristol-Myers Squibb, Eisai, Merck Serono, Novartis, Ono Pharmaceutical, Onxeo; Honoraria: Bayer, Eisai, Merck Sharp & Dohme; Consulting: Novartis. M. Kudo: Grants, Research support: AbbVie, Bayer, Chugai Pharma, Daiichi Sankyo, Eisai, Merck Sharp & Dohme, Otsuka, Sumitomo Dainippon Pharma, Taiho Pharmaceutical, Takeda; Advisory board: Bayer, Bristol-Myers Squibb, Chugai Pharma, Kowa, Merck Sharp & Dohme, Taiho Pharmaceutical; Honoraria: Ajinomoto, Bayer, Eisai, Merck Sharp, Dohme. H.C. Lee: Grants, Research support: Sillajen, Bayer, Ono Pharmaceutical Co; Advisory board: Bayer. K. Nakajima: Stock ownership, Employee: Bayer. M. Peck-Radosavljevic: Grants, Research support: AbbVie, ArQule, Daiichi Sankyo, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, ImClone Systems, Lilly, Merck Sharp & Dohme, Novartis, Roche; Advisory board: AbbVie, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eisai, Ipsen, Lilly, Merck Sharp & Dohme, Roche; Honoraria, Consulting: Bayer. All other authors have declared no conflicts of interest.

711P Hepatocellular carcinoma and liver metastasis treated by hafnium oxide nanoparticles activated by stereotactic body radiation therapy

M. Pracht[1], E. Chajon[1], T. de Baere[2], F. Nguyen[2], J-P. Bronowicki[3], V. Vendrely[4], A-S. Baumann[5], V. Croisé-Laurent[3], E. Rio[6], Y. Rolland[1], S. Le Sourd[1], P. Gustin[2], C. Perret[6], F. Mornex[7], D. Peiffert[5], P. Merle[7], E. Deutsch[2]

[1]Radiation Oncology, Centre Eugene - Marquis, Rennes, France, [2]Radiation Oncology, Institut Gustave Roussy, Villejuif, France, [3]Hepatology and Gastroenterology, Hôpital de Brabois, Vandoeuvre les Nancy, France, [4]Radiotherapy, Groupe Hospitalier Sud - Hôpital Haut-Lévêque, Pessac, France, [5]Radiotherapy, Institut de Cancérologie de Lorraine, Nancy, France, [6]Radiotherapy, Institut de Cancérologie de l'Ouest, Nantes, France, [7]Hepatology and Gastroenterology, Centre Hospitalier de la Croix Rousse, Lyon, France

Background: For patients (pts) with hepatocellular carcinoma (HCC) or liver metastasis (liver mets), stereotactic body radiation therapy (SBRT) is a well-tolerated option. Yet, the risk of injury to normal tissues limits the ability to efficiently sterilize tumor cells. Thus, hafnium oxide nanoparticles, NBXTR3, were developed, which increase the interaction of radiotherapy energy dose deposition within tumor cells when activated by an ionizing energy source like SBRT. NBTXR3 innovative approach does not engage liver function, is characterized by a single injection and fits with radiotherapy standards with no change in patient treatment protocol or equipment occupancy. NBTXR3 is currently being evaluated in this population in a phase I/II clinical trial.

Methods: A 3 + 3 dose-escalation design was implemented for pts with HCC with/without portal vein tumor thrombosis or liver mets, including pts who received previous liver resection or other treatments. Pts were treated with a single intralesional injection of NBTXR3 followed by SBRT (45Gy / 3 fractions / 5 to 7 days). The escalating dose levels of NBTXR3 were 10%, 15%, 22%, 33% and 45% (intraarterial injection) of the baseline tumor volume. The primary endpoints were to identify the recommended dose and observe dose-limiting toxicities (DLTs). Secondary endpoints included NBTXR3 residency/leakage and investigator assessment on target lesions by mRECIST via MRI.

Results: So far, 13 pts are enrolled. Dose levels are completed at 10% (6 pts) and 15% (4 pts) and currently enrolling at 22% (3 pts). To date, no early DLTs and no adverse events related to NBTXR3 were observed. In 9 evaluable pts, the investigator mRECIST assessment on target lesions resulted with the following best observed responses: 3 complete responses, 3 partial responses, 1 stable disease and 2 progressive disease. In the same pts, NBTXR3 did not present leakage and did not affect liver function.

Conclusions: NBTXR3 activated by SBRT currently reveals an encouraging safety profile with a favorable efficacy in a vulnerable population with two different liver affections. These outcomes were the result of a complex multidisciplinary cooperation of different medical expertise from different centers.

Clinical trial identification: NCT02721056.

Legal entity responsible for the study: Nanobiotix.

Funding: Nanobiotix.

Disclosure: All authors have declared no conflicts of interest.

712P Molecular profiling of PDAC and response to chemotherapy: An update from the COMPASS trial

G.M. O'Kane[1], S. Fischer[2], R.E. Denroche[3], G.H. Jang[3], A. Zhang[3], A. Dodd[1], H. Albaba[1], S. Moura[1], S. Holter[4], K. Aung[1], R.C. Grant[1], P. Krzyzanowski[5], E. Elimova[1], N. Dhani[1], D. Hedley[1], F. Notta[3], J.M. Wilson[3], S. Gallinger[1], J.J. Knox[1]

[1]Department of Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, ON, Canada, [2]Department of Pathology, Toronto General Hospital, University Health Network, Toronto, ON, Canada, [3]PanCuRx Translational Research Initiative, Ontario institute for Cancer Research, Toronto, ON, Canada, [4]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto, ON, Canada, [5]Genomics Program, Ontario institute for Cancer Research, Toronto, ON, Canada

Background: Predictive mutational and transcriptional features in advanced PDAC are urgently needed for improved patient stratification and treatment selection.

Methods: As part of the COMPASS trial patients (pts) with advanced PDAC are prospectively recruited prior to first-line combination chemotherapy for whole genome sequencing (WGS) and RNA sequencing (RNASeq). Fresh tumor tissue is acquired by percutaneous core needle biopsy. Laser capture microdissection ensures high-resolution genomic analyses with results available within 8 wks. Tumor responses and clinical outcomes in this update were correlated with molecular characteristics.

Results: 121 pts underwent a biopsy between December 2015 and April 2018; WGS and RNASeq were successful in 120 (99%) and 119 (98%) respectively, meeting all QC endpoints. 113 genomes have been reported in pts planned to receive chemotherapy; the median time from biopsy to report was 35.5 days. The median age was 63 years (29-81), 53% were male, and 17 (15%) had locally advanced disease. 20 pts (18%) were non evaluable for response. 64 (57%) received modified FFX as first line treatment. 24 (21%) tumors displayed the Moffitt basal-like RNA expression signature which associated with chemotherapy resistance, with tumor shrinkage mainly observed in the classical RNA subtype ($p = 0.002$). GATA6 expression (log10 scale) clearly separated Moffitt subgroups with classical tumors exhibiting high expression ($p < 0.0001$). EGFR overexpression was associated with the basal subtype ($p = 0.002$). The tumor of 1 pt at progression, switched from a basal to a classical phenotype. Of 89 pts with ≥ 6 months follow-up, median overall survival in the classical group was 10 mths vs. 5.1 months in the basal group (HR 0.32 95% CI 0.16–0.68, $p = 0.0025$). Signatures of homologous recombination deficiency were found in 4 pts (4%) including 2 with germline BRCA2 mutations, 1 of which was newly detected. 2 of 3 pts with a novel duplicator phenotype responded to folfirinox. 30% of pts had potentially actionable genetic alterations.

Conclusions: Prospective comprehensive profiling of advanced PDAC indicates that chemotherapy response differs according to genomic/transcriptomic subtypes, providing strong rationale for improved first line trial design.

Clinical trial identification: NCT02750657.

Legal entity responsible for the study: University Health Network.

Funding: Ontario Institute for Cancer Research (PanCuRx Translational Research Initiative) through funding provided by the Government of Ontario. Wallace McCain Centre for Pancreatic Cancer Pancreatic Cancer Canada Foundation Princess Margaret Cancer Foundation Wallace McCain Centre for Pancreatic Cancer Pancreatic Cancer Canada Foundation Ontario Institute for Cancer Research (PanCuRx Translational Research Initiative) through funding provided by the Government of Ontario Princess Margaret Cancer Foundation.

Disclosure: All authors have declared no conflicts of interest.

713P Analysis of BRCAness with MLPA in pancreatic ductal adenocarcinoma patients using FFPE sample obtained via EUS-FNAB

K. Okuwaki[1], H. Imaizumi[2], H. Masutani[1], T. Yoshida[3], M. Kida[1], T. Iwai[1], H. Yamauchi[1], T. Kaneko[1], R. Hasegawa[1], E. Miyata[1], K. Adachi[1], M. Tadehara[1], W. Koizumi[1]

[1]Gastroenterology, Kitasato University School of Medicine, Sagamihara, Japan, [2]Gastroenterology, Japan Community Health care Organization, Sagamino Hospital, Sagamihara, Japan, [3]Pathology, Kitasato University School of Medicine, Sagamihara, Japan

Background: A breakthrough in chemotherapy for pancreatic ductal adenocarcinoma (PDAC) may be achieved using precision medicine, which involves identifying cases that are highly likely to respond to a certain treatment and then performing that treatment. BRCAness is a condition resulting from an abnormality in the BRCA pathway, in addition to breast cancer susceptibility gene 1 (BRCA1)/BRCA2 mutation, and is currently a focus of interest as a predictive factor for sensitivity to new anticancer drugs for PDAC. Platinum agents and poly (ADP-ribose) polymerase inhibitors are expected to be effective against BRCAness PDAC. Presently, searching for abnormalities in driver genes such as BRCA 1/2 would require considerable time and expense. Therefore, use of the Multiplex Ligation-dependent Prove Amplification (MLPA) method to diagnose BRCAness is advantageous in being a low-cost method that allows for analysis within a short time frame, and may help to make precision medicine a reality for patients with pancreatic cancer.

Methods: This study included 20 patients with the largest number of in-specimen pancreatic cancer cells among 40 patients with PDAC continuing from endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) conducted at Kitasato University Hospital. Evaluation of the number of cancer cells was conducted by a pathologist. An unstained preparation was created from formalin-fixed paraffin-embedded (FFPE) PDAC tissue obtained via EUS-FNAB, and DNA was extracted. BRCAness was analyzed using the MLPA method.

Results: A BRCAness diagnosis was possible in 15 of 20 (75%) patients using the MLPA method and FFPE tissue obtained via EUS-FNAB in PDAC. Difficulties in BRCAness analysis occurred in 1 patient due to an insufficient amount of DNA and in 4 patients due to poor DNA quality. BRCAness was diagnosed in 1 of 20 (5%) patients.

Conclusions: BRCAness analysis in PDAC patients was possible with the MLPA method using small FFPE obtained via EUS-FNAB, which we believe is the first study to attempt this. Obtaining low-cost analysis results in a short time frame is a key benefit, suggesting this method may be feasible and important in practicing precision medicine to choose a effective drugs in treting PDCA.

Legal entity responsible for the study: Kitasato University School of Medine, Japan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

714P Repeated mutKRAS ctDNA measurements in patients with advanced pancreatic cancer patients: Kinetics, response prediction and therapy monitoring in comparison to protein-based tumor markers

S. Kruger[1], V. Heinemann[1], C. Ross[2], F. Diehl[2], S. Ormanns[3], S. Liebmann[3], C.B. Westphalen[1], M. Haas[1], A. Jung[3], T. Kirchner[3], M. von Bergwelt-Baildon[1], S. Holdenrieder[4], S. Boeck[1]

[1]Department of Internal Medicine III and Comprehensive Cancer Center, Ludwig Maximilians University, Munich, Germany, [2]Research and Development, Sysmex Inostics GmbH, Hamburg, Germany, [3]Institute of Pathology, Ludwig Maximilians University, Munich, Germany, [4]Institute of Laboratory Medicine, German Heart Center, Technical University of Munich, Munich, Germany

Background: The presence of mutated KRAS circulating tumor DNA (^{mut}KRAS ctDNA) in plasma samples has been consistently shown to be a negative prognostic indicator in pancreatic cancer (PC). Only small pilot studies have evaluated the value of serial ^{mut}KRAS ctDNA-measurements in PC.

Methods: We used BEAMing technology to determine levels of ^{mut}KRAS ctDNA, CA 19-9, CEA and CYFRA 21-1 in 284 plasma samples of 54 patients with advanced PC receiving gemcitabine-based first-line chemotherapy. Absolute levels and kinetics of ^{mut}KRAS ctDNA, CA 19-9, CEA and CYFRA 21-1 were correlated to radiological response, progression free- and overall survival.

Results: ^{mut}KRAS ctDNA was present in a majority of advanced PC patients (n = 36/54, 67%) and indicated tissue KRAS mutation status with a high sensitivity (74%) and specificity (100%). Presence of ^{mut}KRAS ctDNA, as well as higher levels of CA 19-9, CEA and CYFRA 21-1 at treatment initiation were significantly correlated to an adverse overall survival. During therapy, changes in ^{mut}KRAS ctDNA levels were more rapid and pronounced than changes in protein-based tumor markers. Kinetics of ^{mut}KRAS ctDNA were an early indicator of response to therapy, while there was no significant correlation between kinetics of CA 19-9, CEA or CYFRA 21-1 and response to chemotherapy during the first four weeks of treatment. Repeated ^{mut}KRAS ctDNA measurements during follow-up indicated progressive disease with high sensitivity (84%) and specificity (100%).

Conclusions: ^{mut}KRAS ctDNA kinetics appear to be a powerful and highly specific tool in early response prediction and therapy monitoring of advanced PC patients receiving chemotherapy.

Legal entity responsible for the study: Stephan Kruger, Stefan Holdenrieder, Stefan Boeck.

Funding: Sysmex Inostics.

Disclosure: C. Ross, F. Diehl: Employee: Sysmex Inostics. All other authors have declared no conflicts of interest.

715P Clinical utility of plasma cell-free DNA in patients with pancreatic cancer

I. Chen[1], K.L. Wind[2], C. Dehlendorff[3], B.S. Sørensen[4], B.V. Vittrup[1], A. Johansen[1], P. Pfeiffer[5], J.K. Bjerregaard[5], S.E. Bojesen[6], S.E. Nielsen[7], N.H. Holländer[8], M.K. Yilmaz[9], L.S. Rasmussen[9], N. Pallisgaard[10], J.S. Johansen[1], K-L.G. Spindler[4]

[1]Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [2]Department of Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [3]Statistics and Pharmacoepidemiology, Danish Cancer Society Research Center, Copenhagen, Denmark, [4]Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [5]Experimental Research in Medical Cancer Therapy, Odense University Hospital, Odense, Denmark, [6]Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Herlev, Denmark, [7]Department of Oncology, North Zealand University Hospital, Hillerød, Denmark, [8]Department of Oncology, Zealand University Hospital in Næstved, Næstved, Denmark, [9]Department of Oncology, Aalborg University Hospital, Aalborg, Denmark, [10]Department of Pathology, Zealand University Hospital in Roskilde, Roskilde, Denmark

Background: Reliable biomarkers in patients (pts) with pancreatic cancer (PC) are highly warranted. The aim of this prospective-retrospective biomarker study was to investigate the clinical value of cell-free DNA (cfDNA) in pts with PC.

Methods: A total of 377 consecutive pts with histologically confirmed PC and 94 healthy controls were included. Total cfDNA levels were determined by a direct fluorescent assay in EDTA plasma samples obtained before operation (stage I and II) or start of palliative chemotherapy (stage III and IV). Serum CA19-9 (IMMULITE 2000, Siemens), hyaluronic acid (HA) (ELISA, R&D), interleukin-6 (IL-6) (ELISA, R&D) and YKL-40 (ELISA, Quidel) were measured. The main outcome was association of cfDNA with overall survival (OS) for pts with PC. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by Cox proportional hazards regression.

Results: Pts with PC had significantly higher level of plasma cfDNA (median (range): 1.15 [0.45, 4.94] ng/uL) compared with healthy subjects (0.52 [0.48, 0.57] ng/uL, ROC analysis AUC 0.89). The level of plasma cfDNA was significantly increased with advanced stage, presence of liver metastases and worse Performance Status (PS). When analyzed as a continuous parameter, cfDNA higher than median of 1.15 ng/uL alone was associated with reduced OS (HR = 1.40, 95% CI 1.13-1.72, P = 0.002) in univariate analyses along with age >50, worse PS, higher stage, presence of liver metastases, and log2-transformed serum levels of CA19-9, HA, IL-6 and YKL-40. In multivariate analysis, plasma cfDNA (median and 75% quartile as cutoff) was not statistically

significantly associated with OS, but CA19-9 and IL-6 along with higher age, PS, stage and presence of liver metastases were associated with shorter OS.

Conclusions: Plasma cfDNA concentrations measured with a simple assay was higher in PC patients than in healthy individuals. High plasma cfDNA levels were associated with a short OS. Adjusted for a number of known prognostic parameters cfDNA was not statistically significantly associated with OS.

Legal entity responsible for the study: Julia Sidenius Johansen.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

716P Cell free tumor-DNA can predict treatment outcome in advanced PDAC

S. Payr[1], J. Beck[2], U. König[1], M. Brunner[1], J. Gaedcke[3], A. Azizian[3], M. Ghadimi[3], V. Ellenrieder[1], E. Schütz[2], A-O. König[1]

[1]Gastroenterology and Gastroenterological Oncology, Universitätsmedizin Göttingen, Göttingen, Germany, [2]Liquid Biopsy center, Chronix Biomedical GmbH, Göttingen, Germany, [3]Department of General-, Visceral-, and Pediatric Surgery, Universitätsmedizin Göttingen, Göttingen, Germany

Background: Determination of chemotherapy response in pancreatic cancer (PDAC) relies on imaging such as CT or MRI scan, where reliable results can be obtained not earlier than 12 weeks after treatment start. Herein we report, that determination of cell-free DNA (cfDNA) can improve treatment monitoring and may allow prediction of treatment response after administration of the first cycle of chemotherapy.

Methods: 26 patients with advanced PDAC were treated with the FOLFIRINOX regime. Cell-free DNA (cfDNA) was determined from blood samples before treatment start and before each cycle (d1 and d15) for 3 months. In a subset, cfDNA was also determined during first FOLFIRINOX administration after infusion of oxaliplatin and irinotecan (8hrs). Tumor status was evaluated before treatment start and after 3 month by CT scan. cfDNA was extracted from at least 2 mL of plasma and $\geq$10ng total cfDNA was used for sequencing library preparation. Sequencing reads, obtained with a NextSeq500 (Illumina) were mapped to the reference genome (HG19) and read counted in 701 bins of autosomes, with an average size of 5.5Mb. After normalization and transformation into log2 ratios, Z-values were calculated versus a healthy reference group (133 cfDNA samples). Z-Scores of bins significantly different from the reference were summed to generate the CNI-score.

Results: The risk of patients (n = 11) with an elevated pre-therapeutic CNI-Score of > 200 for not responding to chemo was 82%. Patients with CNI-Score above the 95thpercentile of the reference population (CNI >24) after cycle 3, had a significantly higher risk to progress (80%), with a 73% accuracy of prediction (p = 0.03). The prediction of therapy failure was even better after 4 cycles with a 90% predictive value and an overall 83% accuracy (p = 0.02). In 13 patients CNI-score was determined after 8hrs of initiation therapy to assess a possible cytolytic tumor burst. Only patients showing a significant increase of CNI-scores, compared to pre-therapeutic values were responders (n = 2), one of three stable patients had a borderline burst, whereas all progressive patients (n = 8) did not show any sign of tumor burst.

Conclusions: Determination of cell free DNA represents a powerful tool to predict outcome very early during medical treatment of advanced PDAC.

Legal entity responsible for the study: Alexander König.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

717P Germline and somatic DNA damage repair gene mutations and overall survival in metastatic pancreatic ductal adenocarcinoma patients treated with FOLFIRINOX

A. Sehdev[1], O. Gbolahan[1], B.A. Hancock[2], M. Stanley[1], S. Shahda[3], J. Wan[4], H.H. Wu[5], M. Radovich[2], B. O'Neil[6]

[1]Medicine, Indiana University, Indianapolis, IN, USA, [2]Surgery, Indiana University, Indianapolis, IN, USA, [3]Department of Clinical Medicine, Indiana University Melvin Bren Simon Cancer Center, Indianapolis, IN, USA, [4]Medical and Molecular Genetics, Indiana University, Indianapolis, IN, USA, [5]Pathology, Indiana University, Indianapolis, IN, USA, [6]Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Background: Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer with lack of predictive biomarkers. We conducted a study to assess DNA damage repair gene mutations (DDRGM) as a predictive biomarker in PDAC patients treated with FOLFIRINOX.

Methods: Indiana University Simon Cancer Center pancreatic cancer database was used to identify patients with recurrent metastatic PDAC, treated with FOLFIRINOX and had tissue available for DNA sequencing. Baseline demographic, clinical and pathologic information was gathered. DNA isolation and targeted sequencing was performed using the Ion AmpliSeq protocol. Chi-square or t-test was used for univariate analyses. Overall survival (OS) analyses was conducted by Kaplan-Meier method, logistic regression (OS categorized as above and below 3rd quartile) and Cox proportional hazard model. Multivariate models were adjusted for age, gender, margin status, CA 19-9, adjuvant chemotherapy, tumor and nodal stage.

Results: Overall, 36 patients were sequenced. DDRGM were found in 12 patients. Mutations were seen in BRCA1 (N = 7), BRCA2 (N = 5), BRCA1/2 (N = 3), PALB2 (N = 3), MSH2 (N = 1) and FANCF (N = 1) of all the DDR genes sequenced (BRCA1, BRCA2, PALB2, CHEK1, CHEK2, RAD51, MLH1, MSH2, ERCC1, ERCC4, PARP1, FANCF, ATR and MDC1). Median age was 65.5 years, 58% were male, 97.2% were Caucasian and 51.4% had any family history of cancer. There were no significant differences between those with DDRGM present and absent except age (64.6 vs. 66.0 years, p = 0.002). The median OS was near significantly superior in those with DDRGM present vs. absent (14 vs. 5 months; HR 0.58 [0.29-1.14], log-rank p = 0.08). Multivariate logistic (OR 1.47 [1.04-2.06], p = 0.04) and Cox regression (HR 0.37 [0.15-0.94], p = 0.04) showed presence of DDRGM was associated with improved OS. Similar analyses limited to only germline BRCA1/2 mutations also showed significantly improved OS with the presence of BRCA1/2 mutations.

Conclusions: In a single institution, retrospective study, we found that the presence of germline and somatic DDRGM as well as germline BRCA1/2 mutations are associated with improved OS in PDAC patients treated with FOLFIRINOX.

Legal entity responsible for the study: Indiana University Institutional Review Board.

Funding: Walther Cancer Foundation.

Disclosure: All authors have declared no conflicts of interest.

718P A three-gene signature to predict lymph node metastasis of pancreatic cancer

C. Liang, X. Yu

Department of Pancreas Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Pancreatic cancer, specifically pancreatic ductal adenocarcinoma (PDAC), represents one of the most aggressive malignancies. Lymph node (LN) status is considered as one of the most significant risk factors for survival of PDAC patients, and it is of great importance for making reasonable therapeutic strategies to individual patients. Imaging techniques are widely used in the evaluation of LN status in PDAC patients, however, their application are limited because of the inconsistent sensitivities and specificities findings.

Methods: Gene Set Enrichment Analysis (GSEA) and leading edge analysis were used to analyze the data from The Cancer Genome Atlas (TCGA) on 177 PDAC patients to identify genes associated with LN metastasis. The identified genes with LN metastasis were indexed by Spearman's rank-correlation test to construct the risk score model. Risk scores were used to predict LN metastasis and overall survival (OS). For validation, we used 80 specimens from patients with PDAC diagnosed at Fudan University Shanghai Cancer Center.

Results: A risk model consisting of three genes (MAPK9, ITGA5, AKT2) was developed. This model could correctly predict the LN metastasis evaluated by receiver operating characteristic (ROC) curves [area under curve (AUC) = 0.668, P = 0.001], and risk score positively associated with the number of metastatic lymph node (NLN; Spearman r = 0.3309, P < 0.0001), especially in the PDAC with greatest dimension $\leq$ 4 cm and total lymph nodes dissected (TLN) > 12 [AUC = 0.80, P = 0.003; Spearman r for MLN = 0.4237, P = 0.0004; Spearman r for lymph node rate (LNR) = 0.3171, P = 0.0089]. In the set of PDAC patients with TLN > 12, patients with high risk had a worse OS than that with low risk with hazard ratio (HR) of 2.657 (P = 0.0044) for all stage and HR of 2.548 (P = 0.045) for stage I and II. Patients from stage I and stage IIA with high risk scores had a similar OS with stage IIB (median survival = 21.13 months vs. 20.23 months, P = 0.8227). In the validation set, high risk scores could also effectively predict the LN metastasis and poor prognosis in resectable PDAC.

Conclusions: Our findings highlight three-gene signature with effective capacity for identification of PDAC patients with poor prognosis that are likely to suffer from LN metastasis.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.

Funding: National Science Foundation for Distinguished Young Scholars of China.

Disclosure: All authors have declared no conflicts of interest.

719P Gemcitabine plus afatinib versus gemcitabine alone in metastatic pancreatic cancer: An explorative randomized AIO phase II trial (ACCEPT)

M. Haas[1], D. Waldschmidt[2], M. Stahl[3], A. Reinacher-Schick[4], J. Freiberg-Richter[5], F. Kaiser[6], S. Kanzler[7], N. Frickhofen[8], T. Seufferlein[9], T. Dechow[10], R.J.C. Mahlberg[11], P. Malfertheiner[12], G. Illerhaus[13], S. Kubicka[14], S. Held[15], C.B. Westphalen[1], S. Kruger[1], S. Boeck[1], V. Heinemann[1]

[1]Department of Medicine III, University Hospital, LMU Munich, Munich, Germany, [2]Department of Gastroenterology and Hepatology, University of Cologne, Cologne, Germany, [3]Department of Medical Oncology, Kliniken Essen-Mitte, Essen, Germany, [4]Department of Hematology, Oncology and Palliative Medicine, St. Josef-Hospital, Ruhr University Bochum, Bochum, Germany, [5]Practice, Hematology and Oncology, Dresden, Germany, [6]VK&K, Studien GbR, Landshut, Germany, [7]Department of Internal Medicine II, Leopoldina Krankenhaus Schweinfurt, Schweinfurt, Germany, [8]Hematology, Medical Oncology and Palliative Care, HELIOS Dr. Horst Schmidt Kliniken Wiesbaden, Wiesbaden, Germany, [9]Department of Internal Medicine I, Ulm Medical University, Ulm, Germany, [10]Practice, Hematology and Oncology, Ravensburg, Germany, [11]Innere Medizin I, Klinikum Mutterhaus der Borromäerinnen, Trier, Germany, [12]Clinic of Gastroenterology, Hepatology, and Infectious Diseases, Otto von Guericke University Magdeburg, Magdeburg, Germany, [13]Department of Hematology and Oncology, Klinikum Stuttgart, Stuttgart, Germany, [14]Cancer Center Reutlingen, Klinikum am Steinenberg Reutlingen, Reutlingen, Germany, [15]Clinassess, GmbH, Leverkusen, Germany

Background: Pancreatic cancer (PC) remains a disease difficult to treat. Afatinib, a novel, oral irreversible ErbB family blocker has shown efficacy in non-small-cell lung cancer bearing driver mutations of the epidermal growth factor receptor. This open-label, multicenter, randomised phase II trial evaluated the efficacy and safety for gemcitabine/afatinib vs. gemcitabine in metastatic PC.

Methods: Patients with histologically proven metastatic PC were randomised in a 2:1 ratio to receive either gemcitabine (1000mg/m^2 i.v. weekly for three weeks followed by one week of rest, repeated every four weeks) and afatinib (40mg orally once daily) vs. gemcitabine alone as first-line treatment for metastatic disease. Overall survival (OS) was the primary endpoint.

Results: Between April 2013 and January 2017, 119 patients from 25 German centers were randomised (79 patients for gemcitabine/afatinib and 40 for gemcitabine), of which 115 received at least one dose of study medication and 108 were eligible for the primary analysis. Median OS was 7.3 months for gemcitabine/afatinib vs. 7.4 months for gemcitabine, HR 1.06 (95% CI 0.68-1.65), p = 0.80. Median progression free survival (PFS) was 3.9 months for gemcitabine/afatinib vs. 3.8 months for gemcitabine, HR 0.87 (95% CI 0.56-1.34), p = 0.52. The objective overall response rate (ORR) was 9.9% for gemcitabine/afatinib vs. 10.8% for gemcitabine, respectively (p > 0.99). The rate of serious adverse events (SAEs) per patient was slightly higher for gemcitabine/afatinib vs. gemcitabine (1.66 vs. 1.53). The rate of adverse events was higher for gemcitabine/afatinib vs. gemcitabine, e.g. for main adverse events known for afatinib like diarrhoea (71% vs. 13%), epistaxis (33% vs. 0%) and skin rash (70% vs. 5%). However, the share of grade ≥3 in these events was low (16% for diarrhoea, 0% for epistaxis, 5% for skin rash; no grades 4 or 5).

Conclusions: The addition of afatinib to gemcitabine did not improve treatment efficacy. The combination had an acceptable safety profile with the main side effects for afatinib ranging within the known scope.

Clinical trial identification: EudraCT: 2011-004063-77; NCT01728818.

Legal entity responsible for the study: LMU Munich.

Funding: Boehringer Ingelheim.

Disclosure: M. Haas: Research funding and travel grant: Boehringer Ingelheim. D. Waldschmidt: Consulting or advisory role: Bayer, Health Pharma BMS, Celgene Novartis, Roche, Pharma AG, Shire Baxalta, Sirtex; Honoraria: Bayer, Health Pharma BMS, Celgene, Novartis, Shire Baxalta, Sirtex; Research funding: Roche, Pharma AG, Shire Baxalta. A. Reinacher-Schick: Honoria: Amgen, Roche, Pfizer, Sanofi-Aventis, Merck, Shire, Celgene, Lilly, BMS, Advisory board member: Amgen, Roche, Pfizer, Sanofi-Aventis, Merck, Celgene, Lilly, BMS Studies sponsored by: Roche, Sanofi-Aventis, Celgene, Ipsen. T. Seufferlein: Research support: Celgene Shire Sanofi-Genzyme; Advisory board membership: Roche Celgene, Bayer, Shire. C.B. Westphalen: Consulting or advisory role: Celgene, Roche, Pharma, AG Shire, RedHill; Honoraria: IPSEN; Research funding: Roche Pharma AG. V. Heinemann: Honoraria: Amgen, Baxalta, Celgene, Merck, Roche, Sanofi, Sirtex, Medical; Consulting or advisory role: Amgen, Baxalta, Boehringer, Ingelheim, Celgene, Merck, Roche, Sanofi, Sirtex Medical; Research funding (institution): Amgen, Bayer, Boehringer Ingelheim, Celgene, IntegraGen, Merck, Roche, Sanofi, Sirtex Medical, Taiho Pharmaceutical; Travel accommodations expenses: Amgen Baxalta, Merck, Roche, Sirtex Medical. All other authors have declared no conflicts of interest.

720P SCALOP-2: A multi-centre randomised trial of induction chemotherapy followed by capecitabine +/-nelfinavir with high or standard dose radiotherapy for locally advanced pancreatic cancer (LAPC): Results of stage 1 - the non-randomised dose-finding component

S. Mukherjee[1], P. Virdee[2], R. Shaw[3], J. Bridgewater[4], G. Radhakrishna[5], S. Falk[6], M. Scott-Brown[7], V.Y. Strauss[2], C. Brooks[3], R. Gillmore[8], N. Patel[9], B. Tranter[10], P. Parsons[11], D. Sebag-Montefiore[12], M. Hawkins[1], P.G. Corrie[13], T.S. Maughan[1]

[1]Oncology, Oxford Institute for Radiation Oncology, Oxford, UK, [2]Centre for Statistics in Medicine, Oxford University, Oxford, UK, [3]Oncology, Oncology Clinical Trials Office, Oxford, UK, [4]Oncology, University College London Hospitals, London, UK, [5]Oncology, Christie NHS Foundation Trust, Manchester, UK, [6]Bristol Haematology and Cancer Centre, Bristol University Hospitals NHS Foundation Trust, Bristol, UK, [7]Arden Cancer Centre, University Hospitals Coventry and Warwickshire, Coventry, UK, [8]Oncology, Royal Free London NHS Foundation Trust, London, UK, [9]Radiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK, [10]Pharmacy, Velindre NHS University Trust, Cardiff, UK, [11]Velindre Cancer Centre, Velindre NHS University Trust, Cardiff, UK, [12]GI Unit, University of Leeds, Leeds, UK, [13]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust - Addenbrooke's Hospital, Cambridge, UK

Background: The anti-retroviral agent, nelfinavir, demonstrates radiosensitising effects in pre-clinical models of pancreatic cancer. The primary objective of Stage 1 was to establish the maximum tolerated dose (MTD) of nelfinavir combined with capecitabine-chemoradiation (CRT) after gemcitabine+nab-paclitaxel (GEMABX) induction chemotherapy.

Methods: Patients with inoperable, histologically/cytologically proven LAPC and WHO performance status 0-1 were eligible for this rolling-six dose-escalation stage. After 3 cycles of induction GEMABX (28-day cycle of nab-paclitaxel 125mg/m^2 and gemcitabine 1000mg/m^2 on days 1, 8, and 15), patients with non-progressive disease had 1 further cycle followed by CRT (50.4Gy/28 fractions, capecitabine 830mg/m^2 bd on radiotherapy days) and 1000mg or 1250mg nelfinavir bd continuously during CRT. Other outcomes included overall survival and progression-free survival.

Results: 27 patients were recruited from 8 UK centres (March 2016-June 2017). Median age was 62 years, 30% were male, 78% had head tumours, and 30% had biliary stents. Baseline median tumour diameter was 36mm. 67% commenced CRT. 11 patients received 1000mg and there was one dose-limiting toxicity (DLT) in this group: grade 3 acute coronary syndrome. The nelfinavir dose was escalated as per the rolling-six design. 7 patients received 1250mg nelfinavir and no DLTs were observed. During GEMABX, common grade ≥3 toxicities among participants were neutropenia (30%), fatigue (22%), and diarrhoea (15%). During CRT, grade ≥3 toxicities included fatigue (6%) and anorexia (6%). No grade 5 adverse events were reported in Stage 1. Survival analysis will be presented.

Conclusions: 1250mg nelfinavir was recommended for combining with capecitabine-CRT in the ongoing randomised component of the trial (Stage 2).

Clinical trial identification: ISRCTN50083238.

Legal entity responsible for the study: University of Oxford, UK.

Funding: Cancer Research UK, Celgene.

Disclosure: S. Mukherjee, P.G. Corrie: Research funding: Celgene. J. Bridgewater: Consultancy: Celgene. N. Patel: Part-time employee of GSK. All other authors have declared no conflicts of interest.

721P A phase I study of IRISOX (irinotecan/S-1/oxaliplatin) in the second-line treatment for gemcitabine-refractory pancreatic cancer

E. Miyata[1], K. Okuwaki[1], H. Imaizumi[2], M. Kida[1], T. Iwai[1], H. Yamauchi[1], T. Kaneko[1], R. Hasegawa[1], K. Adachi[1], M. Tadehara[1], W. Koizumi[1]

[1]Gastroenterology, Kitasato University School of Medicine, Sagamihara, Japan, [2]Gastroenterology, Japan Community Health Care Organization, Sagamino Hospital, Sagamihara, Japan

Background: In Japan, gemcitabine based chemotherapy has been a standard regimen as one of the first-line treatment for unresectable pancreatic cancer. FOLFIRINOX was introduced in the second-line treatment for the gemcitabine-refractory pancreatic cancer of patients with an ECOG performance status score of 0 or 1. However, FOLFIRINOX requires close monitoring and must be limited to patients with good performance status because of significant toxicity. Further FOLFIRINOX requires a central veins port, and a trouble such as the port infection may occur. Therefore, it is difficult to administer FOLFIRINOX as second-line treatment. The first time in the world, we introduced IRISOX which substituted S-1 for fluorouracil and leucovorin in the second-line treatment. We aimed to evaluate the tolerance, safety, and clinical efficacy of IRISOX in the second-line treatment for the gemcitabine-refractory pancreatic cancer in a phase 1 study.

Methods: The primary objective was to determine the maximum tolerated dose (MTD) and recommended dose (RD) of IRISOX. The study was designed in accordance with a standard 3 + 3 method. Patients received 2-week cycles of treatment. Irinotecan was administered as an intravenous infusion at 100, 120, or 150 mg/m^2 on day 1, S-1 was administered orally at 80 mg/m^2 twice daily for 7 days, and oxaliplatin was administered as an intravenous infusion at 85 mg/m^2 on day 1.

Results: Among the 12 patients enrolled, dose-limiting toxicity was observed in a patient at level 1 (irinotecan 100 mg/ m^2 on day 1, S-1 80 mg/m^2 twice daily, and

oxaliplatin 85 mg/m^2 on day 1) , and in two patients at level 2 (irinotecan 120 mg/ m^2 on day 1, S-1 80 mg/m^2 twice daily, and oxaliplatin 85 mg/m^2 on day 1). The MTD was established as level 2. The RD was established as level 1. The most common grade 3-4 toxicity was neutropenia (33.3 %). The overall response rate was 9.0 %. The overall disease control rate was 45.4 %.

Conclusions: Based on the present results, the RD was determined as level 1 (irinotecan 100 mg/ m^2 on day 1, S-1 80 mg/m^2 twice daily, and oxaliplatin 85 mg/m^2 on day 1). IRISOX was well tolerated and showed antitumor efficacy in the second-line treatment for the gemcitabine-refractory pancreatic cancer in a phase 1 study.

Clinical trial identification: UMIN000022964.

Legal entity responsible for the study: Kitasato University School of Medicine, Japan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

722P Exploratory analyses of 400 patients enrolled in 2 FFCD trials of first line treatment for metastatic pancreatic cancer

J. Taieb[1], J.M. Phelip[2], Y. Rinaldi[3], E. Barbier[4], O. Bouche[5], F. Khemissa Akouz[6], A. Gratet[7], C. Petorin[8], L. Miglianico[9], D. Malka[10], H. Laharie Mineur[11], C. Rebischung[12], C. Lepage[13], E. Francois[14], L. Dahan[15]

[1]Gastroenterology and Digestive Oncology Department, Georges Pompidou European Hospital, Sorbonne Paris Cité, Paris Descartes University, Paris, France, [2]Gastroenterology Department, CHU Nord, St. Etienne, France, [3]Gastroenterology Department, European Hospital, Marseille, France, [4]Biostatistics, FFCD, EPICAD INSERM LNC-UMR 1231, University of Burgundy and Franche Comté, Dijon, France, [5]Gastroenterology Department, Robert Debré Hospital, Reims, France, [6]Gastroenterology Department, Saint Jean Hospital, Perpignan, France, [7]Oncology Department, Clinique Pasteur, Toulouse, France, [8]Digestive Oncology Department, CHU Estaing, Clermont-Ferrand, France, [9]Oncology Department, Saint-Grégoire Private Hospital, St. Grégoire, France, [10]Gastroenterology Department, Gustave Roussy, Villejuif, France, [11]Gastroenterology Department, Clinique Tivoli Ducos, Bordeaux, France, [12]Gastroenterology Department, Daniel Hollard Institut, Grenoble, France, [13]HepatoGastroenterology and Digestive Oncology Department, University Hospital Dijon, University of Burgundy and Franche Comté, EPICAD INSERM LNC-UMR 1231, Dijon, France, [14]Medical Oncology Department, Antoine Lacassagne Center, Nice, France, [15]Hepatogastroenterology and Oncology Department, CHU La Timone, Marseille, France

Background: Chemotherapy is effective in metastatic pancreatic ductal adenocarcinoma (mPDAC) but new approaches are still needed to improve patients (pts) survival and quality of life. We have here made exploratory analyses of 400 pts enrolled in 2 previously reported randomized phase II trials.

Methods: Chemotherapy-naive pts with proven mPDAC, bilirubin levels < 1.5 ULN and performance status (PS) 0-2 were randomized to receive either Gemcitabine + nab-paclitaxel (A: MPACT regimen), FOLFIRINOX (B: PRODIGE 4 regimen), FOLFIRINOX in a stop and go strategy with maintenance LV5FU2 at 4 months (C: PANOPTIMOX regimen), sequential gemcitabine for 2 mo, followed by FOLFIRI.3 (D: FIRGEM regimen) or sequential gemcitabine+nab-paclitaxel for 2 mo, followed by FOLFIRI.3 (E: FIRGEMAX regimen). mITT pts were defined as patients receiving at least one dose of treatment, preplanned per-protocol (PP) pts were defined as patients reaching 2 mo of treatment and analyzed considering the real treatment received.

Results: Between Jan 2015 and Nov 2016, 400 pts were enrolled in the 2 trials. Mean age was 63 (38-76), 56% were men, pts PS was 0/1/2 in 40/56/4%. Groups were comparable regarding baseline characteristics. Grade 3-4 toxicities (at least one event per pt) in arms A/B/C/D/E were 90/85/85/91/89% ($p > 0.05$), mainly gastrointestinal, hematological and neurological disorders. Efficacy results are summarized in the table.

Table: 722P

	Gem+ nab (n = 63)	FOLFIRINOX (n = 91)	PANOPTIMOX (n = 92)	FIRGEM (n = 90)	FIRGEMAX (n = 64)
mITT - ORR (%) ($p^{\#}$=0.11)	25	36	34	23	40
Median ITT - PFS (mo) (p*=0.12)	4.2	6.3	5.7	4.5	5.7
Median PP - PFS (mo) (p*=0.05)	6.0	7.7	7.5	6.3	7.6
Median ITT - OS (mo) (p*=0.09)	11.3	10.1	11.2	7.3	11.6
Median PP - OS (mo) (p*=0.08)	12.4	12.2	13.0	9.8	15.8

*Overall Log-rank test # Chi2 test.

Conclusions: FOLFIRINOX seems confirmed as a reference treatment for mPDAC. These exploratory analyses show no major differences between the different treatment options offered in these 2 studies except for the FIRGEM sequential strategy that seems both in ITT and preplanned PP analyses less efficient than the other options. The addition of nab-paclitaxel to this sequential approach seems to dramatically improve patients' oncological outcomes.

Clinical trial identification: NCT02352337 and NCT02827201.

Legal entity responsible for the study: FFCD.

Funding: Celgene.

Disclosure: J. Taieb: Consulting or advisory role: Roche, Merck KGaA, Amgen, Celgene, Lilly, Baxalta, Servier, Sirtex Medical; Speakers' bureau: Amgen, Baxalta, Servier, Roche/Genentech, Sanofi, Merck, Lilly. J.M. Phelip: Consulting or advisory role: Roche, Merck, Amgen, Sanofi, Lilly, Bayer, Servier; Travel accommodations expenses: Roche, Merck, Amgen, Sanofi, Lilly, Bayer, Servier. O. Bouche: Consulting or advisory role: Roche, Merck, Amgen, Bayer; Speaker's bureau: Lilly, Pierre Fabre, Novartis, Servier; Travel accomodations expenses: Lilly, Roche, Merck. F. Khemissa Akouz: Honoraria: Sanofi, Roche, Bayer; Speakers' bureau: Sanofi, Roche; Travel accommodations expenses: Ipsen, Sanofi, Roche, Bayer. A. Gratet: Travel accommodations expenses: Novartis. L. Miglianico: Honoraria, Consulting or advisory role, Travel accommodations expenses: Pfizer, Merck,Pierre Fabre, Roche, Amgen, Bristol-Myers Squibb K.K. D. Malka: Consulting or advisory role: Roche, Sanofi, Merck Serono, MSD, Servier, Bayer, Incyte, Amgen; Travel, accommodations expenses: Roche, Bayer, Sanofi, Merck Serono, Amgen; Honoraria: Roche, Amgen, Bayer, Merck Serono, Servier, Sanofi. C. Lepage: Consulting or advisory role: Advanced Accelerator Applications; Travel accommodations, expenses: Amgen, Novartis, Ipsen, Bayer; Honoraria: Novartis. E. Francois: Consulting or advisory role: Roche, Merck Travel, accommodations, expenses: Roche, Merck, Servier. L. Dahan: Honoraria: Sanofi, Amgen. All other authors have declared no conflicts of interest.

723P First-line (1L) full dose (f) and modified (m) FOLFIRINOX and gemcitabine+nab-paclitaxel (GN) treatment (tx) for metastatic pancreatic adenocarcinoma (mPAC) patients (pts) in routine clinical practice across Europe

J. Taieb[1], A. Carrato[2], B. Westphalen[3], D. Melisi[4], G. Prager[5], T. Macarulla Mercade[6], Å.B.C. Mellbring[7], N. d'Esquermes[8], A. Ferreras[8], F. de Jong[9]

[1]Gastroenterology and Digestive Oncology Department, Georges Pompidou European Hospital, Sorbonne Paris Cité, Paris Descartes University, Paris, France, [2]Medical Oncology, Ramón y Cajal University Hospital, Madrid, Spain, [3]Comprehensive Cancer Center München, Klinikum der Universität München, Munich, Germany, [4]Medical Oncology, University of Verona, Verona, Italy, [5]Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria, [6]Medical Oncology, Vall dHebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [7]Oncology, Shire Sweden AB, Stockholm, Sweden, [8]Advanced Analytics, Genactis, Mougins, France, [9]Global Medical Affairs Oncology, Shire International GmbH, Zug, Switzerland

Background: FOLFIRINOX and GN have shown superior OS but with increased toxicity in fitter and younger pts vs gemcitabine. In routine practice, FOLFIRINOX is often modified at start (eg no 5FU bolus). No randomized phase III data are available and real world data are scarce.

Table: 723P

First-line treatment	N	% pts with dose adjustment	% pts >65 year	% female pts	% pts 0-1 ECOG Performance Score	% pts received 2L	Median OS/PFS (months)
gemcitabine+nab-paclitaxel (GN)	660	20.5%	44.8%	43.2%	76.5%	67.4%	12/7
FOLFIRINOX	912		23.9%	36.3%	87.2%	78.1%	15/10
mFOLFIRINOX	164	6.7%	18.3%	41.5%	89.0%	78.0%	16/10
fFOLFIRINOX	748	26.1%	25.1%	35.2%	86.8%	78.1%	15/10
fFOLFIRINOX modified in cycle 2/3	27		25.9%	48.1%	92.6%	66.7%	
fFOLFIRINOX modified in cycle 3+	168		27.4%	41.1%	88.1%	77.4%	
fFOLFIRINOX never modified	553		24.4%	32.7%	86.1%	78.9%	

Methods: In this observational electronic chart review data were retrospectively recorded of pts ≥18 y who completed 1L mPAC tx JUL14-JAN16. Physicians (HCPs) were recruited across different regions and settings and encouraged to enter pts in/beyond 2L. Baseline characteristics and outcomes of 1L FOLFIRINOX and GN are reported. Data are descriptive.

Results: 2,565 records were completed by 225 HCPs; 500–504 from FR/GER/IT/SP/UK. Of 912 1L FOLFIRINOX pts, 18% started mFOLFIRINOX. Of 748 fFOLFIRINOX pts, 26% were later dose modified. Of 660 1L GN pts, 20% were dose modified. Compared with GN, more FOLFIRINOX pts were <65 y, male and fitter (Table). Compared with fFOLFIRINOX, more mFOLFIRINOX pts were <65 y and female. Female fFOLFIRINOX pts were a little more often dose adjusted. Of FOLFIRINOX/GN pts, 12/23% stopped further tx after 1L, 10/9% were awaiting 2L and 78/67% were in ≥ 2L. mOS/mPFS in this selected population was 15/10 mo for FOLFIRINOX and 12/7 mo for GN. mFOLFIRINOX (16/10 mo) had similar outcomes vs fFOLFIRINOX (15/10 mo). On average, 1.5 reasons were reported to stop tx. Most common for FOLFIRINOX/GN were: radiological PD (39/54%), clinical PD (24/32%), tx completed as planned (36/18%) and toxicity (13/9%). No overall benefit of continued tx by pt (8%/9%) or HCP decision (7%/7%) were noted, no differences between f/mFOLFIRINOX were seen.

Conclusions: In this large retrospective chart review, pt characteristics and outcomes for 1L mPAC f/mFOLFIRINOX tx were similar. GN had somewhat lower mOS/mPFS; however, more GN pts were >65 y, female, less fit, and less received 2L tx.

Editorial acknowledgement: Medical writing support for the preparation of this abstract was provided by Physicians World Europe GmbH, Mannheim, Germany, with financial support from Shire (previously Baxalta), Zug, Switzerland.

Legal entity responsible for the study: Shire.

Funding: Shire.

Disclosure: J. Taieb: Honoraria, Consulting, Speaker roles: Amgen, Roche, Merck, Celgene, Shire, Lilly, Sanofi, Sirtex, Servier. A. Carrato: Advisory boards: Roche, Merck, MSD, Baxter, Shire, Celgene, Bayer. B. Westphalen: Advisory boards: Roche, Celgene, Shire, RedHill; Research support: Roche. D. Melisi: Research funding: Shire, Incyte, Celgene; Consulting role: Eli Lilly, Shire, Baxter, Incyte. G. Prager: Advisory board, Speaker fees: Shire, Celgene, Halozyme. Å.B.C. Mellbring, F. de Jong: Employee, Stockholder: Shire. All other authors have declared no conflicts of interest.

724P Real-world comparative effectiveness of nab-paclitaxel plus gemcitabine (nab-P/G) vs FOLFIRINOX (FFX) in patients (pts) with advanced pancreatic cancer (aPC)

E.G. Chiorean[1], W.Y. Cheung[2], G. Giordano[3], G. Kim[4], S-E. Al-Batran[5]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA, [2]Oncology, Alberta Health Services, Calgary, AB, Canada, [3]Oncology, IRRCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy, [4]Oncology, 21st Century Oncology, Jacksonville, FL, USA, [5]Oncology, Nordwest-Krankenhaus, Frankfurt am Main, Germany

Background: Current guidelines recommend chemotherapy with nab-P/G or FFX as the preferred first-line (1L) treatment for metastatic (m)PC pts with good performance status. However, no clinical trial has directly compared 1L nab-P/G vs FFX in mPC or aPC. We conducted a systematic review of the real-world comparative effectiveness of nab-P/G vs FFX in this setting.

Methods: Embase, Medline, and ASCO GI 2018 were searched through January 2018 for real world, retrospective studies directly comparing 1L nab-P/G vs FFX in mPC/aPC. Radiotherapy studies were excluded.

Results: 550/580 records did not meet eligibility criteria, mainly as they were not comparative (264) nor 1L (188). After removing 5 duplicates, the remaining 25 studies (16 mPC; 9 aPC) assessed > 5464 pts who received nab-P/G or FFX. Generally, a lower proportion of pts in the nab-P/G group (range, 59% - 100%) had an ECOG PS score of 0 or 1 vs FFX (82% - 100%) (12 studies). Median overall survival (OS; 19 studies) ranged from 5.5 mo to "not reached" for nab-P/G, and 8.6 to 15.9 mo for FFX (Table); median progression-free survival (12 studies) ranged from 4 to 8.5 mo and 3.7 to 11.7 mo, respectively. In 2 studies that reported OS based on ECOG PS, the median OS for pts with ECOG PS 0/1 was 12.1 and 14.1 mo for nab-P/G vs 11.4 and 13.7 mo for FFX. Overall response rates ranged from 10% to 41% for nab-P/G and 6% to 34% for FFX (4 studies), and disease control rates ranged from 50% to 92% and 56% to 89%, respectively (5 studies). Safety outcomes were heterogeneously reported in 1667 pts (10 studies) receiving nab-P/G or FFX (Table).

Conclusions: Several real-world studies have compared the effectiveness of nab-P/G vs FFX, highlighting the clinical significance. A systematic review of these studies shows that nab-P/G and FFX have comparable effectiveness in mPC/aPC. Differences were observed in the toxicity profiles for the 2 regimens, which may drive treatment decisions. Table. Studies reporting OS, PFS, and safety.

Editorial acknowledgement: Editorial assistance was provided by Narender Dhingra, MediTech Media.

Legal entity responsible for the study: Celgene Corporation.

Funding: Celgene Corporation.

Disclosure: E.G. Chiorean: Advisor: Celgene, Genentech, Novocure, Pfizer; Research funding: Boehringer Ingelheim, Celgene, Ignyta, Incyte, Lilly, Stemlive. G. Giordano: Honoraria: Celgene, Sanofi; Consultancy: Celgene; Travel accomodation expenses, Celgene. G. Kim: Consultant, Speaker: Celgene, Ipsen. S-E. Al-Batran: Consultancy: Bristo-Myers Squibb, Celgene, Lilly, Merck, Roche, Servier; Speaker: Celgene, Lilly, Nordic Bioscience, Roche; research funding, Celgene, Hospira, Lilly, Medac, Novartis, Roche, Vibor. All other authors have declared no conflicts of interest.

725P Efficacy and safety of nab-paclitaxel plus gemcitabine (AG) vs. FOLFIRINOX (FFX) as first line chemotherapy for metastatic pancreatic cancer (mPC): Retrospective analysis

K. Lee, I. Hwang, J. Kang, C. Yoo, K-P. Kim, J.H. Jeong, H-M. Chang, B-Y. Ryoo

Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Nab-Paclitaxel plus Gemcitabine (AG) and FOLFIRINOX (FFX) have been established as standard first-line treatment in metastatic pancreatic cancer (mPC) based on the superior efficacy compared to gemcitabine monotherapy. Although FFX is recommended for patients with relatively young age and good performance status (PS), there is lack of data for optimal choice between these two regimens. We performed retrospective analysis comparing the efficacies and safety of AG and FFX in mPC patients as first line therapy.

Methods: A total of 308 patients with mPC who were treated with AG (n = 149) or FFX (n = 159) as first-line treatment between January 2013 and December 2016 at Asan Medical Center, Seoul, Korea were included. Treatment outcomes including survivals, response rates and toxicities of each regimen were evaluated.

Results: Patients treated with AG were older (62 vs. 60 years, p = 0.02) and they had higher Charlson Comorbidity Index (CCI) score (≥9, 46.3% vs. 32.7%, p = 0.02). There were no significant differences between the two groups in terms of other baseline characteristics. The response rates (34% vs 34%, p = 0.88) and median progression-free survival (PFS) (6.8 vs 5.1 months, p = 0.19) were comparable, but median overall survival (OS) was significantly better with AG (11.4 vs 9.6 months; p = 0.002). In subgroup analyses, PFS with AG was longer in patients with age ≥ 65 years, peritoneal metastasis, and higher CCI than that with FFX. While grade 3-4 peripheral neuropathy was more common in the AG group (10% vs 3%), grade 3 nausea was more frequent in the FFX group (2% vs 17%); granulocyte colony-stimulating factor was required only in the FFX group (n = 27, 18%).

Conclusions: AG was well tolerated and showed comparable efficacy outcomes with FFX. Of note, AG might be preferentially considered as the first-line treatment in mPC patients with peritoneal metastasis, comorbid medical conditions or old age. As both regimens are feasible as first-line treatment for mPC, further investigations are needed for the personalized uses of these regimens.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 724P

Study	n (1L)		Median 1L OS, mo		Median 1L PFS, mo		Grade ≥ 3 AEs		
	nab-P/G	FFX	nab-P/G	FFX	nab-P/G	FFX	AE	nab-P/G	FFX
Beyer 2016 (mPC)	19	57	7	12	NR	NR		NR	NR
Park 2016 (mPC)	18	9	6.1	9.9	NR	NR		NR	NR
Braiteh 2017 (mPC)	122	80	8.6[a]	8.6[a]	NR	NR	Neutropenia Febrile neutropenia Anemia Thrombocytopenia	28% 1% 13% 11%	30% 3% 6% 14%
Caponnetto 2017 (mPC)	20	23	NR	NR	6	5		NR	NR
Cartwright 2017 (mPC)	255	159	9.8[b]	11.4[b]	NR	NR		NR	NR
Cherniawsky 2017 (aPC)[c]	NR	NR	10	11	6.9	8.8		NR	NR
Javed 2017 (mPC)	80	191	7.0	9.0	NR	NR		NR	NR
Kasi 2017 (aPC)[c]	47 (33)	107 (56)	10.8	15.9	5.7	11.7	Neutropenia Peripheral neuropathy Diarrhea Anemia Thrombocytopenia Elevated transaminases Elevated creatinine	17% 6% 0% 31% 6% 6% 4%	33% 6% 5% 14% 28% 4% 3%
Maeda 2017 (aPC)[c]	9 (NR)	16 (NR)	11.5	13.1	6.1	6.3		NR	NR
Mañes-Sevilla 2017 (mPC)	20	15	9.2	11.4	5.4	7.1	Any	35%	41%
Muranaka 2017 (aPC)[c]	22 (17)	16 (1)	Not reached	9.9	6.5	3.7	Neutropenia Peripheral neuropathy Febrile neutropenia Diarrhea Anemia Nausea Anorexia Thrombocytopenia Vomiting	55% 0% 9% 0% 18% 0% 5% 14% 0%	69% 0% 19% 0% 6% 6% 6% 6% 0%
Papneja 2017 (aPC)[c]	33 (21)	86 (70)	9	9	4	6		NR	NR
Shahda 2017 (aPC)[c]	NR	NR	11.4-14.4[d]	11.3-12.3[d]	4.6-6.1[d]	5.3-9.4[d]		NR	NR
Wang 2017 (aPC)[c]	87 (66)	92 (55)	10.5 (10.0)	14.1 (9.4)	8.5 (8.3)	8.4 (6.6)		NR	NR
Watanabe 2017[e] (mPC)	65	70	14.0	11.5	6.5	5.7	Neutropenia Peripheral neuropathy Febrile neutropenia Diarrhea Anorexia	45% 5% 2% 2% 3%	47% 4% 9% 1% 13%
Barrera 2018 (mPC)	31	44	8.1	9.9	4.6	5.8	Neutropenia Peripheral neuropathy Fatigue	13% 7% 26%	20% 4% 11%
Franco 2018 (aPC)[c]	49 (NR)	87 (NR)	13	13	NR	NR		NR	NR
Helen 2018 (aPC)[c]	NR	NR	NR (5.5	NR (8.8)	NR	NR		NR	NR
Hwang 2018 (mPC)	149	159	11.4	9.6	6.8	5.0		NR	NR
Kim 2018 (mPC)	337	317	12.1[f]	13.8[f]	NR	NR		NR	NR
Total[g]	1363 (1253)	1528 (1306)							

[a]Reported as database persistence, a proxy for OS.

[b]For pts with ECOG PS 0/1, OS was 12.1 mo for nab-P/G and 11.4 mo for FFX.

[c]aPC includes mPC. The numbers in parentheses are for pts with mPC.

[d]Biomarker study observing homologous recombination deficiency low vs high in each treatment regimen with data presented here as a range.

[e]Modified FFX (no bolus 5-FU and reduced dose irinotecan).

[f]For pts with ECOG PS 0/1, OS was 14.1 mo for nab-P/G and 13.7 mo for FFX.

[g]Represents minimum as some studies did not report the number of pts. The numbers in parentheses are for pts with mPC. 1L, first line; AE, adverse event; aPC, advanced pancreatic cancer; FFX, FOLFIRINOX; mPC, metastatic pancreatic cancer; nab-P/G, nab-paclitaxel/gemcitabine; NR, not reported; OS, overall survival; PFS, progression-free survival.

726P FOLFIRINOX for recurrent pancreatic cancer after resection: Nationwide multicenter observational study by Japan adjuvant study group of pancreatic cancer (JASPAC)

S. Morinaga[1], M. Takita[2], A. Yoshizawa[3], K. Kamei[4], S. Nakamori[5], S. Ishihara[6], H. Kuramochi[7], Y. Yokoyama[8], T. Uchiyama[9], G. Murohisa[10], M. Kobayashi[11], A. Todaka[12], A. Fukutomi[13]

[1]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, [2]Department of Clinical Study, Kanagawa Cancer Center, Yokohama, Japan, [3]Department of Biostatistics, Kanagawa Prefectural Hospital Organization, Yokohama, Japan, [4]Department of Surgery, Kinki University Faculty of Medicine, Osakasakai, Japan, [5]Department of Hepatobiliary and Pancreatic Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [6]Department of Surgery, Fujita Health University, Toyoake, Japan, [7]Department of Chemotherapy, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Japan, [8]Department of Gastrointestinal Surgery, Nagoya University Hospital, Nagoya, Japan, [9]Department of Surgery, Kikugawa General Hospital, Kikugawa, Japan, [10]Department of Gastrointestinal Medicine, Seirei Hamamatsu General Hospital, Hamamatsu, Japan, [11]Clinical Trial Promotion Section, Pharma Valley Center, Shizuoka, Japan, [12]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [13]Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

Background: There are concerns about more severe toxicities of FOLFIRINOX use in case with recurrent disease after pancreatic resection, because a certain number of these patients suffer from malnutrition, weight loss, and diabetes mellitus induced by pancreatic exocrine or endocrine insufficiency. Today, FOFIRINOX is widely adopted also in recurrent disease after resection beside metastatic disease studied in the ACCORD trial, yet can be associated with significant severe toxicity. We aimed to clarify toxicity and tolerance of FOLFIRNOX use in patients with recurrent disease after resection.

Methods: This study was carried out as an incidental research of JASPAC 06 study which examined multi-institutional experience with FOLFIRINOX use in pancreatic cancer by registration study. We focused on toxicity and tolerance of FOLFIRINOX use in case with recurrent disease after resection, and correlated them with those of locally advanced or metastatic disease group.

Results: From Nov. 2014 to May. 2015, 399 patients were registered in JASPAC 06, 80 patients (20%) had recurrent disease, 78 (20%) had locally advanced disease, and 241 (60%) had metastatic disease. There were no difference in background such as age, sex, ECOG PS, pathology and CA19-9 level between recurrent disease group and locally advanced or metastatic disease group. FOLFIRINOX was initiated as modified manner in 69% of recurrent group and 67% of locally advanced or metastatic group. The major grade 3-4 toxicities observed in recurrent group and locally advanced or metastatic disease group were neutropenia (68% vs 63%), febrile neutropenia (4% vs 15%, $p = 0.007$), thrombocytopenia (4% vs 3%), anemia (8% vs 10%), fatigue (4% vs 3%), anorexia (14% vs 14%). The median treatment duration and median treatment cycle in recurrence group and locally advanced or metastatic group was 2.9 months vs 4.1 months, and 4cycle vs 6cycle. There was no difference in relative dose intensity between two groups.

Conclusions: Toxicity and tolerance of FOLFIRINOX use in recurrent disease after pancreatic resection were similar to those of use in locally advanced or metastatic disease.

Legal entity responsible for the study: Japan Adjuvant Study Group of Pancreatic Cancer.

Funding: Yakult Honsha Co., Ltd., Daiichi Sankyo Co., Ltd. and Pharma Valley Center.

Disclosure: S. Nakamori: Eisai Co. Ltd. A. Todaka: Honoraria: Yakult Honsha Co., Ltd, Daiichi Sankyo Co., Ltd. A. Fukutomi: Honoraria: Yakult Honsha Co., Ltd, Daiichi Sankyo Co., Ltd; Advisory role: Yakult Honsha Co., Ltd. All other authors have declared no conflicts of interest.

727P A phase II study of nab-paclitaxel and gemcitabine in Korean patients with metastatic pancreatic cancer

S.J. Lee[1], D-Y. Oh[2], J-H. Kang[3], H.J. Choi[4], M.A. Lee[5], S.Y. Oh[6], S-T. Kim[7], Y.S. Park[8], B-Y. Ryu[9], J.O. Park[1]

[1]Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [3]Internal Medicine, Gyeongsang National University School of Medicine, Jinju, Jinju, Republic of Korea, [4]Internal Medicine, Yonsei University College of Medicine Department of Internal Medicine, Seoul, Republic of Korea, [5]Internal Medicine, Seoul St. Mary's Hospital, of the Catholic University, Seoul, Republic of Korea, [6]Internal Medicine, Dong-A University College of Medicine, Busan, Republic of Korea, [7]Medicine, Samsung Medical Center, Seoul, Republic of Korea, [8]Hematology-Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [9]Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Nab-paclitaxel (nab-P) in combination with gemcitabine (G) significantly improved overall survival in patients with pancreatic cancer and is considered as standard first line therapy. However, the efficacy and safety data in Korean patients are lacking as the phase III study was done only in Western countries.

Methods: This open-label, multicenter, phase II, single-arm study was conducted at seven hospitals in South Korea (NCT02426281). Patients with pathologically confirmed metastatic pancreatic cancer were enrolled. Patients received nab-P (125mg/m^2) followed by G (1000mg/m^2) on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Through a randomized phase III trial, Von Hoff et al. observed a median PFS of 3.7 months from the G alone arm and 5.5 months from the nab-P + G arm. This study is to confirm this outcome from the Korean population. We will not be interested in the combination therapy of nab-P + G if its median PFS is 3.7 months or shorter and will be highly interested in it if its median PFS is 5.5 months or longer. (90% of power and by the one-sample log-rank test with a one-sided alpha=5%).

Results: A total of 65 patients were enrolled between May 2015 and November 2016. The median age of patients was 60 years (range 43-83), 75% of patients were male, and all had an ECOG performance status of 0 or 1. The median PFS was 7.0 months (95% CI; 5.6-8.3), which met primary endpoints. Median overall survival was 12.9 months (95% CI; 10.1-15.6) and the objective response rate was 41.5 % (95% CI; 29.5-53.5) according to RECIST v1.1. The median relative dose intensity was 84% for nab-paclitaxel and 88% for gemcitabine. Grade 3-4 adverse events included neutropenia (62%), anemia (14%), neuropathy (12%) and febrile neutropenia (9%). There was one treatment-related deaths of septic shock.

Conclusions: In Korean patients with metastatic pancreatic cancer, nab-paclitaxel plus gemcitabine regimen showed comparable efficacy and safety profile to previous phase III study of Western countries. Based on this result, we are conducting a phase II trial with the nab-P + G in an expansion cohort of locally advanced pancreatic cancer.

Clinical trial identification: NCT02426281.

Legal entity responsible for the study: Joon Oh Park (PI).

Funding: Nab-paclitaxel was provided by Celgene.

Disclosure: All authors have declared no conflicts of interest.

728P Nab-paclitaxel plus gemcitabine for unresectable pancreatic cancer: A pooled meta-analysis

Y. Zhang, S. Shi, X. Yu

Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: About 80%-85% of patients with pancreatic cancer are unresectable at first diagnosis. Several studies have examined nab-paclitaxel plus gemcitabine (NG) in patients with locally advanced pancreatic cancer (LAPC) and metastatic pancreatic cancer (MPC). The objective of this analysis was to evaluate the effectiveness of NG as first-line treatment in this specific patient population.

Methods: We searched Pubmed for eligible studies from the day of inception to April 15th, 2018 for studies of chemo(radiation)therapy-naïve patients who accepted NG as first-line treatment of unresectable pancreatic cancer (UPC). Overall objective response rate (ORR), 1-year overall survival (OS) and 6-month progression free survival (PFS) rates were estimated by randomized-effect model. Subgroup analyses were conducted in LAPC and MPC.

Results: Of 890 patients included from 16 studies, 53 patients were LAPC and 837 patients were MPC. Median OS from the start of NG of all patients ranged from 8.7 months to 20.0 months with a 1-year survival rate of 50.9% (95%CI 40.1% to 61.8%). Median PFS ranged from 2.2 months to 8.4 months with a 6-month PFS rate of 52.8% (95%CI 33.2% to 72.3%). In single arm analysis, the overall ORR in unresectable pancreatic cancer was 34.4% (95%CI 25.3% to 43.5%). In patients with LAPC, 90.6% (48/53) underwent surgery and the R0 resection rate was 81.2% (ranging from 70% to 100%), achieving a 1-year survival rate of 97.5%. In patients with MPC, the ORR was 30.8% and the 1-year survival rate was 44.6%. Five hundred and fifty six grade 3/4 adverse events and no death caused by toxicity were reported in 15 studies consisting of 871 patients.

Conclusions: This is the first meta-analysis to evaluate the effectiveness of NG for UPC. More than 50% of patients with UPC treated with NG survived longer than 12 months. NG showed favorable tumor reducing effect with acceptable toxicity profile. Randomized controlled trials are needed to confirm the efficacy of NG in patients with LAPC.

Legal entity responsible for the study: The authors.

Funding: National Science Fund for Distinguished Young Scholars (81625016).

Disclosure: All authors have declared no conflicts of interest.

729P Prognostic implication of inflammation-based scores in patients with metastatic pancreatic cancer (mPC) treated with first-line nab-paclitaxel plus gemcitabine (AG)

I. Hwang[1], J. Kang[2], C. Yoo[1], J.H. Jeong[1], K-P. Kim[1], H-M. Chang[1], B-Y. Ryoo[1]

[1]Medical Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Oncology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: AG is standard first-line chemotherapy for patients with mPC. However, prognostic factors for patients with mPC treated with AG are largely unknown. This retrospective analysis was performed to identify the prognostic factors including

inflammation-based prognostic scores in mPC patients treated with AG as first-line treatment.

Methods: A total of 203 patients with histologically confirmed recurrent (n = 55) or metastatic (n = 148) pancreatic cancer who were treated with first-line AG in Asan Medical Center, Seoul, Korea, between January 2013 and January 2018, were included in this analysis. As inflammation-based scores, baseline Neutrophil-lymphocyte ratio (NLR), Platelet-lymphocyte ratio (PLR) and modified Glasgow prognostic score (mGPS) were tested. Cox-proportional hazards model were used to identify prognostic factors in univariate and multivariate analyses.

Results: Median age was 62 years (range, 32-82) and 116 patients (57%) were male. With median follow-up duration of 21.5 months (range, 0.5-34.3), median overall survival (OS) and progression-free survival (PFS) in overall patients were 15.1 (95% CI 12.6-17.6) and 7.1 (95% CI, 6.2-8.0) months, respectively. In multivariate analysis, elevated CA19-9 level (HR 1.75, p = 0.008), liver metastasis (HR 1.8, p = 0.001), distant lymph node metastasis (HR 1.4, p = 0.04), and high mGPS (≥1 vs.0: HR 1.6, p = 0.005) were significantly associated with poorer OS. For PFS, poor performance status (PS) (ECOG PS ≥ 2 vs 0/1: HR 2.1, p = 0.048), liver metastasis (HR 1.4, p = 0.03), distant lymph node metastasis (HR 1.5, p = 0.02), and elevated CA 19-9 level (HR 1.1, p = 0.02) were significantly related with poorer outcomes. Neither NLR nor PLR was significantly associated with PFS or OS.

Conclusions: CA 19-9 level, liver and distant lymph node metastasis were independent prognostic factors in mPC patients treated with first-line AG. Among the inflammation based prognostic scores, mGPS may be the reliable indicator for the prediction of OS.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

730P A pilot study of gemcitabine, nab-paclitaxel, PEGPH20 (PAG) and rivaroxaban for advanced pancreatic adenocarcinoma: Interim safety and efficacy analysis

K. Yu[1], S. Mantha[1], C. Tjan[1], E. Kaufmann[1], R.B. Brenner[1], M. Lowery[1], G. Ku[1], N. Raj[2], M. Shcherba[1], Z. Goldberg[1], J. Li[1], A. Zervoudakis[1], A. Hamilton[1], E. Won[1], R.K.G. Do[1], E.M. O'Reilly[1]

[1]Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: PEGPH20 (P) degrades hyaluronan (HA), a key component of pancreatic adenocarcinoma (PDAC) tumor microenvironment, leading to reduction of tumor interstitial pressure, decompression of tumor blood vessels and improvement in delivery of chemotherapeutics. A prior study of P with chemotherapy in PDAC (HALO-202) found an increased risk of thromboembolic (TE) events, 43%, effectively reduced with enoxaparin prophylaxis. Rivaroxaban (R) is a safe and effective oral anticoagulant for treating cancer-related TE.

Methods: Patients considering frontline therapy for advanced PDAC and with KPS ≥ 70 were studied. 28 patients without prior TE (cohort 1) and 14/28 planned patients with prior TE (cohort 2) were enrolled. Patients received treatment with PAG (P; 3 μg/kg IV 2x/wk x 3 wks in C1, then 1x/wk x 3 wks in C2+, plus standard dose and schedule nab-paclitaxel and gemcitabine (AG)) every 28 days, with R (15 mg twice daily for 21 days, followed by 20 mg once daily). Primary endpoint is TE event rate. Secondary endpoints include PFS, OS, major bleeding rate and RR.

Results: All 42 patients are evaluable for efficacy and safety. Key patient characteristics: median age = 61, M/F 22/20, stage III/IV 5/37. Median follow-up is 10.9 mo. One (2.4%) grade 4 TE event occurred. Two grade 3 GI hemorrhages occurred, both resolved with supportive measures. Best responses: complete response 2 (4.8%), partial response 19 (45.2%), stable disease 15 (35.7%), progressive disease 2 (4.8%), and overall disease control rate of 85.7%. Median PFS is 7.0 mo, mOS has not been reached. Safety and efficacy are similar across both cohorts (see Table).

Table: 730P

Variable	Cohort 1	Cohort 2	Overall
Safety	n = 28	n = 14	n = 42
TE Events	1 (3.6%)	0 (0%)	1 (2.4%)
Major Bleeding	2 (7.1%)	0 (0%)	2 (4.8%)
Efficacy			
Complete Response	1 (3.6%)	1 (7.1%)	2 (4.8%)
Partial Response	14 (50.0%)	5 (35.7%)	19 (45.2%)
Stable Disease	8 (28.6%)	7 (50.0%)	15 (35.7%)
Progressive Disease	2 (7.1%)	0 (0%)	2 (4.8%)
Not Evaluable	3 (10.7%)	1 (7.1%)	4 (9.5%)
PFS	6.0 mo	8.0 mo	7.0 mo
OS	Not Reached	Not Reached	Not Reached

Conclusions: Interim analysis shows R is safe and effectively prevents TE events in patients receiving PAG. Responses and disease control rate are encouraging in this tumor HA-level unselected patient population. Updated safety and efficacy data will be reported.

Clinical trial identification: NCT02921022.

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center.

Funding: Halozyme Therapeutics, Inc.

Disclosure: All authors have declared no conflicts of interest.

731P Phase II clinical trial of gemcitabine plus oxaliplatin combination therapy (GEMOX) in patients with advanced pancreatic adenocarcinoma with a family history of pancreatic/breast/ovarian/prostate cancer or personal history of breast/ovarian/prostate cancer (FABRIC study)

H. Takahashi[1], C. Morizane[2], S. Nomura[3], N. Okano[4], M. Tsuda[5], N. Mizuno[6], H. Satake[7], K. Tsuji[8], K. Shioji[9], H. Ishii[10], K. Yasui[11], H. Miyakawa[12], A. Ishiguro[13], T. Ogura[14], M. Ueno[15], A. Ikeda[16], T. Terashima[17], M. Ikeda[18], T. Okusaka[2], J. Furuse[4]

[1]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [2]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, [3]Biostatistics Section, Office of Clinical Research Support, National Cancer Center Hospital East, Kashiwa, Japan, [4]Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan, [5]Department of Gastroenterological Oncology, Hyogo Cancer Center, Hyogo, Japan, [6]Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan, [7]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [8]Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan, [9]Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan, [10]Clinical Research Center, Shikoku Cancer Center, Matsuyama, Japan, [11]Department of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan, [12]Division of Gastroenterology, Sapporo Kosei General Hospital, Kyoto, Japan, [13]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan, [14]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan, [15]Division of Hepatobiliary and Pancreatic Oncology, Kanagawa Cancer Center, Yokohama, Japan, [16]Division of Gastroenterology, Kobe University Graduate School of Medicine, Kobe, Japan, [17]Advanced Preventive Medical Sciences Research Center, Kanazawa University, Kanazawa, Japan, [18]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Presence/absence of family/personal history of breast/ovarian/pancreatic cancer has been reported to be a useful predictive marker in patients with pancreatic adenocarcinoma (PA) receiving platinum-based chemotherapy (Fogelman D, 2015). We planned a prospective phase II study to evaluate the efficacy and safety of platinum-based chemotherapy in this population.

Methods: Eligible patients were those with chemotherapy-naïve metastatic PA with one or more of the following: 1) family history of pancreatic (P)/breast (B)/ovarian (O)/prostate (PR) cancer in a first-degree relative, 2) at least two family members with P/B/O/PR cancer within third-degree relatives, and 3) personal history of B/O/PR cancer. Patients received gemcitabine 1,000 mg/m^2 and oxaliplatin 100 mg/m^2 every two weeks (GEMOX). The primary endpoint was the one-year survival rate, and the outcome in 19 of 43 patients (pts) (44%) were desired. The target sample size was determined as 43, with a one-sided alpha of 5% and a power of 80%.

Results: A total of 45 pts were enrolled. The first consecutive 43 pts were included in the efficacy analysis. The one-year survival rate (90% confidence interval) was 27.9% (17.0-41.3) and did not meet the expected threshold. The response rate was 27.9%. A tendency towards prolonged survival was observed in patients with two or more family histories of P/B/O/PR cancer (HR 0.65, 95% CI [0.34-1.23]). Presence of a family/personal history of B/O/PR cancer tended to be associated with a better response and longer survival. In this study population, patients with a family history of pancreatic cancer seemed to show a poorer response. The most common adverse events of grade 3 or higher severity were neutropenia (36%), leukopenia (27%) and thrombocytopenia (23%).

Conclusions: GEMOX did not show expected efficacy in patients with metastatic PA with a family/personal history of P/B/O/PR cancer. Selection of GEMOX based on family/personal history alone is not recommended, especially in patients with a family history of P cancer.

Clinical trial identification: UMIN000017894 (registeration date: 17-Jun-2015).

Legal entity responsible for the study: National Cancer Center Hospital.

Funding: Japan Agency for Medical Research and Development (AMED), National Cancer Center Research and Development Fund.

Disclosure: H. Takahashi: Honoraria: Taiho Pharmaceutical; Research funding: Bayer Pharmaceutical, Bristol-Myers Squibb. C. Morizane: Honoraria: Pfizer, Novartis, Yakult Honsha, Lilly, Nobelpharma, Fujifilm, Teijin Pharma, Taiho Pharmaceutical; Consulting or advisory role: Yakult Honsha, Novartis, Taiho Pharmaceutical; Research funding (Recipient: institution): Pfizer, Nobelpharma, Eisai, Yakult Honsha, Ono Pharmaceutical, Taiho Pharmaceutical. S. Nomura: Honoraria: Taiho Pharmaceutical N. Okano: Honoraria: Taiho Pharmaceutical, Merck Serono; Research funding (Recipient: institution): J-Pharma, Taiho, Sumitomo Dainippon, Janssen, Daiichi

Sankyo, MSD, Yakult, Takeda, Chugai, Ono, Astellas, Zeria, Novartis, Nanocarrier, Shionogi, Onco Therapy Science, Eli Lilly Japan, Bayer, Bristol-Myers Squibb, Merck Serono, Kyowa Hakko Kirin, Eisai, NanoCarrier, Mochida, Baxalta, Sanofi. N. Mizuno: Research funding: Taiho Pharmaceutical Co. Ltd., Merck Serono, AstraZeneca, Zeria Pharmaceutical, NanoCarrier, Eisai, MSD, Novartis, Dainippon Sumitomo Pharma, Aslan Pharmaceuticals, Pharma Valley Center, Incyte Inc. (Recipient: institution); Honoraria: Taiho Pharmaceutical Co. Ltd., Novartis, Ono Pharmaceutical, Teijin Pharma (Recipient: self); Advisory role: Teijin Pharma. H. Satake: Honoraria: Bayer, Chugai Pharma, Eli Lilly Japan, Merck Serono, Takeda, Taiho Pharmaceutical, Yakult Honsha. H. Ishii: Honoraria: Taiho, Yakult, Eisai, Towa; Consulting or advisory role: Ono; Research funding (Recipient: institution): Taiho. M. Ueno: Honoraria: Taiho Pharmaceutical, Yakult Honsha, AstraZeneca, Novartis, Lilly, Teijin Pharma, Shire, Ono Pharmaceutical; Research funding: Taiho Pharmaceutical, Shire, Daiichi Sankyo, Eisai, AstraZeneca, Ono Pharmaceutical, MSD, Merck Serono, NanoCarrier, Dainippon Sumitomo Pharma, Incyte. M. Ikeda: Honoraria: Novartis Pharma, Bayer Yakuhin, Bristol-Myers Squibb, Abbott Japan, Eisai, Eli Lilly Japan, Taiho Pharmaceutical, Chugai Pharmaceutical, Daiichi-Sankyo, Yakult, Otsuka Pharmaceutical, Nobelpharma; Consulting or advisory role: Nano Carrier, Bayer Yakuhin,Eisai,Kyowa Hakko Kirin, Novartis Pharma,Shire, MSD; Research Funding (Recipient: institution): Bayer Yakuhin, Kyowa Hakko Kirin, Yakult, Taiho Pharmaceutical, Eli Lilly Japan, Ono Pharmaceutical, Eisai, AstraZeneca, Zeria Pharmaceutical, Baxter, Chugai Pharmaceutical, Bristol Myers Sqiibb, Merck Serono, Kowa, Nano Carrier, ASLAN Pharmaceuticals T. Okusaka: Membership on an advisory board or board of directors: Dainippon Sumitomo Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd., Zeria Pharmaceutical Co., Ltd. , Daiichi Sankyo Co., Ltd.; Corporate-sponsored research: Eli Lilly Japan K.K., Eisai Co., Ltd., Novartis Pharma K.K., Yakult Honsha Co., Ltd., Taiho Pharmaceutical Co., Ltd., Kowa Company, LTD, Kyowa Hakko Kirin Co., Ltd., Ono Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., Pfizer Japan Inc., AstraZeneca K.K., Dainippon Sumitomo Pharma Co., Ltd., Nano Carrier Co., Ltd., Baxter, Chugai Pharmaceutical Co., Ltd. J. Furuse: Honoraria: Taiho, Chugai, Yakult, Sumitomo Dainippon, Eli Lilly Japan, Astellas, Ono, Pfizer, Bayer, Novartis, Merck Serono, Takeda, Eisai, MSD, Shionogi, J-Pharma, Daiichi Sankyo, Mochida, Nippon Kayaku, EA pharma, Sawai, Teijin Pharma; Consulting or advisory role: Taiho, Chugai, Yakult, Sumitomo Dainippon, Eli Lilly Japan, Astellas, Ono, Pfizer, Bayer, Novartis, Merck Serono, Takeda, Eisai, MSD, Shionogi, J-Pharma, Daiichi Sankyo, Kyowa Hakko Kirin, Sanofy, Sandoz, Otsuka, Zeria, Fujifilm, Astra Zeneca, Asahi Kasei, Shire; Research funding (Recipient: institution): J-Pharma, Taiho, Sumitomo Dainippon, Janssen, Daiichi Sankyo, MSD, Yakult, Takeda, Chugai, Ono, Astellas, Zeria, Novartis, Nanocarrier, Shionogi, Onco Therapy Science, Eli Lilly Japan, Bayer, Bristol-Myers Squibb, Merck Serono, Kyowa Hakko Kirin, Eisai, NanoCarrier, Mochida, Baxalta, Sanofi. All other authors have declared no conflicts of interest.

732P GEMOX plus hypofractionated radiotherapy for unresectable locally advanced pancreatic cancer: Results from a phase II study

A. Passardi[1], E. Scarpi[2], E. Neri[3], E. Parisi[3], G. Ghigi[3], G. Ercolani[4], A. Gardini[5], G. La Barba[5], F. Pagan[6], A. Casadei Gardini[7], L.G. Frassineti[7], F. Ferroni[8], M. Valgiusti[1], S.A.M.Z.M. Darwish[9], A. Romeo[3]

[1]*Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy,* [2]*Biostatistics and Clinical Trials Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy,* [3]*Radiotherapy Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy,* [4]*Medical and Surgical Sciences, University of Bologna, Bologna, Italy,* [5]*General and Oncologic Surgery, Morgagni-Pierantoni Hospital, AUSL Romagna, Forlì, Italy,* [6]*Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy,* [7]*Medical Oncology, Istituto Tumori della Romagna I.R.S.T., Meldola, Italy,* [8]*Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy,* [9]*Medical Oncology, Tanta University Hospital, Tanta, Egypt*

Background: A more accurate identification of tumors by image-guided radiation therapy (IGRT) and improved radiation delivery by advanced technology have led to a wider use of hypofractionated radiation schedules for the treatment of locally advanced pancreatic cancer (LAPC). The aim of this prospective phase II study was to evaluate the effect of neoadjuvant GEMOX plus accelerated hypofractionated radiotherapy on the resectability of LAPC.

Methods: From April 2011 to August 2016, a total of 42 patients with non resectable LAPC were enrolled onto the study, of whom 40 were evaluable. Median age was 67 years (range 41-78). Patients were treated as the following: gemcitabine (GEM) 1000 mg/m2 on day 1, and oxaliplatin (OX) 100 mg/m2 on day 2, every two weeks (GEMOX regimen) for 4 cycles, 15 days off, hypofractionated radiotherapy, 15 days off, a further 4 cycles of GEMOX, restaging. Radiotherapy was delivered by helical tomotherapy at a dose of 35 Gy (with an inhomogeneous dose distribution inside the target volume of up to 30% of the prescription dose) in 7 fractions (one fraction per day) over 9 days on the gross tumor volume; 28 Gy-35 Gy was administered on the clinical target volume (CTV) 1-2 on the basis of nodal status.

Results: Overall 5 patients (12.5%) obtained a partial tumor response and 20 (50%) a stable disease. Of these, 9 underwent surgical laparotomy (5 radical pancreatic resection 1 termoablation and 3 explorative laparotomy), 1 patient became operable but refused surgery. The overall resectability rate was 25%, while the R0 resection rate was 12.5%. Toxicity to GEMOX was similar to that reported elsewhere. Radiotherapy was well tolerated and the most frequently encountered adverse events were mild to moderate nausea and vomiting, abdominal pain and fatigue. At a median follow-up of 50 months, the median progression free survival and overall survival were 9.3 (95% CI 6.2-14.9) and 15.8 (95% CI 8.2-23.4) months, respectively.

Conclusions: Our results show the feasibility of using accelerated hypofractionated radiotherapy on tumor volume and locoregional lymph nodes in LAPC. Treatment was well tolerated and survival rates are promising.

Clinical trial identification: EudraCT / RSO2010-020379-22.

Legal entity responsible for the study: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

733P NAPOLI-1 phase III trial outcomes by prior surgery, and disease stage, in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

T. Macarulla Mercade[1], G. Bodoky[2], J. Siveke[3], K-H. Lee[4], J. Chen[5], B. Mirakhur[6], A. Dean[7], L-T. Chen[8], F. de Jong[9]

[1]*Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain,* [2]*Oncology, St. László Hospital, Budapest, Hungary,* [3]*Medical Oncology, University Hospital Essen West German Cancer Center, Essen, Germany,* [4]*Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea,* [5]*Biostatistics, Shire plc, Cambridge, MA, USA,* [6]*Medical Affairs, Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA,* [7]*Medical Oncology, Saint John of God Hospital Subiaco, Subiaco, Australia,* [8]*National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan,* [9]*Global Medical Affairs Oncology, Shire International GmbH, Zug, Switzerland*

Background: The NAPOLI-1 phase 3 trial (NCT01494506) reported significantly increased median OS with nal-IRI+5-FU/LV vs 5-FU/LV (6.1 mo vs 4.2 mo; HR = 0.67; p = 0.012) in mPDAC patients who progressed after gemcitabine-based therapy. We report subgroup analysis outcomes in NAPOLI-1 patients who had undergone prior surgery and by disease stage at diagnosis.

Methods: This post-hoc analysis investigated outcomes with or without prior surgery, and by disease stage at diagnosis (stage IIA, IIB, or III, vs IV). P values are descriptive.

Results: In the NAPOLI-1 trial, OS and PFS were increased in ITT patients who had undergone prior surgery compared to those who did not (Table). In patients with prior surgery receiving nal-IRI+5-FU/LV (n = 40), OS and PFS were increased vs 5-FU/LV (n = 43) (HR = 0.84 and 0.72). Patients without prior surgery had significantly increased OS and PFS with nal-IRI+5-FU/LV (n = 77) vs 5-FU/LV (n = 76) (HR = 0.56, p = 0.003 and HR = 0.47, p < 0.001). OS was significantly increased in ITT patients with disease stages IIA (n = 36, HR = 0.59, p = 0.013), IIB (n = 77, 0.54, <0.001), and III (n = 75, 0.57, <0.001) vs stage IV (n = 213). A consistent OS increase was also seen in patients treated with nal-IRI+5-FU/LV: stage IIA (HR = 0.63, ns) stage IIB (HR = 0.50, p = 0.024) and stage III (HR = 0.43, p = 0.021) vs stage IV.

Conclusions: OS and PFS were increased in ITT patients who had undergone surgery prior to trial inclusion. Patients treated with nal-IRI+5-FU/LV showed a consistent increase in OS and PFS vs 5-FU/LV. ITT patients with stages IIA, IIB, and III had significantly improved OS vs those with stage IV disease. Treatment with nal-IRI+5-FU/LV showed a survival benefit across disease stages IIA, IIB, and III, vs stage IV. Limited patient numbers should be taken into consideration when interpreting these findings.

Clinical trial identification: NCT01494506.

Editorial acknowledgement: Medical writing support for the preparation of this abstract was provided by Physicians World Europe GmbH, Mannheim, Germany, with financial support from Shire (previously Baxalta), Zug, Switzerland.

Legal entity responsible for the study: Merrimack Pharmaceuticals.

Funding: The analysis was funded by Shire, the study was funded by Merrimack Pharmaceuticals.

Disclosure: G. Bodoky: Consulting, Advisory role: Bayer, Ipsen, Janssen, Lilly, Novartis, Pfizer, Roche; Support for travel, accommodation and expenses: Janssen, Lilly, Novartis, Pfizer, Roche. J. Siveke: Consulting, Advisory role: Merrimack Pharmaceuticals, Baxalta (now part of Shire), Celgene, Lilly; Research funding: Celgene, Bristol-Myers Squibb, 4SC, Novartis, Boehringer Ingelheim; Travel, accommodation, expenses: Roche, Celgene, Shire. J. Chen, F. de Jong: Employee, Stockholder: Shire. B. Mirakhur: Employee: Ipsen, Stockholder: Ipsen, GlaxoSmithKline. A. Dean: Honoraria: Specialised Therapeutics Australia; Consultant/Advisor: Baxalta (now part of Shire), Celgene. L-T. Chen: Honoraria, Consultant, Advisor: Bristol-Myers Squibb, Ono Pharmaceutical, Lilly, MSD, PharmaEngine, Merrimack Pharmaceuticals, TTY Biopharm, SynCoreBio, Five Prime, Novartis; Patent: Hunilife Technology; Research funding: Novartis, GlaxoSmithKline, Merck Serono, TTY Biopharm, Polaris, SyncoreBio, Pfizer, Celgene. All other authors have declared no conflicts of interest.

Table: 733P

Prior surgery

	All ITT		Yes*		No*	
	Yesn=142	Non=275	nal-IRI+5-FU/LVn=40	5-FU/LVn=43	nal-IRI+5-FU/LVn=77	5-FU/LVn=76
mOS	6.8	4.4	8.4	6.1	5.3	3.4
HR,	0.62		0.84		0.56	
P value	<0.001		0.547		0.003	
mPFS	2.6	2.2	2.8	2.6	3.3	1.4
HR,	0.84		0.72		0.47	
P value	0.129		0.217		<0.001	
Disease stage at diagnosis						
	Stage IIA			Stage IIB		
	All ITT	nal-IRI+5-FU/LV	5-FU/LV	All ITT	nal-IRI+5-FU/LV	5-FU/LV
	n = 36	n = 6	n = 9	n = 77	n = 26	n = 22
mOS	6.4	8.6	6.1	6.1	10.2	5.6
HR,†	0.59	0.63	0.42	0.54	0.50	0.43
P value	0.013	0.390	0.070	<0.001	0.024	0.012
	Stage III			Stage IV		
	All ITT	nal-IRI+5-FU/LV	5-FU/LV	All ITT	nal-IRI+5-FU/LV	5-FU/LV
	n = 75	n = 21	n = 19	n = 213	n = 61	n = 62
mOS	6.3	9.0	7.0	4.2	4.7	3.1
HR,†	0.57	0.43	0.49	-	-	-
P value	<0.001	0.021	0.039			

*Comparing treatments;
†vs Stage IV

734P Impact of dose reduction or dose delay on the efficacy of liposomal irinotecan (nal-IRI)+5-fluorouracil/leucovorin (5-FU/LV): Survival analysis from NAPOLI-1

L-T. Chen[1], T.M. Macarulla[2], J. Blanc[3], B. Mirakhur[4], F.A. de Jong[5], B. Belanger[6], T. Bekaii-Saab[7], J. Siveke[8]

[1]Internal Medicine, National Health Research Institutes – National Institute of Cancer Research, Tainan, Taiwan, [2]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital (HUVH), Barcelona, Spain, [3]CHU Bordeaux, Groupe Hospitalier Hau-Lévêque, Pessac, France, [4]Medical Affairs, Ipsen Biopharmaceuticals,Inc., Basking Ridge, NJ, USA, [5]Medical Affairs, Shire GmbH, Zug, Switzerland, [6]Biometry R&D, Ipsen Biopharmaceuticals,Inc., Basking Ridge, NJ, USA, [7]Internal Medicine, Division of Hematology/Medical Oncology, Mayo Clinic, Phoenix, AZ, USA, [8]Division of Solid Tumor Translational Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany

Background: Chemotherapy dose modifications to manage adverse events (AEs) is common in clinical practice. In NAPOLI-1 (NCT01494506), a randomized phase 3 study in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy, nal-IRI+5-FU/LV improved overall survival (OS; primary endpoint) vs 5-FU/LV (6.1 mos vs 4.2 mos; HR = 0·67, 95% CI 0.49–0.92; P = 0.012). The study protocol permitted dose modifications (reduction or delay) to address toxicity. In this exploratory post-hoc analysis, we evaluated the impact of nalIRI dose modifications on overall survival (OS) and progression-free survival (PFS).

Methods: All pts enrolled under protocol v2 who received nal-IRI+5-FU/LV during the first 6 wks were included in the analysis. Pts were grouped according to those with dose modification or those without dose modification. Dose reduction was defined as any decrease from initial dose, delay as any dosing delay >3 days from target date. Pts without dose modification received the first 3 scheduled doses of nal-IRI+5-FU/LV without qualifying delay/reduction. OS and PFS (KaplanMeier estimates) were compared within the nal-IRI+5-FU/LV arm. Unstratified hazard ratios (HRs) were calculated using Cox regression.

Results: Among pts in the nal-IRI+5-FU/LV arm (n = 93), 40 pts had no dose modification and 53 had a dose modification (delay, n = 49; reduction, n = 34). Within the nal-IRI+5-FU/LV arm, there was no significant difference in median OS or PFS between pts with vs without dose modification (Table).

Conclusions: Dose modification of nal-IRI+5-FU/LV in the first 6 wks does not significantly impact OS or PFS compared to patients without dose modifications. This suggests that tolerability-guided dose modification of nal-IRI does not adversely affect efficacy outcomes.

Table: 734P

	Median OS			Median PFS		
	Pts (n)	Months	HR (95% CI)	Pts (n)	Months	HR (95% CI)
nal-IRI+5-FU/LV Delay	49	8.4	1.10 (0.71, 1.70)	49	4.2	1.03 (0.66, 1.61)
nal-IRI+5-FU/LV No delay	43	8.3		43	4.0	
nal-IRI+5-FU/LV Reduction	34	9.4	0.87 (0.54, 1.39)	34	4.2	0.91 (0.56, 1.48)
nal-IRI+5-FU/LV No reduction	48	8.4		48	4.1	

Clinical trial identification: NCT01494506.

Editorial acknowledgement: Editorial assistance for the abstract was provided by The Medicine Group (New Hope, PA); Philip Sjostedt, BPharm; Susan Martin, PhD.

Legal entity responsible for the study: Ipsen Biopharmaceuticals, Inc.

Funding: Ipsen Biopharmaceuticals, Inc.

Disclosure: L-T. Chen: Consulting, Advisory role: Bristol-Myers Squibb, Five Prime Therapeutics, Lilly, Merrimack, MSD, Novartis, Ono Pharmaceutical, PharmaEngine, Syncope, Taiwan, TTY Biopharm Research funding (Inst): GlaxoSmithKline, Merck Serono, Novartis, Polaris, TTY Biopharm, Patents, Royalties, Other intellectual property: Anti-alpha-enolase (ENO-1) monoclonal antibody to HuniLife Technology, Taiwan. J. Blanc: Honoraria: Baxalta/Shire, Bayer Schering Pharma, Gilead Sciences; Consulting, Advisory role: Baxalta/Shire, Bristol-Myers Squibb, Novartis, Onxeo; Travel, accommodations, expenses: Bayer Schering Pharma. B. Mirakhur, B. Belanger: Employee, Stock and other ownership interests: Ipsen Biopharmaceuticals, Inc. F.A. de Jong: Employee: Shire; Stock and other ownership interests: Amgen, Shire. T. Bekaii-Saab: Consulting, Advisory role: Amgen, Bayer, Boehringer Ingelheim, Celgene, Genentech/Roche, Glenmark, Lilly, Merrimack, NCCN, Pfizer, Research to practice, Sirtex Medical, Taiho Pharmaceutical; Other relationship: Exelixis, Merck, Polaris. J. Siveke: Consulting, advisory role: Baxalta, Celgene, Lilly, Merrimack Research funding:

4SC, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Novartis; Travel, accommodations, expenses: Celgene, Roche. All other authors have declared no conflicts of interest.

735P Real-world dosing patterns of patients (pts) with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI) in US oncology clinics

D. Ahn[1], A. Barzi[2], R.A. Miksad[3], A. Surinach[4], F.A. Corvino[4], A. Valderrama[5], K. Mamlouk[5], S. Pulgar[5], T. Bekaii-Saab[1]

[1]Division of Medical Oncology, Department of Internal Medicine, Mayo Clinic, Phoenix, AZ, USA, [2]Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA, [3]Research Oncology, Flatiron Health, New York, NY, USA, [4]Real World Data Analytics, Genesis Research, Hoboken, NJ, USA, [5]Health Economics and Outcomes Research, Ipsen Biopharmaceutical, Basking Ridge, NJ, USA

Background: nal-IRI + 5FU/LV therapy demonstrated significant survival improvement in mPC pts previously treated with gemcitabine-based therapy (NAPOLI-1). The generally recommended nal-IRI initiation dose is 70 mg/m^2 (free base, equivalent to 80 mg/m^2 salt based dosing). This retrospective observational analysis describes the real-world dosing patterns of nal-IRI.

Methods: Using the Flatiron Health® longitudinal database, data was extracted and analyzed for adult pts with mPC treated with nal-IRI between Nov 2015 to Aug 2017. Dose intensity (DI) over the first 6 weeks of treatment, dose modifications anytime (mods), and overall duration of exposure (DOE) to nal-IRI were assessed. All dosing is expressed in terms of the free base.

Results: 257 mPC pts (median age: 67y; IQR 61–74) treated with nal-IRI were identified; DI was calculated for 231 pts with available dose, height, and weight data. Mean DI was 177.8 mg/m^2 (SD: 74.9 mg/m^2). Median DOE was 7.3 (IQR: 3.4 – 17.1) weeks (wks). Median dose at initiation was 69.4 (IQR 56.7–70.2) mg/m^2. Stratified into groups based on median DI (190 mg/m^2), more pts below median DI initiated at a lower dose (LD) (30 - 65 mg/m^2) compared to the pts at/above the median DI (44.4% vs 13.8%). Pts below median DI were also older: median age 70y (IQR 63 - 76) vs 65y (IQR 61 - 72). Mean DI was similar for pts who initiated nal-IRI in 1st/2nd line (176.4 mg/m2; n = 131) vs later lines (179.6 mg/m2; n = 100). In 1st/2nd line pts, median DOE was 8.9 (IQR: 3.1 – 19) wks vs 6.3 (IQR :3.4 – 12.1) wks in 3rd+ line. Median DOE in pts initiated at the recommended dose of 65-75 mg/m^2 (n = 152) was 8.1 wks. DOE in LD (n = 67) and higher dose (75–90 mg/m^2; n = 11) pts was 7.1 and 6.1 wks, respectively. 27.2% of pts experienced a dose mod (18.3% in 1st/2nd line; 8.9% in 3rd+ line). Pts with dose mods had a median DOE of 13.1 vs 6.1 wks in pts without mods.

Conclusions: This real-world analysis showed similar DI results to the NAPOLI-1 trial, while dose mods were slightly lower. Pts with higher DI had longer DOE. Pts who experienced a dose mod, initiated nal-IRI in 1st/2nd line, were at/above median DI had, on average, longer DOE. Larger pt cohort analyses will elucidate dosing patterns and outcomes in nal-IRI treated pts.

Legal entity responsible for the study: Ipsen Biopharmaceuticals.

Funding: Ipsen Biopharmaceuticals.

Disclosure: D. Ahn: Advisory board: Eisai. A. Surinach, F.A. Corvino: Employee: Genesis Research that received funding from Ipsen Biopharmaceuticals to conduct study. A. Valderrama, S. Pulgar: Employee: Ipsen Biopharmaceuticals. K. Mamlouk: Consultant: Ipsen Biopharmaceuticals. All other authors have declared no conflicts of interest.

736P Multicenter, phase II trial of biweekly S-1, leucovorin (LV), oxaliplatin and gemcitabine (SLOG) in metastatic pancreatic adenocarcinoma (mPDAC): Final report of TCOG T1211 study

N-J. Chiang[1], K.K. Tsai[1], J-S. Chen[2], S-H. Yang[3], H-H. Hsiao[4], Y-S. Shan[5], L-T. Chen[6]

[1]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan, [2]School of Medicine, Chung Gung University, Tao Yuan, Taiwan, [3]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan, [4]Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [5]Medical Oncology, National Cheng Kung University, Tainan, Taiwan, [6]Internal Medicine, National Health Research Institutes, Tainan, Taiwan

Background: Our previous studies showed a triplet GOFL regimen consisting of gemcitabine plus modified FOLFOX4 was well-tolerated and moderate active in advanced PDAC, and the feasibility of replacing infusion 5-FU/LV with oral S-1/LV, the SLOG regimen, in a dose-escalating, phase I study. Herein, we report the phase II results of the SLOG in mPDAC patients.

Methods: Patients with chemo-naïve mPDAC, ECOG PS 0-1, and 20-75 y/o of age were eligible. Intravenous fixed-rate infusion of 800 mg/m^2 gemcitabine followed by 2-hr infusion of 85mg/m^2 oxaliplatin on D1 plus oral S-1/LV 35/20 mg/m^2, twice daily, D1-D7 were given Q 14 days as a cycle. The primary endpoint was objective response rate (ORR). Simon's optimal two-stage design was used with estimated p_0=25% and p_1=40%.

Results: Between Jun. 2013 and Oct. 2015, a total of 54 patients were included, with median age of 59 y/o, ECOG PS = 1 in 82%, and the presence of liver metastases in 66.7%. At the cut-off Feb.01, 2017, nine patients remained alive and their median follow-up time was 21.3 months. The ORR was partial response in 22 patients (ORR=40.7%, 95% CI, 28-55%) and stable diseases in 19 patients (35.2%). Long-term disease control rate (stable disease >16 weeks) was 64.8% (95% CI, 51-77%). The median progression-free survival and overall survival was 7.6 (95% CI, 4.4-10.7) and 11.4 (95% CI, 8.1-16.3) months, respectively. One-year and two-year survival rates were 46% and 17%, respectively. The most common treatment-related grade 3-4 adverse events included neutropenia (40.7%), anorexia (14.8%), nausea (11.1%), thrombocytopenia (9.3%), and diarrhea (7.4%).

Conclusions: Current study demonstrated SLOG is a highly active regimen with manageable and favorable safety profiles for mPDAC patients. A randomized phase II trial comparing SLOG vs. modified FOLFIRINOX in advanced PDAC patients is ongoing.

Clinical trial identification: NCT01415713.

Legal entity responsible for the study: Taiwan Cooperative Oncology Group, National Health Research Institutes.

Funding: National Health Research Institutes.

Disclosure: J-S. Chen: Honoraria: Ono, Eli Lilly, MSD, TTY, Novartis. Y-S. Shan: Honoraria: TTY, PharmaEngine. L-T. Chen: Research funding: Novartis, Merck Serono, TTY, Polaris, SyncorePharm, Pfizer, BMS; Honoraria: Ono, Eli Lilly, MSD, PharmaEngine, TTY, SyncorePharm, Novartis, Astra Zeneca, Ipsen; Patents & royalties: ENO-1 mAb/HuniLife; Membership on any entity's Board of directors or advisory committees: PharmaEngine. All other authors have declared no conflicts of interest.

737P A phase II trial of gemcitabine, S-1 and LV combination therapy in patients with advanced pancreatic cancer

K.O. Saito[1], Y. Nakai[1], H. Isayama[2], K. Ishigaki[1], T. Saito[1], N. Takahara[1], S. Mizuno[1], H. Kogure[1], K. Koike[1]

[1]Department of Gastroenterology, The University of Tokyo, Tokyo, Japan, [2]Department of Gastroenterology, Juntendo University, Tokyo, Japan

Background: The aim of this single center, open label, single arm phase II trial was to assess the efficacy and toxicity of gemcitabine, S-1 and leucovorin (LV) combination therapy for advanced pancreatic cancer (UMIN-CTR 000010678).

Methods: Chemotherapy-naïve patients with histologically or cytologically proven advanced pancreatic cancer were enrolled. Gemcitabine was administered at a dose of 1,000 mg/m^2 by 30min infusion on days 1, S-1 40mg/m^2 orally twice daily and LV 25mg orally twice daily on days 1 to 7 every 2 weeks. Primary end point was progression free survival (PFS), and secondary endpoints were overall survival (OS), response rate, disease control rate and adverse events.

Results: A total of 49 patients with advanced pancreatic cancer (19 locally advanced and 30 metastatic) were enrolled between May 2013 and March 2017. Median age was 68 (range, 44-84) and PS was 0 in 26 and 1 in 23. Overall response rate and disease control rate were 32.7% and 87.8%. The median PFS and OS were 10.8 (95% confidence interval [CI], 7.4-13.5) and 20.7 (95% CI 13.0-NA) months with 1-year survival rate of 73.4%. The median PFS of locally advanced and metastatic diseases was 12.7 and 7.4 months, and the median OS of locally advanced and metastatic diseases was 26.1 and 18.8 months, respectively. Conversion surgery was performed in 2 patients among 19 locally advanced diseases. The reasons for treatment failure was disease progression in 31, unacceptable toxicities in 4, deteriorated general conditions in 6, consent withdrawn in 3, others in 3. A second line chemotherapy was introduced in 29 patients. Major Grade 3-4 toxicities were neutropenia (22.4%) and mucositis (14.3%). No toxicity related death was observed.

Conclusions: In this phase II trial, gemcitabine, S-1 and LV combination therapy was tolerable and can potentially be a treatment option for advanced pancreatic cancer.

Legal entity responsible for the study: The University of Tokyo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

738P Antibiotics may enhance the efficacy of gemcitabine treatment for advanced pancreatic cancer

Y. Sunakawa, H. Arai, N. Izawa, T. Mizukami, Y. Horie, A. Doi, M. Hirakawa, T. Ogura, T. Tsuda, T.E. Nakajima

Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan

Background: It has been reported that bacteria can metabolize gemcitabine (gem) into its inactive and contribute to the drug resistance. It was also reported that the resistance was abrogated by cotreatment with antibiotics [Geller LT, et al. Science 2017], in which, many of human pancreatic ductal adenocarcinoma samples contained causal bacteria which potentially mediates tumor resistance to gem. We therefore hypothesized the use of antibiotics may affect clinical outcomes of gem therapy in patients (pts) with pancreatic cancer (PC).

Methods: We retrospectively investigated pts with advanced PC who were treated with gem alone as first-line treatment in our single institute between 2009 and 2017. The association of use of antibiotics before gem treatment with progression-free survival (PFS) and overall survival (OS) was analyzed using Cox proportional hazards model and log-rank test.

Results: One hundred twenty-four pts were treated with gem alone as first-line therapy and had the following characteristics: median age of 72yrs, 59% male, 39%/54%/4%/3% for PS0/1/2/3, 53%/26%/19% for primary tumor of head/body/tail, median PFS of 3.4 months, and median OS of 7.7 months. In 124 pts, 59% used antibiotics before treatment with gem. One hundred pts discontinued due to disease progression, while 24 pts due to toxicity or pts' wish. Pts who received antibiotics had significantly longer PFS than pts who did not receive antibiotics (4.2 vs. 2.1 months, HR 0.64, 95%CI 0.43-0.96, P = 0.029). The association was not statistically significant after multivariate analysis adjusted for PS, tumor location, and number of metastatic sites (HR 0.73, 95%CI 0.45-1.17, P = 0.19). Median OS was numerically longer in pts with use of antibiotics than in pts without antibiotics (8.0 vs. 5.5 months).

Conclusions: Our study indicated that antibiotic use before gem therapy was associated with favorable outcome in pts with advanced PC treated with gem. These findings warrant further exploratory studies and suggest scientific approach to identify antibiotics as an enhancer for gem.

Legal entity responsible for the study: Takako Eguchi Nakajima.

Funding: Has not received any funding.

Disclosure: Y. Sunakawa: Honoraria: Taiho Pharmaceutical, Chugai Pharma, Yakult Honsha, Takeda, Merck Serono, Bayer Yakuhin, Eli Lilly Japan, Sanofi. N. Izawa: Honoraria: Taiho Pharmaceutical Co., Ltd., Merck Serono Co., Ltd. T.E. Nakajima: Personal financial interests: Eli Lilly, Sanofi, Chugai, Sawai, Bayer, Bristol, Taiho, Merck, Ono, Takeda, Mochida, MSD; Institutional financial interests: Ono, Taiho, A2 Health Care, JCRO, Daiichi-Sankyo, Mediscience Planning. All other authors have declared no conflicts of interest.

739P Quality of life (QoL) in patients with metastatic pancreatic cancer receiving first-line Nab-paclitaxel/gemcitabine chemotherapy: Results of the large QoL study AIO-QoliXane/PARAGON

C. Schönherr[1], T.O. Götze[2], G. zur Hausen[3], A. Reichart[4], C. Pauligk[5], R. Schlag[6], G.M. Siegler[7], S. Dörfel[8], A. Aldaoud[9], L. Hahn[10], J. Schubert[11], M-O. Zahn[12], H-G. Höffkes[13], M. Reiser[14], M. Koenigsmann[15], W. Blau[16], O. Waidmann[17], N. Homann[18], J. Trojan[19], S-E. Al-Batran[2]

[1]IKF Klinische Krebsforschung GmbH, IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest, Frankfurt, Germany, [2]Institute of Clinical Cancer Research (IKF), Nordwest-Krankenhaus, Frankfurt am Main, Germany, [3]IKF Klinische Krebsforschung GmbH, Nordwest-Krankenhaus, Frankfurt am Main, Germany, [4]Institut für Klinisch-Onkologische Forschung, Krankenhaus Nordwest gGmbH, Frankfurt am Main, Germany, [5]Institut für Klinisch-Onkologische Forschung, Nordwest-Krankenhaus, Frankfurt am Main, Germany, [6]Hämatoonkologische Praxis Dr. R. Schlag, Hämatoonkologische Praxis Dr. R. Schlag, Berlin, Bayern, Germany, [7]Medizinische Klinik 5, Klinikum Nuernberg Nord, Nürnberg, Germany, [8]Onkozentrum Dresden, Onkozentrum Dresden, Dresden, Germany, [9]Pankreaszentrum Leipzig, HELIOS Park-Klinikum, Leipzig, Germany, [10]Dokusan Gesellschaft für med. Studien, Dokusan Gesellschaft für med. Studien, Herne, Germany, [11]Klinik für Innere Medizin II, Elblandklinikum Riesa, Riesa, Germany, [12]MVZ Onkologische Kooperation Harz, MVZ Onkologische Kooperation Harz, Goslar, Germany, [13]MVZ Osthessen, MVZ Osthessen, Fulda, Germany, [14]PIOH, PIOH (Köln Zentrum) - Praxis Internistischer Onkologie und Hämatologie, Cologne, Germany, [15]Gesellschaft für Medizinstatistik u. Projektentwicklung, MediProjekt Hannover, Hannover, Germany, [16]Medizinische Klinik IV/V, Universitätsklinik Giessen, Giessen, Germany, [17]Klinische Studienzentrale, Universitätsklinikum Frankfurt(Johannes-Wolfgang Goethe Institute), Frankfurt am Main, Germany, [18]Med. Klinik II, Klinikum Wolfsburg, Wolfsburg, Germany, [19]University Cancer Center, Universitätsklinikum Frankfurt(Johannes-Wolfgang Goethe Institute), Frankfurt am Main, Germany

Background: Nab-paclitaxel/gemcitabine (NPG) is standard first-line therapy for metastatic pancreatic cancer (mPC), but the pivotal study did not include QoL analyses.

Methods: QoliXane/PARAGON is a platform for Outcome, Quality of Life, and Translational Research on Pancreatic Cancer. In this prospective QoL-study, patients (pts) were recruited from 95 German centers. QoL was prospectively measured (prior to and every month thereafter): therapy and efficacy were prospectively collected. QoL and efficacy endpoints were analyzed in the intention-to-treat population (ITT), defined as all pts who were enrolled. The primary endpoint was the rate of pts without deterioration of QoL/Global Health Score (QoL/GHS) at 3 mos.

Results: 601 pts were included. Median progression-free survival was 6 mos (95% CI: 5.26, 6.25). Median overall survival (OS) was 10 mos (8.22, 11.74). 1-year OS was 41%. Median survival by ECOG PS of 0, 1, 2, and 3 was 11.1 mos, 8.9 mos, 4.8 mos, and 2.1 mos (p<.0001). The KM-analysis showed that 61% and 41% of pts had maintained QoL/GHS after 3 and 6 mos, respectively. Median time to deterioration of QoL/GHS was 4.7 mos [4.04, 5.59]. Mean QoL/GHS improved from 46.1 at baseline to 52.8 after 6 mos. In the QoL response analysis, 35%, 37% and 28% of evaluable pts had improved, stable and worse QoL/GHS after 3 mos, respectively. In the Cox regression analysis, a 10-point increase in baseline QoL/GHS correlated to 13% decreased risk of death (HR = 0.87; 0.83-0.91; p<.0001).

Conclusions: The QoliXane/PARAGON is among the largest studies on QoL of pancreatic cancer ever conducted. It shows that a relevant group of patients have improved or maintained QoL after 3 and 6 months and that QoL is a predictor of patient's outcome.

Clinical trial identification: NCT02691052.

Legal entity responsible for the study: IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest.

Funding: Celgene.

Disclosure: C. Schönherr, G. zur Hausen: Celgene. T.O. Götze: COIs: Lilly, MSD, BMS, Celgene, Shire, Bayer. S-E. Al-Batran: Advisory role: Merck, Roche, Celgene, Lilly, Nordic Pharma, Bristol-Myers Squibb, MSD Sharp & Dohme: Speaker: Roche, Celgene, Lilly, Nordic Pharma, AIO gGmbH, MCI, promedicis, Forum für Medizinische Fortbildung; CEO/founder of IKF Klinische Krebsforschung GmbH; Research grants: Sanofi, Merck, Roche, Celgene, Vifor, Medac, Hospira, Lilly, German Cancer Aid (Krebshilfe), German Research Foundation, the Federal Ministry of Education and Research. All other authors have declared no conflicts of interest.

740P Final results of a phase II quality of life (QOL) randomized, cross-over (CO) study with gemcitabine (Gem) and nab-paclitaxel (n-P) in locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC): QOLINPAC

G. Chiritescu[1], K. Dumon[1], C. Verslype[1], G. Houbiers[2], M. Peeters[3], J. Janssens[4], D. van Daele[5], S. Laurent[6], J. Arts[7], K. Hendrickx[8], I. Borbath[9], M. Ferrante[10], F.M. Bastin[11], J-C. Goeminne[12], J-L. van Laethem[13], E. Vanderstraeten[14], J. Decaestecker[15], W. van Vaerenbergh[16], B. Delhougne[17], E. Van Cutsem[1]

[1]Digestive Oncology, University Hospitals Leuven, Leuven, Belgium, [2]Oncology, Centre Hospitalier Chrétien (CHC), Liège, Belgium, [3]Medical Oncology, U.Z.A. University Hospital Antwerp, Edegem, Belgium, [4]Gastroenterology, A.Z. Turnhout, Turnhout, Belgium, [5]Gastroenterology, CHU Sart-Tilman, Liege, Belgium, [6]Gastroenterology, UZ Gent, Ghent, Belgium, [7]Gastroenterology, AZ Sint Lucas, Brugge, Assebroek, Belgium, [8]Gastroenterology, Onze Lieve Vrouw Ziekenhuis Aalst, Aalst, Belgium, [9]Hepato-Gastroenterology, Cliniques Universitaires St. Luc, Brussels, Belgium, [10]Gastroenterology, A.Z. Sint Maarten, Mechelen, Belgium, [11]Gastroenterology, CHU de Charleroi - Site Vesale, Montigny-le-Tilleul/Charleroi, Belgium, [12]Oncology, Clinique Ste Elisabeth, Namur, Belgium, [13]Gastroenterology, Erasme University Hospital-(Universite Libre de Bruxelles), Brussels, Belgium, [14]Gastroenterology, A.Z. Maria Middelares, Ghent, Belgium, [15]Gastroenterology, AZ Delta campus Wilgenstraat, Roeselare, Belgium, [16]Digestive Oncology, Heilig Hart Ziekenhuis, Lier, Belgium, [17]Gastroenterology, CHR Citadelle, Liege, Belgium

Background: QOL parameters may be predictive of treatment efficacy in PDAC.

Methods: Eligible consenting patients (pts) received n-P/Gem or Gem in standard regimens. CO was possible at progression. Monthly EORTC QLQ-C30 v3.0 QOL questionnaires were used. Deterioration-free rate of global health status (GHS) at 3 months (mths) was the primary endpoint. Safety, efficacy and molecular studies on blood were secondary endpoints.

Results: One hundred forty-six pts (125 metastatic), median age 65, were included in 17 hospitals of the Belgian Group of Digestive Oncology network between May 2014 and Nov 2015 and randomized to n-P/Gem (72) or Gem (74); 37 crossed-over. Median duration on treatment was 5 mths (0-28). Ninety-nine pts (68%) experienced at least one serious adverse event; 6 events had fatal outcome, one was possibly related to Gem (sepsis). Gastrointestinal toxicity and infections were frequent. Hemolytic uremic syndrome occurred in 5 pts. Overall, 1465 QOL questionnaires were completed; 85% of pts responded to a series of at least three. Deterioration-free rate of GHS at 3 mths was 83% (60/72) with n-P/Gem, 60% (28/47) with Gem alone and 96% (26/27) after CO. Median times to definitive deterioration were 12.8, 8.9 and 12.3 mths respectively. Baseline GHS scores correlated at 0.05 significance level with survival time in the n-P/Gem group. Other QOL indicators showed equivalent patterns. Tumour response was locally assessed in 43% of pts (95%CI 31-55) with n-P/Gem, 19% (95%CI 6-32) with Gem and 24% (95%CI 10-39) in the CO group (p = 0.006) with 2 pts in complete response. Median PFS was 6.8 mths (95%CI 5.5-8.1) in all pts, with 7.4 in n-P/Gem, 7.2 in Gem and 5.4 mths in CO (1st progression). Median PFS for 2nd progression in CO was 10.8 mths. Overall survival was 11.9 mths (95%CI 10-14) with 10.7, 8.8 and 13 mths in the three groups.

Conclusions: Survival was long and response rates significantly higher in pts receiving the combination. Pts receiving n-P/Gem reported better quality of life scores for longer duration compared to pts on Gem alone. QOL analyses and translational studies will be presented at the congress. Academic study with support from Celgene.

Clinical trial identification: EudraCT: 2013-004101-75, NCT02106884.

Legal entity responsible for the study: Academic study governed by the Belgian Group of Digestive Oncology network. Sponsored and coordinated by University Hospitals Leuven.

Funding: Celgene.

Disclosure: I. Borbath: Research grants: Celgene. E. Van Cutsem: Grants, Research support: Amgen, Bayer, Boehringer, Celgene, Ipsen, Lilly, MSD, Merck, Novartis, Roche, Servier; Honoraria, Consultation fees: Bayer, Celgene, Lilly, Novartis, Servier. All other authors have declared no conflicts of interest.

741P Health-related quality of life (HRQoL) in patients with early-stage pancreatic cancer (ESPC) receiving adjuvant or neoadjuvant chemotherapy (A/NAC): A systematic literature review (SLR)

T. Macarulla Mercade[1], A. Hendifar[2], C-P. Li[3], M. Reni[4], H. Riess[5], M.A. Tempero[6], A. Dueck[7], M.F. Botteman[8], C. Deshpande[8], E. Lucas[8], D-Y. Oh[9]

[1]Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [2]IM/Hematology/Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [3]Medical Oncology, Taipei Veterans General Hospital, Taipei City, Taiwan, [4]Medical Oncology, Ospedale San Raffaele Srl, Milan, Italy, [5]Medical Oncology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [6]Medical Oncology, University of California, San Francisco, Helen Diller Comprehensive Cancer Center, San Francisco, CA, USA, [7]Health Sciences Research, Mayo Clinic, Phoenix, AZ, USA, [8]Medical, Pharmerit International, LP, Bethesda, MD, USA, [9]Medical Oncology, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

Background: Few studies have evaluated HRQoL in patients with ESPC (resectable or borderline resectable) who received A/NAC. This SLR aimed to summarize the available evidence on HRQoL in this population.

Methods: Key electronic databases (all years), conference abstracts (2013-2017), and clinical trial registries were searched according to PRISMA guidance to identify relevant studies reporting HRQoL as assessed by patient-reported outcomes measures (PROMs) in A/NAC for ESPC. HRQoL scores were compared with reference values (ie, norms) and assessed longitudinally when possible. Minimally important difference (MID) estimates for the most frequently used PROMs were also assessed.

Results: Of 645 identified records, 37 PROMs and HRQoL outcomes studies were retained. The EORTC QLQ-C30 and/or QLQ-PAN26 were used in 31 studies; other PROMs were used in 11 studies, including the Functional Assessment of Cancer Therapy (n = 4), 36-Item Short Form Survey (n = 2), and the Center for Epidemiologic Studies Depression Scale (n = 2). At baseline (before and/or immediately after surgery), EORTC QLQ-C30 global health status/QoL scores for patients with ESPC were similar to reference values for PC but lower than those for all cancers. Among studies that reported QoL over time, longitudinal QoL trends varied: 4 studies reported improvement from baseline, whereas 4 studies reported initial declines, upon which QoL increased to or above baseline (n = 3) or below baseline (n = 1) within 3 to 6 months. An MID of 10 was identified for EORTC QLQ-C30. An MID for QLQ-PAN26 does not seem to have been comprehensively assessed to date.

Conclusions: The EORTC QLQ-C30 and QLQ-PAN26 are the most commonly used HRQoL PROMs for studies of A/NAC in ESPC. Poor HRQoL was reported by EORTC QLQ-C30 global health status/QoL scores, indicating a high unmet need. Some studies indicated improved HRQoL over time; however, this may reflect survivor selection bias. The MID for QLQ-C30 may be useful in understanding the clinically relevant impact of ESPC treatment on HRQoL. Future research should validate the QLQ-PAN26 and establish its MID in A/NAC for ESPC.

Editorial acknowledgement: Medical writing assistance was provided by Narender Dhingra, MBBS, PhD, MediTech Media, Ltd, funded by Celgene Corporation. All listed authors were fully responsible for all content and editorial decisions for this abstract.

Legal entity responsible for the study: Celgene Corporation.

Funding: Celgene Corporation.

Disclosure: M. Reni: Grants, Personal fees, Non-financial support: Celgene; Grants and personal fees: Baxalta, Merck, Serono, Helsinn; Personal fees: Lilly, Pfizer, Baxalta, Merck, Serono, Astra Zeneca, Novocure, Halozyme, Novartis, Shire, during the conduct of the study. H. Riess: Personal fees: Celgene, Roche, Shire, outside the submitted work. M.A. Tempero: Consultant: AbbVie, Advance Medical, BioPharm Communications, BMS, Celgene, Eisai, Ignyta, Pharmacyslics, Pharmcyte Biotech, Tocagen, Inc.; Ad Boards: AstraZeneca, CPRIT, Immunovia; Research contract: Halozyme. M.F. Botteman: Grants, Personal fees: Celgene, during the conduct of the study; Grants, Personal fees: Pharmaceutical and device manufacturers, outside the submitted work. C. Deshpande: Employee: Pharmerit International, which received research funding from Celgene corporation for this study. E. Lucas: Grants: Celgene, during the conduct of the study; Grants: Pharmaceutical and device manufacturers, outside the submitted work. All other authors have declared no conflicts of interest.

742P Outcome following centralisation of pancreatic cancer care in Ireland

R. Abdul Rahman[1], M. Moriarty[2], G. McVey[2], P. Ridgway[3], D. Maguire[3], E. Hoti[3], J. Geoghegan[3], K. Conlon[3], R. McDermott[1]

[1]Medical Oncology, St. Vincent's University Hospital, Dublin, Ireland, [2]Radiation Oncology, St. Luke's Hospital, Rathgar, Ireland, [3]Hepatobiliary Surgery, St Vincents University Hospital, Dublin, Ireland

Background: Centralisation of pancreatic cancer surgery led to increased resection rates and significantly better survival rates in high volume centres (Gooiker et al, Br J Surg 2014). Pancreas cancer care was centralised to two high volume cancer centres in Ireland since 2010. The National Cancer Registry (NCRI) is a publicly appointed body, established in 1991, to collect and classify information on all cancer cases which occur in Ireland. We analysed these data with the objective to examine the outcomes of pancreatic cancer care since the centralisation of pancreatic cancer surgery in Ireland.

Methods: Pancreatic cancer data have been collected by NCRI since 1994. Only those with stage 1 – 3 adenocarcinoma of the pancreas (PDAC) were included in the final analyses. Descriptive statistics, Pearson chi-square test and survival analysis using Kaplan Meier curve with log-rank test and cox regression was performed.

Results: Between Jan 1994 and Dec 2013, of the 8230 patients with pancreatic cancer identified from the NCRI database, 4298 pts had histologically proven adenocarcinoma. Among these, 1177/27% of patients (pts) had stage 1 – 3 disease. 52% of these were male and 74% of pts were over 60 years of age. Stage 1, 2 and 3 disease comprised 25%, 32% and 42% of pts respectively. Overall 48 % of pts had surgery. Pre- and post-2010 resection rates increased from 44% to 49% ($p = 0.14$). 44% of pts had chemotherapy with significantly increased chemo utilisation post-2010, 39% vs 54% ($p < 0.0005$). 21% of pts had radiotherapy. Pre- and post- radiation rates were 19% versus 23% ($p = 0.12$) respectively. Overall survival (OS) for all pts were 9.0 mos (95% CI 8.1 – 9.9). This significantly improved post-centralisation of care, 8 mos to 14 mos, HR 0.67 (95% CI 0.58-0.78, $p < 0.0005$). In those who underwent resection, OS was 17 mos vs 25 mos pre- and post-2010, HR 0.66 (95% CI 0.51-0.84, $p = 0.01$). Among resected pts, 52% and 20% had chemo- and radio-therapy within the first year respectively. Also noted was that there were significantly fewer pts who received no treatment at all, 24% vs 35%, $p < 0.0005$.

Conclusions: Centralisation of PDAC surgery in Ireland has resulted in an improvement in utilisation rates of surgery, chemotherapy and radiotherapy leading to significantly improved overall survival for patients.

Legal entity responsible for the study: Rozana Abdul Rahman and Ray McDermott.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

743P Initial treatment and survival in a national unselected Danish cohort of 4161 patients with pancreatic cancer

L.S. Rasmussen[1], B. Vittrup[2], M. Ladekarl[3], P. Pfeiffer[4], M.K. Yilmaz[1], L.Ø. Poulsen[1], K. Østerlind[5], H. Skuladottir[6], C.P. Hansen[7], M.B. Mortensen[8], F.V. Mortensen[9], M. Sall[10], U.G. Falkmer[1], C. Fristrup[11]

[1]Department of Oncology, Clinical Cancer Research Center, Aalborg University Hospital; Department of Clinical Medicine, Faculty of Medicine, Aalborg University, Aalborg, Denmark, [2]Department of Oncology, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark, [3]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [4]Department of Oncology, Odense University Hospital, Odense, Denmark, [5]Department of Oncology, North Sealand Hospital, Hillerød, Denmark, [6]Department of Oncology, Herning Hospital, Herning, Denmark, [7]Department of Surgical Gastroenterology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [8]Department of Surgery, Odense Pancreas Center (OPAC), Odense University Hospital, Odense, Denmark, [9]Department of Surgical Gastroenterology, Aarhus University Hospital, Aarhus, Denmark, [10]Department of Surgical Gastroenterology, Aalborg University Hospital, Aalborg, Denmark, [11]Department of Surgery, Odense University Hospital; Danish Pancreatic Cancer Database, Odense, Denmark

Background: Nationwide data on the effect of primary treatment on median overall survival (mOS) in an entire unselected population of patients (pts) with pancreatic cancer (PC) have not been reported before. The aim of the present study was to investigate the effect of initial treatment on mOS in all incident pts with PC in Denmark in a recent five-year period (2011 to 2016).

Methods: From 1 May 2011 to 30 April 2016, 4260 pts diagnosed with PC were identified in the national Danish Pancreatic Cancer Database. Last follow up was 10 September 2017. Excluded were 99 pts (2%), 56 due to combined preoperative chemotherapy followed by resection, 22 due to other malignancies, 13 due to incorrect registration of treatment, 6 pts treated with unknown chemotherapy and 2 were lost to follow up, leaving 4161 pts included. The mOS was analysed from the date of the initial treatment, either resection or chemotherapy or from the date of diagnosis in case of best supportive care (BSC).

Results: Initial treatment and mOS for all 4161 pts.

Table: 743P

Treatment	Pts, No.	mOS, months	95% CI
Resection*			
N +	466	17.5	15.4-20.1
N-	215	36.9	28.6-44.7
Chemotherapy			
Gem	958	5.1	4.8- 5.6
FOLFIRINOX	414	10.0	8.9-11.0
GemCap	125	8.4	6.8-9.8
GemS1	111	9.0	7.2-10.3
GemPac	85	7.1	5.5-9.7
Others	53	9.3	8.2-14.0
BSC	1696	1.6	1.5-1.8

Abbreviations: CI: confidence interval, N: lymph node status, without – or with +, Gem: gemcitabine, FOLFIRINOX: 5-flourouracil, leukovorin, irinotecan and oxaliplatin, Cap: capecitabine, S1: tegafur/gimeracil/oteracil, Pac: nab-paclitaxel, others: other regimens. *There were 38 pts without histopathological reports on lymph node status.

Conclusions: The initial resected lymph node negative pts had the longest survival; double that of lymph node positive pts. Pts initially treated with chemotherapy had slightly shorter mOS than found in randomized trials, reflecting patient characteristics in an unselected population. The outcome of gemcitabine monotherapy was poor, possibly reflecting less treatment effect and selection of less fit pts. The BSC group was larger than expected and further investigations, particularly in early diagnosis of PC are of utmost importance.

Legal entity responsible for the study: The authors.

Funding: The Axel Muusfeldt foundation.

Disclosure: All authors have declared no conflicts of interest.

744P Trends of care of non-metastatic pancreas cancer patients in Ireland

R. Abdul Rahman[1], G. McVey[2], M. Moriarty[2], D. Maguire[3], E. Hoti[3], P. Ridgway[3], K. Conlon[3], J. Geoghegan[3], R. McDermott[1]

[1]Medical Oncology, St. Vincent's University Hospital, Dublin, Ireland, [2]Radiaiton Oncology, St. Luke's Hospital, Rathgar, Ireland, [3]Hepatobiliary Surgery, St Vincents University Hospital, Dublin, Ireland

Background: Surgery offers the only chance of cure in non-metastatic pancreatic cancer. However, chemo- and radio-therapy also play important roles in pancreatic cancer care. How each of these different modalities of treatment impact on pancreatic cancer outcome is unclear. The National Cancer Registry (NCRI) is a publicly appointed body, established to collect and classify information on all cancer cases which occur in Ireland. We analysed these data with the objective to examine the trend of care of stage 1 to 3 pancreas cancer in Ireland.

Methods: Pancreatic cancer data have been collected by NCRI since 1994. Only those with stage 1 – 3 adenocarcinoma of the pancreas (PDAC) were included in the final analyses. Descriptive statistics, Pearson chi-square test and survival analysis using Kaplan Meier curve with log-rank test and cox regression was performed.

Results: Between Jan 1994 and Dec 2013, of the 8230 patients with pancreatic cancer identified from the NCRI database, 4298 pts had histologically proven adenocarcinoma. Among these, 1177/27% of patients (pts) had stage 1 – 3 disease. 52% were male and 74% of pts were over 60 years of age. Stage 1, 2 and 3 disease comprised 25%, 32% and 42% of pts respectively. Overall 48 % of pts had surgery, 44% had chemotherapy and 21% had radiotherapy. 364, 31% pts did not have any therapy at all. Compared to those who did not have any treatment, there was an incremental benefit in overall survival (OS) with the more number of different modalities of treatment involved (Table). OS was 3 mos with no treatment, 8 mos with either chemo or radiation (HR 0.57), 11 mos with chemo and radiation (HR 0.46), 18 mos with surgery only (HR 0.27) and 20 mos with surgery with chemo and/or radiation therapy (HR 0.24).

Table: 744P

	N	OS	HR
No treatment	364, 31%	3 months	
Multimodality therapies including surgery	287, 25%	20 months	0.24 (95% CI: 0.20 – 0.28)
Surgery only	245, 21%	18 months	0.27 (95% CI: 0.22 – 0.32)
Multimodality therapy (no surgery)	95, 8%	11 months	0.46 (95% CI: 0.36 – 0.58)
Single modality therapy (no surgery)	179, 16%	8 months	0.57 (95% CI: 0.48 – 0.69)

Conclusions: Multimodality therapy with surgery improves OS in non-metastatic pancreatic cancer with incremental benefit seen from even single modality therapy.

Legal entity responsible for the study: Rozana Abdul Rahman, Ray McDermott.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

745P Anti-hypertensive medication, sRAGE, and risk of pancreatic cancer: Results from the women's health initiative study

Z. Wang[1], D.L. White[2], L. Chen[3], E.A. Whitsel[4], P.A. Richardson[3], J. Garcia[5], H.B. El-Serag[3], L. Jiao[3]

[1]Dan L Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA, [2]Center for Translational Research on Inflammatory Diseases, Michael E. DeBakey VA Medical Center, Houston, TX, USA, [3]Center for Innovations in Quality, Effectiveness and Safety (IQuESt), Michael E. DeBakey VA Medical Center, Houston, TX, USA, [4]Gillings School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]Section of Endocrinology, Department of Medicine, University of Washington, Seattle, WA, USA

Background: Pancreatic cancer is the 4th leading cause of cancer death in the United States. With its anti-inflammatory property, soluble receptor for advanced glycation end-product (sRAGE) has been associated with lower risk of pancreatic cancer. Anti-hypertensive (anti-HT) medications were shown to modulate sRAGE levels and AGE/RAGE signaling pathway. However, few large-scale population based study have evaluated the associations between antihypertensive medications and risk of pancreatic cancer.

Methods: A total of 145,551 postmenopausal women aged 50 to 79 years with no prevalent cancer from Women Health Initiative (WHI) were included with a mean follow-up of 13.8 year. Medication data including product and generic name, duration of use, and dosage form were collected at baseline recruitment (1993-98). We examined four anti-HT drugs including β-blockers, diuretics, angiotensin converting enzyme inhibitors (ACEi) and calcium channel blockers (CCBs). Serum levels of sRAGE were measured in a subset of 1,466 study participants using immunoassay. Cox proportional hazard regression model was performed to obtain hazard ratio (HR) and its 95% confidence interval (CI) for each anti-HT medication use and its duration of use in association with risk of pancreatic cancer.

Results: By August 29, 2014, a total of 841 incident pancreatic cancer cases were ascertained through annual self-administered questionnaires and confirmed by central adjudication. Increased risk of incident pancreatic cancer was found among ever users of short-acting CCB (HR = 1.66, 95% CI: 1.20-2.29) and long-term (> 3 years) users of short-acting CCB (HR = 2.07, 95% CI: 1.42-3.02) compared to ever users of other anti-HT medications. Average sRAGE levels were lower in short-acting CCB ever users than those who took other anti-HT medication (1,158 pg/ml versus 1,446 pg/ml, P = 0.032).

Conclusions: We found a positive association between short-acting CCB use and risk of incident pancreatic cancer in postmenopausal women. Future studies are warranted to confirm these findings and elucidate potential mechanisms by which short-acting CCBs may influence development of pancreatic cancer, such as modulating RAGE signaling pathway.

Legal entity responsible for the study: Li Jiao.

Funding: National Cancer Institute.

Disclosure: All authors have declared no conflicts of interest.

746P Usefulness of the first screening using apolipoprotein A2 isoforms as the enrichment strategy for pancreatic cancer and its risk diseases

Y. Sato[1], T. Kobayashi[1], S. Nishiumi[1], S. Okaya[2], M. Yoshida[1], Y. Kodama[1], K. Nagashima[3], K. Honda[2]

[1]Gastroenterology, Kobe University Graduate School of Medicine, Kobe, Japan, [2]Department of Biomarkers for Early Detection of Cancer, National Cancer Center Hospital, Tokyo, Japan, [3]Research Center for Medical and Health Data Science, The Institute of Statistical Mathematics, Tokyo, Japan

Background: We recently reported the usefulness of apolipoprotein A2 isoforms (apoA2-i) as a plasma/serum biomarker for the early detection of pancreatic cancer (PC) and its risk diseases, and the level of ApoA2-ATQ/AT, which is one of apoA2-i, was significantly decreased in early stage PC and risk diseases. To evaluate the possibility of usefulness as the screening biomarker, we prospectively tested the performance of ApoA2-ATQ/AT as a first screening method for PC and its risk diseases in general population.

Methods: Study participants were prospectively enrolled from the subjects of medical checkup at 6 institutions between Oct 2015 and Jan 2017. We measured the plasma level of ApoA2-ATQ/AT by using ELISA, and all participants with the positive results from the level of ApoA2-ATQ/AT (ApoA2-ATQ/AT < 35 μg/mL) were recommended for 2nd examination with contrast enhanced-CT (CECT), MRI, or EUS.

Results: Among a total of 5,120 participants registered in this study, 83 were positive (Positive rate: 1.6%). In the 83 subjects with the positive results, 55 (66.3%) underwent 2nd examination. Finally, pancreatic diseases were detected in 23 (41.8%) of 55. They included 1 PC, 12 pancreatic cystic lesions (PCL), and 3 chronic pancreatitis (CP). Furthermore, 14.5% of ApoA2-ATQ/AT positive subjects had abnormal ultrasonographic findings in the pancreas, while the subjects with ultrasonographic abnormalities of the pancreas under a medical checkup were 3.2% of the participants who underwent transabdominal ultrasonography. Taken together, ApoA2-ATQ/AT could significantly accumulate the subjects with abnormal ultrasonographic findings by 4.53 times in comparison with a normal medical checkup for general population.

Conclusions: Plasma ApoA2-ATQ/AT as a first screening method in general population could improve an efficiency of detection of PC and its high-risk diseases.

Legal entity responsible for the study: Kobe University Graduate School of Medicine, Department of Gastroenterology.

Funding: Japan Agency for Medical Research and Development.

Disclosure: All authors have declared no conflicts of interest.

747P Survival-associated factors and a prognostic nomogram in resected pancreatic cancer: A large international population-based cohort study

L. Huang[1], Y. Balavarca[2], L. van der Geest[3], V. Lemmens[3], L. van Eycken[4], H. De Schutter[5], T.B. Johannesen[6], V. Zadnik[7], M. Primic-Žakelj[7], M. Mägi[8], R. Grützmann[9], M.G. Besselink[10], P. Schrotz-King[2], H. Brenner[1], L. Jansen[1]

[1]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany, [2]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany, [3]Netherlands Cancer Registry (NCR), Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, Netherlands, [4]Belgian Cancer Registry (BCR), Brussels, Belgium, [5]Research Department, Belgian Cancer Registry, Brussels, Belgium, [6]Registry Department, The Cancer Registry of Norway (CRN), Oslo, Norway, [7]Epidemiology and Cancer Registry, Institute of Oncology Ljubljana, Ljubljana, Slovenia, [8]Estonian Cancer Registry, National Institute for Health Development, Tallinn, Estonia, [9]Department of Surgery, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany, [10]Dutch Pancreatic Cancer Group (DPCG), Department of Surgery, Cancer Center Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background: Pancreatic cancer (PaC) remains extremely lethal worldwide even after resection. This large international population-based study aimed at exploring factors associated with survival in resected PaC, and at developing and globally validating a survival-predicting nomogram.

Methods: Data of PaC patients resected in 2003-2014 were obtained from multiple European national cancer registries and the US SEER-18 Program. Multivariable Cox proportional hazards models were constructed to investigate the associations of patient and tumor characteristics with overall survival. Prognostic factors remaining after backward selection in SEER-18 were used to build a nomogram, which was subjected to bootstrap internal validation and external validation using the European databases. Predictive accuracy was assessed using the concordance-index.

Results: Totally 24,863 resected PaC patients were included, with median survival of 12-19 months and 3-year survival rates of 14%-28%. In main analysis, patient age, tumor T, N, and M stages, histology, and differentiation were significantly associated with survival, with country-specific association patterns and strengths. Additionally, hospital type, tumor size, harvested lymph node number, performance status, and certain comorbidities were associated with survival in countries with available information. A nomogram incorporating the backward-selected variables in the main analysis was established. Calibration curves showed good agreement between nomogram-prediction and actual observation. The concordance-index of the nomogram was significantly higher than that of the TNM staging for predicting survival.

Conclusions: In these international population-based cohorts, resected PaC patients have distinct characteristics independently associated with survival. A personalized postoperative survival-predicting nomogram is established and internationally validated, which would be practical and helpful clinically and aid to patient stratification in international studies.

Legal entity responsible for the study: Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ).

Funding: German Cancer Aid (Deutsches Krebshilfe).

Disclosure: All authors have declared no conflicts of interest.

748P Predicting survival of pancreatic cancer using supervised machine learning

M.H. Osman

Faculty of Medicine, Zagazig University, Zagazig, Egypt

Background: Pancreatic cancer is one of the major deadliest cancers, ranking fourth among causes of cancer-related deaths. Pancreatic cancer patients suffer from a poor prognosis with a 5-year survival rate of only 6%. Predicting pancreatic cancer survival is challenging due to different tumor characteristics, treatments and patient populations. Reliable predictions can help in achieving more personalized care and better management. In this study we test the ability of machine learning to predict pancreatic cancer survival.

Methods: Pancreatic cancer patients were identified through the Surveillance, Epidemiology and End Results database (2010-2014). Clinical data for patients were extracted including: age, sex, race, tumor site, tumor histology, grade, cancer sequence number, TNM stage, surgery, tumor size, tumor extension, and survival months. Patients' records were randomly divided into a training set (80%) and a validation set (20%) to predict survival at 6, 12 and 24 months. Different supervised machine learning models were tested to identify models with best predictions.

Results: We identified 14631 patients with median survival of 13 months. Random Forest algorithm achieved better results compared to other tested models. For evaluating model performance, the Area Under the Receiver Operating Characteristic Curve (AUC) of survival prediction was calculated. The trained model yielded AUCs of 85.3% at 6 months, 84.6% at 12 months and 83.2% at 24 months. The most important characteristics which influenced model prediction were: age at diagnosis (19.9%), tumor size (18.5%), surgery (14.6%), and tumor extension (8.4%).

Table: 748P Performance metrics of the trained machined learning model

	Area Under Curve (AUC)	Precision (positive predictive value)	Accuracy	Recall (sensitivity)	F1 Score
6-months Survival	85.3%	81%	81.6%	82%	81%
12-months Survival	84.6%	78%	77.8%	78%	78%
24-months Survival	83.2%	80%	80.1%	81%	80%

Conclusions: Predicting survival of patients with pancreatic cancer can be achieved using machine learning with good performance of prediction. Improved survival prediction can help in making better treatment decisions and planning social and care needs.

Legal entity responsible for the study: Mohamed H. Osman.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

749P The prognostic value of the modified glasgow prognostic score (mGPS) in predicting overall survival (OS) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) receiving liposomal irinotecan (nal-IRI)+5-fluorouracil and leucovorin (5-FU/LV)

L-T. Chen[1], T.M. Macarulla[2], B. Belanger[3], B. Mirakhur[4], F.A. de Jong[5], J. Siveke[6]

[1]Internal Medicine, National Health Research Institutes – National Institute of Cancer Research, Tainan, Taiwan, [2]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital (HUVH), Barcelona, Spain, [3]Biometry R&D, Ipsen Biopharmaceuticals,Inc., Cambridge, MA, USA, [4]Medical Affairs, Ipsen Biopharmaceuticals,Inc., Basking Ridge, NJ, USA, [5]Medical Affairs, Shire GmbH, Zug, Switzerland, [6]Division of Solid Tumor Translational Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany

Background: mGPS has been identified as a prognostic factor of OS in patients with pancreatic cancer. Here we report the association between mGPS and OS in a post-hoc analysis of the NAPOLI-1 study (NCT01494506), which demonstrated improved

survival for nal-IRI+5-FU/LV vs 5-FU/LV in the treatment of patients with mPDAC previously treated with gemcitabine-based therapy.

Methods: All patients treated in the NAPOLI-1 study with available baseline plasma Creactive protein (CRP) and albumin data (data cutoff: Nov 16, 2015) were included in this post-hoc analysis. Eligible patients were stratified by mGPS (mGPS-0: CRP ≤10 mg/L regardless of albumin level; mGPS-1: CRP >10 mg/L, albumin ≥35 g/L; and mGPS-2: CRP >10 mg/L, albumin <35 g/L). OS was assessed in individual and pooled treatment arms. A stepwise Cox regression model of OS was used to evaluate the prognostic significance of mGPS.

Results: Baseline plasma C-reactive protein and albumin data was available for N = 184 patients: mGPS-0, n = 79; mGPS-1, n = 88; mGPS-2, n = 17. For patients in pooled treatment arms, median OS was worse for the mGPS-1 group than for the mGPS-0 group (4.0 vs 8.0 months, respectively), but was comparable between the mGPS-2 and mGPS-1 groups (3.2 vs 4.0 months, respectively). Multivariate analysis revealed both mGPS-1 and mGPS-2 were independent predictive factors of death (mGPS-1: HR, 3.34; 95% CI, 2.25–4.95, P < 0.0001; mGPS-2: HR, 5.89; 95% CI, 3.21–10.80, P < 0.001). Similarly, analysis by treatment arm showed OS of patients treated with nal-IRI+5-FU/LV was significantly worse in the mGPS-1 (N = 26) and mGPS-2 (N = 5) groups than in the mGPS-0 (N = 27) group (4.6, 3.3 vs 9.3 months, respectively)

Conclusions: Data from this post-hoc analyses of mGPS in patients with mPDAC previously treated with gemcitabine-based are consistent with the reports of the prognostic value of the mGPS in estimating OS. Median OS was significantly improved in pts with a mGPS-0 vs mGPS-1 or mGPS-2, including the treatment group of patients receiving nal-IRI+5-FU/LV.

Clinical trial identification: NCT01494506.

Editorial acknowledgement: Editorial assistance was provided by The Medicine Group (New Hope, PA, USA); Philip Sjostedt, BPharm; Susan Martin, PhD.

Legal entity responsible for the study: Ipsen Biopharmaceuticals, Inc.

Funding: Ipsen Biopharmaceuticals, Inc.

Disclosure: L-T. Chen: Consulting or advisory role: Bristol-Myers Squibb, Five Prime Therapeutics, Lilly, Merrimack, MSD, Novartis, Ono Pharmaceutical, PharmaEngine, Syncope, Taiwan, TTY Biopharm; Research funding (Inst): GlaxoSmithKline, Merck Serono, Novartis, Polaris, TTY Biopharm; Patents, Royalties, Other intellectual property: Anti-alpha-enolase (ENO-1) monoclonal antibody to HuniLife Technology, Taiwan. B. Belanger, B. Mirakhur: Employee stock, Other ownership interests: Ipsen Biopharmaceuticals, Inc. F.A. de Jong: Employee: Shire Stock, Other ownership interests: Amgen, Shire. J. Siveke: Consulting, Advisory role: Baxalta, Celgene, Lilly, Merrimack; Research funding: 4SC; Boehringer Ingelheim, Bristol-Myers Squibb, Celgene;, Novartis, Travel, accommodations, expensive: Celgene, Roche. All other authors have declared no conflicts of interest.

750P Prognostic value of the neutrophil-lymphocyte ratio and CA 19-9 in predicting survival inpatients with metastatic pancreatic cancer

I. Dede[1], M. Cetin[2], S. Cetin[3]

[1]Oncology, Mustafa Kemal University Faculty of Medicine, Hatay, Turkey, [2]Medical Microbiology, Mustafa Kemal University, Antakya- Hatay, Turkey, [3]Biostatistics, Ondokuzmayis University, Samsun, Turkey

Background: The predictive value of different prognostic biomarkers has been studied in various cancer types. The aim of our study is to determine the degree of risk and prognostic significance of the pre-treatment neutrophil-to-lymphocyte ratio (NLR) and CA19-9 level in patients with metastatic pancreatic cancer and establish its relation with survival.

Methods: In our study, clinical and laboratory data of 118 patients with metastatic pancreatic cancer at the time of diagnosis were retrospectively analyzed. Overall survival (OS) rates were calculated using the Kaplan–Meier method. The Cox regression analysis was used to determine the prognostic factors affecting pancreatic cancer.

Results: The mean age of the patients was 67 ± 9.57 years. The patients were analyzed during the follow-up, and theirmedian OSwas 12 months (95% CI: 9.73–14.26). According toROC [Editor1] curve analysis, the cut-off value was 3.54 (AUC:0.653,95%CI:0.56–0.73, p = 0.006)for NLR and 437 (AUC:0.670,95%CI:0.57–0.75, p = 0.002) for the CA19-9 level. Astatistically significant differencewas observed between the CA19-9 level (p < 000.1) and NLR (p < 000.1) and OS. As a result of the multivariate Cox regression analysis, NLR (≥3.54 vs < 3.54, HR = 2.17, 95% CI: 1.17–4.03, p = 0.013) andthe CA19-9 level (≥437 vs < 437, HR = 1.81, 95% CI: 1.08–3.03, p = 0.022) were found to be significant prognostic factors in OS analysis.

Conclusions: In our study, the pre-treatment NLR and CA19-9 level were found to be reliable predictive markers for poor prognosis in patients with metastatic PC. According to the results of our study, the NLR and CA19-9 level can be used in predicting the survival of patients with pancreatic cancer. We believe that our findings will shed light on the management of treatment protocols for patients diagnosed with metastatic pancreatic cancer.

Legal entity responsible for the study: Isa Dede.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

751P Effects of random glucose (Glc) levels on outcomes of patients (pts) with pancreatic ductal adenocarcinoma (PDAC)

R. Pihlak[1], R. Almond[2], P. Srivastava[3], H. Raja[3], R. Broadbent[4], L. Hopewell[5], C. Higham[5], A. Lamarca[4], R. Hubner[4], J.W. Valle[1], M.G. McNamara[1]

[1]Medical Oncology/Division of Cancer Sciences, The Christie NHS Foundation Trust/University of Manchester, Manchester, UK, [2]Analytics and Development, Clinical Outcome Unit, The Christie NHS Foundation Trust, Manchester, UK, [3]Faculty of Biology, Medicine and Health, University Manchester, Manchester, UK, [4]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [5]Endocrinology Department, The Christie NHS Foundation Trust, Manchester, UK

Background: Pancreatic ductal adenocarcinoma is a dismal disease with poor outcomes; ∼85% of pts with PDAC have impaired Glc tolerance or diabetes. This study explored how random Glc levels influence pt outcomes.

Methods: Consecutive pts with PDAC (all stages) (Jan 12-Jul 17) were included; 3 blood Glc level thresholds were referenced: >8 mmol/L (requiring monitoring), ≥14 mmol/L (requiring antidiabetic treatment), >11mmol/L on 2 occasions (fulfilling WHO diabetes criteria). Survival outcomes/prognostic factors were analysed by log-rank, Kaplan Meier and multivariable Cox regression.

Results: Of 640 pts: 53 % were male, median (med) age 68y, 64% ECOG PS 0/1, 22% PS 2, 14% PS 3/4; 26% stage 1/2 disease, 74% stage 3/4; 81% treated with palliative intent (chemotherapy in 325) and 15% adjuvant; 29% pts had a previous diabetes diagnosis. Med baseline Glc: 7.3mmol/L (range 3.8-37.1); 377 (59%) and 145 (23%) pts had Glc >8mmol/L and ≥14 mmol/L respectively, either at baseline or during treatment, 124 (19%) had Glc >11mmol/L on 2 occasions (of whom 81 were known diabetic). Med PFS and OS for all stages were 6.7 (95%CI 6.0-7.1) and 8.1 (95%CI 7.4-8.8) months (mo) respectively. Med OS for stage 1/2: 11.3 mo (95%CI 9.4-13.8), stage 3/4 disease 5.3 mo (95%CI 4.8-6). Previous diabetes diagnosis and antidiabetic treatment did not significantly impact OS (P = 0.26, P = 0.5 respectively). Baseline Glc levels (>8mmol/L and ≥14 mmol/L; Table), but not hyperglycaemia during treatment, significantly affected OS in all pts. Multivariable analysis (once adjusted for age and primary site) found increasing stage (P < 0.001), high minimum Glc (ever)(P < 0.001), high CA19-9 (P < 0.001), worse ECOG PS (P < 0.01) , and low albumin (P = 0.02) were prognostic for worse OS.

Conclusions: This study demonstrated for the first time that baseline Glc above thresholds and the absolute minimum random Glc confers worse outcomes, irrespective of previous diabetes diagnosis. Whether this risk is modifiable is subject to further research.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 751P

Patients	All	OS (95%CI) months									
		N	≤8 mmol/L	N	>8 mmol/L	P value	N	<14 mmol/L	N	≥14 mmol/L	P value
Stage 1-4	640	360	9.7 (8.3-11.3)	232	7.1 (5.7-8.3)	0.002	515	8.5 (7.8-10.1)	77	7.1 (5.1-9.0)	0.001
Palliative	519	274	7.6 (6.7-8.3)	201	6.2 (5.1-7.1)	0.5	408	7.1 (6.2-7.8)	67	5.5 (4.6-8.3)	0.23
Curative	115	83	27.4 (21.8-34.0)	29	18.9 (14.0-NA)	0.25	103	27.8 (21.8-45.8)	9	12.9 (9.2-NA)	<0.0001

752P Clinical utility of serum type III collagen in patients with pancreatic carcinoma

I. Chen[1], N. Willumsen[2], C. Dehlendorff[3], A. Johansen[1], B.V. Vittrup[1], M. Krüger[1], P. Pfeiffer[4], J.K. Bjerregaard[4], S.E. Bojesen[5], S.E. Nielsen[6], N.H. Holländer[7], M.K. Yilmaz[8], L.S. Rasmussen[9], M. Karsdal[2], J.S. Johansen[1]

[1]Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [2]Biomarkers and Research, Nordic Bioscience A/S, Herlev, Denmark, [3]Statistics and Pharmacoepidemiology, Danish Cancer Society Research Center, Copenhagen, Denmark, [4]Experimental Research in Medical Cancer Therapy, Odense University Hospital, Odense, Denmark, [5]Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Herlev, Denmark, [6]Department of Oncology, North Zealand University Hospital, Hillerød, Denmark, [7]Department of Oncology, Zealand University Hospital in Næstved, Næstved, Denmark, [8]Department of Oncology, Aalborg University Hospital, Aalborg, Denmark, [9]Oncology, Aalborg University Hospital, Aalborg, Denmark

Background: Collagen is highly expressed in pancreatic cancer (PC) stroma. Collagen accumulation compromises penetration of macromolecules into tumor tissues and is associated with poorer outcome and increased tumor invasion. The aim of this biomarker study was to investigate the clinical utility of serum pro-peptide of type III collagen (PRO-C3) in patients (pts) with PC.

Methods: A cohort from the Danish BIOPAC study (ClinicalTrials.gov ID: NCT03311776) including 851 consecutive subjects with histologically confirmed PC, ampullary carcinoma (n = 45), distal biliary tract cancer (n = 32) and benign lesions (n = 88) were enrolled. Serum PRO-C3 was determined by ELISA (Nordic Bioscience, PRO-C3 protocol). The main outcome was survival among pts with PC (male/female: 458/393; age <50 vs. 50-69 vs. ≥70: 41/477/333; ECOG Performance Status (PS) of 0/1/2+: 315/340/110; stage 1 + 2/3/4: 234/142/456; diabetes yes/no: 207/629; smoking yes/no: 508/265; alcohol yes/no: 183/588; body mass index: low/normal/overweight: 62/426/254; Charlson Age-Comorbidity index (CACI) 0/1-2/3+: 34/296/504) in relation to PRO-C3 levels. Serum CA19-9, hyaluronic acid (HA), C-reactive protein (CRP), interleukin-6 (IL-6) and YKL-40 were measured. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by Cox proportional hazards regression.

Results: HA, CRP, IL-6, YKL-40, higher PS and stage were all risk factors for poor outcome in univariate analyses, as was log2-transformed PRO-C3 (HR = 1.15, 95% CI 1.09-1.22, P < 0.001). No statistically significant difference for serum PRO-C3 was observed in multivariate model, while CA19-9, CRP, YKL-40 along with higher PS and stage remained independently significant. PRO-C3 was positively correlated with higher stage (P = 0.012) and was significantly higher in pts with PC compared to subjects with benign lesions (P < 0.001).

Conclusions: Compared with subjects with benign lesions serum PRO-C3 was higher in pts with PC, and increased with greater stage. Higher levels were associated with shorter OS. Serum PRO C3 did not provide independent prognostic value compared to other markers. Further investigations are warranted based on these initial results.

Legal entity responsible for the study: Julia Sidenius Johansen.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

753P Venous thromboembolism in Asian patients with pancreatic cancer who underwent palliative chemotherapy: Low prevalence, but a poor prognostic factor for early onset

W-C. Chou[1], J-S. Chen[2], Y-Y. Chen[3], C-H. Lu[4], P-H. Chang[5]

[1]Hematology and Oncology, Chang Gung Memorial Hospital-Linkou, Taoyuan, Taiwan, [2]Hematology/ 0ncology, Chang Gung Memorial Hospital-Taipei, Taipei City, Taiwan, [3]Hematology and Oncology, Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung, Taiwan, [4]Hematology and Oncology, Chiayi Chang Gung Memorial Hospital, Puzi City, Taiwan, [5]Hematology and Oncology, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan

Background: Venous thromboembolism (VTE) is a common complication in patients with pancreatic cancer. VTE in Asian patients with cancer is known to be less prevalent than in Western patients; however, few studies have reported the epidemiology and clinical outcomes of VTE in Asian patients with pancreatic cancer. This study investigated the incidence, risk factors, and clinical outcome of VTE in patients with pancreatic cancer who underwent palliative chemotherapy.

Methods: Medical records of VTE incidence in patients after initiation of chemotherapy for newly diagnosed locally advanced or metastatic pancreatic cancer from 2010 to 2016 at four institutes in Taiwan were retrospectively reviewed. The clinical characteristics of 838 patients were analyzed to identify independent predictors of VTE and survival outcome.

Results: With a median follow-up period of 7.7 months (0.6–55.6), VTE occurred in 67 (8.0%) of the 838 patients. The 6-, 12-, 24-, and 36-month cumulative incidences of VTE were 5.0%, 8.9%, 19.4%, and 24.5%, respectively. Of the 67 patients who developed VTE, 26.9%, 53.8%, and 70.2% of VTE occurred within 2, 4, and 6 months of chemotherapy initiation, respectively. Predictors of VTE were white blood cell count >11,000/μL of peripheral blood and presence of liver metastases. Khorana risk score was not a significant predictor of VTE. Patients with VTE were not significantly associated with a poorer survival outcome than were those without VTE. However, occurrence of VTE within 2 months after the initiation of chemotherapy was an independent poor prognostic factor for overall survival.

Conclusions: This was the largest study to evaluate the incidence, predictors, and effects of VTE in Asian patients with pancreatic cancer that underwent palliative chemotherapy. The incidence of VTE in Asian patients was found to be half that in Western patients. Only patients with early onset VTE had a poorer prognosis than those without VTE. Awareness of the clinical characteristics and survival outcome of patients with VTE may assist clinicians and patients in choosing the appropriate prophylaxis and management of VTE for Asian patients with pancreatic cancer.

Legal entity responsible for the study: Wen-Chi Chou.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

754P Targeted therapy based on the genetic alterations prolongs the progression-free survival of patients with advanced biliary tract cancer

F. Feng[1], Q. Cheng[1], D. Zhang[2], B. Li[1], H. Qin[2], C. Xu[1], M. Han[2], Y. Yu[1], Z. Li[1], J-Y. Li[2], Z. Qiu[1], L. Xiong[2], C. Liu[1], F. Li[2], B. Yi[1], X. Jiang[1]

[1]Department of Biliary I, Eastern Hepatobiliary Surgical Hospital (EHSH), 2nd Military Medical University, Shanghai, China, [2]Research and Development Institute of Precision Medicine, 3D Medicine Inc., Shanghai, China., Shanghai, China

Background: Targeted therapy based on a certain genetic alteration has been proven to be an effective treatment in some kinds of cancers. We aimed to evaluate the clinical efficacy of personalized targeted therapy for advanced biliary tract cancer (BTC) patients based on individual actionable mutations.

Methods: In this single-center study, the targeted next generation sequencing (NGS) was employed for consecutive 49 patients with BTC and the recommendation of biologic agent was offered according to most potentially targetable genetic alteration of each person. Among 32 patients with stage IV and R2 resection, 21 patients underwent conventional chemotherapy (mGEMOX), while the rest 11 patients received a personalized targeted agent alternative to chemotherapy. The progression-free survival (PFS), overall survival (OS) and disease control rate (DCR) were assessed.

Results: The genomic landscape of 49 patients demonstrated that TP53 (n = 31, 63.3%) variation was most prevalent and was followed by KRAS (n = 12, 24.5%), ARID1A (n = 6, 12.2%), PIK3CA (n = 6, 12.2%), SMAD4 (n = 6, 12.2%), CDKN2A (n = 5, 10.2%) and ERBB4 (n = 5, 10.2%). Further analysis of copy number alterations (CNAs) showed low recurrent amplified genes, such as PIK3CA, SMAD4, FGFR3, SRC, PIK3R2, CDK4, ERBB2, and CDK6. After a median follow-up of 12 months, the targeted group had a significant prolonged PFS (4.5 months vs. 1.5 months, P = 0.014) and a trend of prolonged OS (12.9 months vs. 4.1 months, P = 0.104) in comparison with the chemotherapy group. The DCR in targeted group was a little higher but without significance (63.6% vs. 33.3%, P = 0.142). In addition, the ratio of patients with more than Grade 2 treatment-related toxicities in the targeted therapy group was a little higher compared to that of chemotherapy group but without significance (36.4% vs. 19.0%, P = 0.397).

Conclusions: This mono-center small cohort study suggested that personalized targeted therapy for advanced BTC patients based on individual most potentially actionable mutation detected by NGS, which offered such patients a longer PFS and trends of better OS and DCR, could be an option alternative to conventional chemotherapy.

Legal entity responsible for the study: Shanghai Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China.

Funding: Science and Technology Commission of Shanghai Municipality (NO. 15411951900), National Natural Science Foundation of China (NO. 81472280), Special Fund on the Application and Transformation of Precision Medicine in Second Military Medical University (NO.2017JZ11).

Disclosure: L. Xiong: Chairman, Chief Executive Officer: 3D Medicine, Inc. F. Li: Vice President: 3D Medicine, Inc. J.Y. Li, H. Qin, M. Han, D. Zhang: Employee: 3D Medicine, Inc. All other authors have declared no conflicts of interest.

755P Evaluation of genetic alterations in biliary tract cancer using targeted exome sequencing

H. Chae[1], C. Yoo[1], D. Kim[2], J.H. Jung[1], H-M. Chang[3], B-Y. Ryoo[1], K-P. Kim[1]

[1]Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Medical Oncology, Asan Medical Center, Seoul, Democratic People's Republic of Korea

Background: Biliary tract cancer (BTC) is a heterogeneous group of cancers anatomically divided into gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC). None of molecular target agents has been proven to improve the prognosis of BTC yet. To gain a deeper understanding of BTC's pathophysiology and find its new potential therapeutic targets, this study aims to investigate genetic profiles of BTC and their clinical implication.

Methods: A total of 124 patients with adenocarcinoma of biliary tract from Jan 2014 to Feb 2018 were enrolled. With DNA specimen extracted from previously-collected tumor tissue, somatic mutation and copy number analyses were performed using targeted exome sequencing. Data regarding baseline patient characteristics and treatment outcomes were retrospectively obtained from medical records.

Results: Twenty-five patients with GBC (20.2%), 55 with ICC (44.4%) and 44 with ECC (35.5%) were included in the analysis. Genetic mutation were observed in 104 patients (83.8%) and the rest 20 (16.1%) did not have any genetic alterations. The most commonly mutated gene was TP53 (n = 55, 44.4%), followed by KRAS (n = 36, 29.0%), ARID1A (n = 15, 12.1%) and IDH1 (n = 12, 9.7%). IDH1/2 mutation appeared more frequently in ICC (n = 12, 21.8%, P = 0.012) compared to GBC (n = 1, 4.0%) or ECC (n = 1, 2.3%) while ERBB2 and ERBB3 mutation were found only in GBC and ECC. ERBB2 amplification was observed in 7 patients (4 with GBC and 3 with ICC). Among those, one patient showed 3+ for HER2 test by immunohistochemistry (IHC) while four patients were 2+. Survival outcomes were analyzed among 122 patients who had eventually received palliative chemotherapy for their advanced disease. Patients harboring TP53 mutation had shorter PFS (5.7 vs. 7.1 months, P = 0.08) and OS (15.2 vs. 37.8 months, P = 0.03) compared to those without TP53 mutation, while IDH1 mutation was likely to be related to favorable PFS (10.6 vs. 6.1 months, P = 0.069). On the other hand, there were no significant differences in PFS or OS depending on KRAS or ARID1A mutation.

Conclusions: Genetic profile of BTC is heterogeneous according to its anatomic location. Our results indicate that subgroup of BTC may benefit from targeted therapy such as anti-IDH and anti-HER2 inhibitor.

Legal entity responsible for the study: Institutional Review Board of the Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

756P Interim results of fight-202, a phase II, open-label, multicenter study of INCB054828 in patients (pts) with previously treated advanced/metastatic or surgically unresectable cholangiocarcinoma (CCA) with/without fibroblast growth factor (FGF)/FGF receptor (FGFR) genetic alterations

A. Hollebecque[1], M. Borad[2], V. Sahai[3], D.V.T. Catenacci[4], A. Murphy[5], G. Vaccaro[6], A. Paulson[7], D-Y. Oh[8], L. Féliz[9], C. Lihou[10], H. Zhen[11], G.K. Abou-Alfa[12]

[1]Drug Development, Institut Gustave Roussy, Villejuif, France, [2]Medical Oncology, Mayo Clinic Cancer Center, Scottsdale, AZ, USA, [3]Medical Oncology, University of Michigan, Ann Arbor, MI, USA, [4]Medicine and Biological Sciences, The University of Chicago Medical Center, Chicago, IL, USA, [5]Medical Oncology, Johns Hopkins University, Baltimore, MD, USA, [6]Medical Oncology, Oregon Health & Science University, Portland, OR, USA, [7]Medical Oncology, Texas Oncology, P.A., U.S. Oncology Research Network, Woodlands, TX, USA, [8]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [9]Clinical Development, Incyte Corporation, Geneva, Switzerland, [10]Clinical Research, Incyte Corporation, Willmington, DE, USA, [11]Biostatistics, Incyte Corporation, Willmington, DE, USA, [12]Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background: Dysregulation of FGFR signaling by FGFR translocations is involved in the pathogenesis of CCA. FGFR2 translocations occur almost exclusively in pts with intrahepatic CCA (iCCA) with an incidence of 13%–15%.[1] INCB054828, a selective, potent oral inhibitor of FGFR1, 2, and 3, is being evaluated in a phase 2 study (NCT02924376) of pts with previously treated CCA.

Methods: Pts are enrolled into cohort A (FGFR2 translocations), cohort B (other FGF/FGFR genetic alterations [GA]), or cohort C (no FGF/FGFR GAs) and receive oral INCB054828 13.5 mg once daily on a 21-day cycle (2 weeks on, 1 week off) until disease progression or unacceptable toxicity. The primary endpoint is objective response rate (ORR) per RECIST v1.1 in cohort A based on independent review. Secondary endpoints include ORR in cohorts B and C, progression-free survival (PFS), overall survival, and safety. We report interim efficacy and safety data.

Results: At data cutoff (27 Nov 2017) 47, 22, and 18 pts were enrolled in cohorts A, B, and C, respectively. In cohort A, 94% (44/47) had iCCA, 98% (46/47) had ECOG PS $\leq$ 1, and 60% (28/47) received $\geq$ 2 prior therapies. Of 45 evaluable pts in cohort A, 8 (18%) had a confirmed partial response (PR; 1/8 with unconfirmed complete response) and 26 (58%) had stable disease (3/26 had unconfirmed PRs); the best ORR was 24% (95% CI, 12%–37%). Median PFS was 6.8 months (95% CI, 3.6–9.2 months). No responses were observed in cohorts B or C; median PFS was 1.4 and 1.5 months, respectively. The most common treatment-emergent adverse events (TEAEs) in all pts (N = 87) were hyperphosphatemia (56%), alopecia (36%), and diarrhea (32%). Hyperphosphatemia was managed with diet, phosphate binders, or dose modification. Most frequent grade 3/4 TEAEs were hyponatremia (8%) and hypophosphatemia (7%).

Conclusions: INCB054828 was generally well tolerated and showed preliminary efficacy in pts with previously treated advanced iCCA with FGFR2 translocations. Long-term follow-up data will be presented. 1. Graham RP, et al. Hum Pathol. 2014;45:1630-1638.

Clinical trial identification: NCT02924376.

Editorial acknowledgement: Medical writing assistance was provided by Michael R. Convente, PhD, of Scientific Pathways, Inc, and funded by Incyte.

Legal entity responsible for the study: Incyte Corporation.

Funding: Incyte Corporation.

Disclosure: A. Hollebecque: Honoraria: Servier, Merck, Serono; Membership on any entity's Board of directors, advisory committees: Amgen, Gritstone Oncology. M. Borad: Research funding: Incyte Pharmaceuticals. V. Sahai: Consultancy, Honoraria: Halozyme, Celgene, NewLink; Research funding: Bristol-Myers Squibb, Celgene; Membership on any entity's Board of directors, Advisory committees: Celgene, Halozyme. D.V.T. Catenacci: Consultancy (Includes expert testimony): Merck, Bristol-Myers Squibb, Lilly, Five Prime, Genentech/Roche, Amgen, Taiho, Foundation Medicine, Guardant Health; Research funding: Genentech/Roche; Honoraria: Merck, Bristol-Myers Squibb, Lilly, Five Prime, Genentech/Roche, Amgen, Taiho, Foundation Medicine, Guardant Health; Speakers Bureau: Foundation Medicine, Guardant Health, Lilly, Merck, Genentech. A. Murphy: Research funding: Bristol-Myers Squibb. G. Vaccaro: Consultancy (Includes expert testimony): Exelixis; Research funding: Celgene, Merck Sharpe, Dohme, Lilly, Astellas, EMD Serono, Incyte, Bristol-Myers Squibb, Array BioPharma, Newlink Genetics; Honoraria: Bayer. A. Paulson: Equity Ownership: Immunomedics; Membership on any entity's Board of directors, Advisory committees: Ipsen, Bristol-Myers Squibb, Eisai, Taiho, Merrimack. D-Y. Oh: Research funding: AstraZeneca. L. Féliz, C. Lihou, H. Zhen: Employee, Equity ownership: Incyte. G.K. Abou-Alfa: Consultancy (Includes expert testimony): Agios, Amgen, Antengene, Aptus, Aslan, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Boston Scientific, Carsgen, Celgene, Casi, CytomX, Daiichi, Debio, Delcath, Eisai, Exelixis, Gilead, Halozyme, Inovio, Ipsen, Merck, Onxeo, PCI Biotech, Roche, Sanofi, Servier, Silenseed, Sillajen, Sirtex, Vicus, Yakult; Research funding: Agios, Array, AstraZeneca, Bayer, Bristol-Myers Squibb, Casi, Celgene, Exelixis, Genentech, Incyte, Lilly, Mabvax, Medimmune, Momenta, Novartis, OncoMed Pharmaceuticals, Roche.

757P M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in Asian patients with pretreated biliary tract cancer: Preliminary results from a phase I trial

C. Yoo[1], D-Y. Oh[2], H.J. Choi[3], M. Kudo[4], M. Ueno[5], S. Kondo[6], L-T. Chen[7], M. Osada[8], C. Helwig[9], I. Dussault[10], M. Ikeda[11]

[1]Medical Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea, [3]Medical Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea, [4]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan, [5]Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan, [6]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, [7]Internal Medicine, National Cheng-Kung University Hospital, National Institute of Cancer Research, Tainan, Taiwan, [8]Medical Oncology, Merck Serono, Tokyo, Japan, [9]Biostatistics, Merck KGaA, Darmstadt, Germany, [10]Clinical Biomarkers, Immuno-Oncology, EMD Serono, Billerica, MA, USA, [11]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Biliary tract cancers (BTCs) are a group of aggressive cancers with limited treatment options. Overall response rates (ORRs) with 2L chemotherapy in BTC are <10%, and no standard of care exists. M7824 is an innovative first-in-class bifunctional fusion protein composed of a human anti–PD-L1 IgG1 monoclonal antibody fused with 2 extracellular domains of the transforming growth factor β (TGF-β) receptor II (a TGF-β "trap"). We report on the safety and efficacy of M7824 in patients (pts) with pretreated BTC.

Methods: In this expansion cohort of the ongoing phase 1, open-label trial NCT02699515, Asian pts who progressed after platinum-based 1L treatment received M7824 1200 mg q2w until confirmed progressive disease, unacceptable toxicity or trial withdrawal. The primary objective is safety/tolerability; secondary objectives include assessment of best overall response per RECIST v1.1. Tumor cell PD-L1 expression was evaluated (antibody clone 73-10).

Results: As of March 20, 2018, 30 pts with pretreated BTC received M7824 for a median duration of 8.9 (range, 2-57.6) wk; 5 pts remained on treatment. The most common treatment-related adverse events (TRAEs) were pyrexia, maculopapular rash (both 13.3%) rash and lipase increase (both 10%); 10 pts (33.3%) experienced grade $\geq$3 TRAEs. 3 deaths due to AEs were reported; 1 death was due to septic shock (bacteremia, etiology unknown) after 14 doses, and 2 deaths due to interstitial lung disease (ILD), 1 on treatment after 3 doses and 1 with grade 3 ILD after 3 doses that recovered, initiated chemotherapy due to PD, and worsened with death 6 months after initial ILD diagnosis and last M7824 dose. 7 pts had an objective response (ORR, 23.3%, including one late PR pending confirmation), with 4 of 6 PRs ongoing (0.7+, 2.8, 3.9+, 5.5+, 5.6, and 6.9+ mo) and 1 CR ongoing for 5.6+ mo. 1 additional pt had ongoing PR for 7.6+ mo after initial pseudoprogression. Confirmed ORR by PD-L1 expression was 25% and 15.4% in pts with PD-L1 + ($\geq$1%) and PD-L1− tumors, respectively.

Conclusions: M7824 monotherapy has promising efficacy in Asian pts with pretreated BTC, including long-lasting responses in 8 of 30 pts (27%).

Clinical trial identification: NCT02699515.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: C. Yoo: Research funding: CKD pharm, Shire; Honoraria: Bayer, Ipsen. D-Y. Oh: Research funding: AstraZeneca. M. Ueno: Research Funding: Taiho Pharmaceutical, Shire, Daiichi Sankyo, Eisai, AstraZeneca, Ono Pharmaceutical, MSD, Merck Serono, NanoCarrier, Dainippon Sumitomo Pharma, Incyte; Honoraria: Taiho Pharmaceutical, Yakult Honsha, AstraZeneca, Novartis, Lilly, Teijin Pharma, Shire, Ono Pharmaceutical. S. Kondo: Research Funding: MSD, Bayer, Aslan, Pfizer, AstraZeneca, Lilly. M. Osada: Employee: Merck Serono, Tokyo, Japan. C. Helwig: Employee: Merck KGaA, Germany; Equity ownership: Merck KGaA, Germany. I. Dussault: Employee: EMD Serono. M. Ikeda: Research Funding: Bayer Yakuhin, Kyowa Hakko Kirin, Yakult, Taiho Pharmaceutical, Eli Lilly Japan, Ono Pharmaceutical, Eisai, AstraZeneca, Zeria Pharmaceutical, Baxter, Chugai Pharmaceutical, Bristol Myers Squibb, Merck Serono, Kowa, Nano Carrier, ASLAN Pharmaceuticals; Honoraria: Novartis Pharma, Bayer Yakuhin, Bristol-Myers Squibb, Abbott Japan, Eisai, Eli Lilly Japan, Taiho Pharmaceutical, Chugai Pharmaceutical, Daiichi-Sankyo, Yakult, Otsuka Pharmaceutical, Nobelpharma; Membership board of directors or advisory committees: Nano Carrier, Bayer Yakuhin, Eisai, Kyowa Hakko Kirin, Novartis Pharma, Shire, MSD. All other authors have declared no conflicts of interest.

758P A new ProTide, NUC-1031, combined with cisplatin for the first-line treatment of advanced biliary tract cancer (ABC-08)

M.G. McNamara[1], J. Bridgewater[2], D. Palmer[3], H. Wasan[4], W.D. Ryder[5], C. Gnanaranjan[6], E. Ghazaly[7], T.R.J. Evans[8], J.W. Valle[1]

[1]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [2]Oncology, University College London Hospitals, London, UK, [3]Medical Oncology, Clatterbridge Cancer Centre, Liverpool, UK, [4]Medical Oncology, Imperial College London - Hammersmith Hospital, London, UK, [5]MAHSC-CTU, The Christie NHS Foundation Trust, Manchester, UK, [6]Cancer Institute, Barts Cancer Institute-Queen Mary University of London, London, UK, [7]Centre for Haemato-Oncology, Barts Cancer Centre, London, UK, [8]Institute of Cancer Sciences, Beatson Institute for Cancer Research, Glasgow, UK

Background: Cisplatin + gemcitabine (cis/gem) is the global standard of care for 1st-line treatment of patients (pts) with locally advanced/metastatic biliary tract cancer (BTC). No agents have regulatory approval for this disease. Cis/gem achieves an objective response rate (ORR) of 26% and median overall survival (OS) of 11.7 months (ABC-02). Inherent/acquired resistance mechanisms limit gemcitabine efficacy. NUC-1031, a phosphoramidate transformation of gemcitabine, is designed to overcome resistance mechanisms associated with poor gemcitabine response.

Methods: Pts with locally advanced/metastatic BTC, ECOG PS of 0-1 and no prior systemic therapy received NUC-1031 (625 or 725 mg/m^2) combined with cisplatin (25 mg/m^2) on days 1 + 8 every 21 days. Primary endpoints: safety and determination of RP2D. Secondary endpoints: ORR, pharmacokinetics, progression-free and OS.

Results: 14 pts (median age 61 yrs, 8 male; 5 hilar, 4 distal bile duct, 2 intrahepatic, 2 ampullary and 1 gallbladder) were enrolled across cohorts 1 (625 mg/m^2, n = 8) and 2 (725 mg/m^2, n = 6). 11 pts completed >1 cycle and were efficacy evaluable, receiving a median of 6.5 cycles (range 3.5-12). ORR was 64% (1 CR, 6 PRs) and DCR: 73%. PFS/OS data collection is ongoing. High, durable intracellular levels of the active anti-cancer metabolite dFdCTP were generated in PBMCs ($t_{1/2}$=22 h). Treatment was well tolerated with no unexpected AEs/DLTs. Grade 3 TEAEs included neutropenia (14%), fatigue (14%), pyrexia (14%), ALT (7%), AST (7%), GGT (7%) and nausea (7%). Based on high response rate and favourable safety profile, 625 mg/m^2 was deemed RP2D. An expansion cohort is ongoing (n = 6).

Table: 758P

	ITT			Efficacy evaluable		
	625 mg/m^2 (n = 8) n (%)	725 mg/m^2 (n = 6) n (%)	Total (n = 14) n (%)	625 mg/m^2 (n = 6) n (%)	725 mg/m^2 (n = 5) n (%)	Total (n = 11) n (%)
CR	1 (13)	0 (0)	1 (7)	1 (17)	0 (0)	1 (9)
PR	3 (38)	3 (50)	6 (43)	3 (50)	3 (60)	6 (55)
ORR	4 (50)	3 (50)	7 (50)	4 (67)	3 (60)	7 (64)
SD	0 (0)	1 (17)	1 (7)	0 (0)	1 (20)	1 (9)
DCR	4 (50)	4 (67)	8 (57)	4 (67)	4 (80)	8 (73)

Conclusions: NUC-1031 + cisplatin demonstrated a very high ORR, with a favourable safety profile, and may provide an improved treatment option over cis/gem for advanced BTC. Further development of NUC-1031 in BTC is planned.

Clinical trial identification: NCT02351765.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: NuCana.

Disclosure: All authors have declared no conflicts of interest.

759P Phase II study of evofosfamide (TH-302) monotherapy as a second-line treatment in advanced biliary tract cancer

J.S. Yoon[1], K-H. Lee[2], G.J. Cheon[3], Y-J. Bang[2], D-Y. Oh[2]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [2]Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea, [3]Department of Nuclear Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Background: Evofosfamide (TH-302), a nitroimidazole-linked prodrug of a brominated version of isophosphoramide mustard, is converted to an activated form and acts as a DNA crosslinking agent when exposed to a hypoxic environment. Biliary tract cancer (BTC) is well known to contain large hypoxic area, and there is no standard 2nd line chemotherapy in advanced BTC. This study is a prospective, open-label, single-arm phase II trial to evaluate the efficacy and safety of evofosfamide as 2nd line treatment in advanced BTC.

Methods: Patients (pts) with unresectable or recurred BTC whose disease progressed after 1st line chemotherapy were enrolled. Pts received evofosfamide at a dose of 340 mg/m^2 via intravenous (IV) infusion over 30 minutes on Day 1, 8, and 15 of every 28-day cycle. The primary end point was progression-free survival (PFS) rate at 4-months. Secondary end points included overall survival (OS), PFS, objective response rate (ORR), disease control rate (DCR), metabolic response by 18 F-FDG PET, and safety profile. Response evaluation was done every 8 weeks using RECIST v.1. Metabolic response was evaluated by PERCIST v.1, and toxicity was assessed by CTCAE v4.03.

Results: A total of 20 pts were treated with IP and 16 were response-evaluable. The median age was 58.7 years (range 54.90 - 62.29). The primary origin of tumor was intrahepatic cholangiocarcinoma in 9 pts, extrahepatic BTC 3, gallbladder cancer 6, and ampulla of vater 2. 16 pts had ECOG PS 0, and 4 had ECOG 1. There was no objective response, stable disease was observed in 9 pts, results in DCR 56.3%. The PFS rate at 4-months was 31.25%. The median PFS was 3.80 months (95% CI 1.03 - 6.57), and the median OS was 6.37 months (95% CI 3.94 - 8.79). Liver metastasis was associated with poor PFS. Reduction of tumor metabolic activity was observed in 8 pts out of 14 (57.1%). Majority of adverse events (AEs) were grade 1/2 ; neutropenia(30%), anemia (50%), thrombocytopenia (40%), nausea (15%), arthralgia (5%). Grade 3 anemia was observed in 15%, anorexia 5% and arthralgia 5%. There was no treatment-related death.

Conclusions: Evofosfamide monotherapy showed promising efficacy in terms of disease stabilization and PFS and OS, and acceptable AE profiles used as 2nd line treatment in advanced BTC.

Clinical trial identification: NCT02433639.

Legal entity responsible for the study: Do-Youn Oh, Seoul National University Hospital.

Funding: Merck Serono.

Disclosure: All authors have declared no conflicts of interest.

760P PhotoChemical internalization of gemcitabine followed by gemcitabine/cisplatin in perihilar cholangiocarcinoma: Results from a phase I dose escalation trial

J. Trojan[1], R. Sturgess[2], D. Harrison Palmer[3], B. Neu[4], S. Kasper[5], A. Dechene[6], C. Jürgensen[7], J. Schirra[8], R. Jakobs[9], A. Högset[10], L. Finnesand[11], H. Olivecrona[11]

[1]Gastrointestinale Onkologie, Goethe University Medical Center, Frankfurt am Main, Germany, [2]The Aintree Digestive Diseases Unit, University Hospital Aintree, Liverpool, UK, [3]Institute of Translational Medicine, University of Liverpool Cancer Research UK Centre, London, UK, [4]Medizinische Klinik II - Gastroenterologie, Hepatologie und Onkologie, Krankenhaus Landshut-Achdorf, Landshut, Germany, [5]Medical Oncology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany, [6]Gastroenterology and Hepatology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany, [7]Medizinische Klinik II - Gastroenterologiekologie, Charité, Berlin, Germany, [8]Medizinische Klinik und Poliklinik II, Klinikum der Ludwig-Maximilians-Universität, Munich, Germany, [9]Medical Department C, Klinikum Ludwigshafen, Ludwigshafen, Germany, [10]CSO, PCI Biotech AS, Oslo, Norway, [11]Clinical Development, PCI Biotech AS, Oslo, Norway

Background: Cholangiocarcinoma is a rare cancer with a poor survival and an approximate response rate of 26% and a median PFS/OS of 8.0 and 11.7months respectively with current standard treatment (gemcitabine/cisplatin). Photochemical Internalisation (PCI) is a novel technology that utilizes wave-length specific light (652nm) and a photosensitizer ($TPCS_{2a}$; Amphinex®) to enhance the local therapeutic effect of a variety of molecules, including gemcitabine.

Methods: This was a Phase I, dose escalation, multicenter trial of a single PCI induction of gemcitabine (1000 mg/m^2) in 16 patients with inoperable perihilar cholangiocarcinoma (CCA). Following the procedure, patients received standard therapy with gem/cis for up to 8 cycles. Patients were on-study for 6 months, and are currently followed for survival. Adverse events, including biliary complications, and tumor effects were characterized.

Results: A total of 16 patients were treated in four different dose cohorts. 11 patients completed the 8 cycles of combination therapy; 5 patients were early withdrawals. PCI of gemcitabine was well tolerated with no Dose Limiting Toxicities, and with a general safety profile characteristic of the patient population included. At 6 months, in the two highest dose cohorts independent reading showed that 7 out of 8 patients had radiologically evaluable tumours. Of these, 2 were complete and 2 partial responses, with one stable disease. In 17/19 target lesions before treatment, a > 20% reduction in tumour size was seen, with 12 lesions undetectable at 6 months. Median OS ended at 14.4 months. As of March 2018, 4 of the 16 patients are alive 24.3 to 38.8 months after treatment (overall study average 17.4 months).

Conclusions: In this dose escalation trial of PCI of gemcitabine in perihilar CCA patients, a safe and tolerable dose of light and Amphinex® was established. The overall safety profile and promising results, including a proportion of patients with highly durable objective tumor response, are encouraging. A larger, controlled and randomized study is underway.

Clinical trial identification: NCT01900158.

Legal entity responsible for the study: PCI Biotech AS.

Funding: PCI Biotech AS.

Disclosure: A. Högset, L. Finnesand, H. Olivecrona: Employee: PCI Biotech AS. All other authors have declared no conflicts of interest.

761P FOLFIRINOX as a first-line chemotherapy for patients (pts) with advanced biliary tract cancer (BTC)

A. Ulusakarya[1], W. Karray[1], J. Abdou[1], A. Karaboué[2], M. Haydar[1], S. Krimi[1], Y. Gumus[1], W. Almohamad[1], E. Goldschmidt[1], P. Biondani[1], J.F. Morère[1]

[1]Medical Oncology Department, AP-HP, Hôpital Paul Brousse, Villejuif, France, [2]Medical Oncology Department, GHI Le Raincy-Montfermeil, Montfermeil, France

Background: FOLFIRINOX is a first-line regimen in the treatment of pancreatic cancer. Historically, BTC and pancreatic cancers were treated similarly with gemcitabine alone or combined with a platinum compound. A growing body of evidence supports the role of fluoropyrimidines in the treatment of BTC.

Methods: We retrospectively analyzed data of all our pts with locally advanced (LA) or metastatic (M) BTC who received FOLFIRINOX as a first-line therapy from 12/2013 to 11/2017 at Paul Brousse university hospital. The main endpoints were OS, TTP, ORR, DC, secondary resection and toxicity.

Results: There were 42 pts: 17 male (40%) and 25 female (60%) pts aged 36 to 84 years (median: 67). Pts had PS of 0 (55%) and 1 (45%). They had intrahepatic cholangiocarcinoma (iCCA) (21 pts, 50%), gallbladder carcinoma (8 pts, 19%), perihilar CCA (7 pts, 17%), distal CCA (4 pts, 10%) and ampulloma (2 pts, 5%). No biopsy could be obtained in 2 pts. BTC was LA or M in 9 (21%) and 33 pts (79%) respectively. Biliary stent was placed in 14 pts (33%). A median (m) of 10 courses was given with m treatment duration of 6 months (mo). At the cutoff on 01/01/2018, regimen was ongoing in 7 pts (18%). Dose intensity (m) was 74, 34 and 1150 mg/m^2/w for irinotecan, oxaliplatin and 5FU respectively. The most common nonhematological toxicity was sensory neuropathy: grade 1/2 in 15 pts (36%), no grade 3/4. We observed 15 PR (36%), 16 SD (38%), and 10 PD (24%); 1 pt has not been evaluated for efficacy. Fifteen pts (36%) were alive, 24 pts (57%) died, 3 pts (7%) were lost to follow-up. Four out of 5 pts who underwent resection were alive without disease. At a median follow-up time of 12 mo (1 to 26), mTTP was 9 mo [95%CL, 5 – 12] and mOS was 15 mo [14 – 16]. mTTP was better for LA (not reached) than M-BTC (8 mo), $p = 0.05$; OS was statistically similar. mTTP was worse in pts with iCCA than other primaries (7 mo [4 – 10] vs 14 mo [9 – 19], $p = 0.005$); OS was not significantly different. ORR and DC were associated with both better TTP and OS. ORR: mTTP (16 vs 5 mo, $p < 0.001$), mOS (19 vs 11 mo, $p = 0.01$); DC: mTTP (10 vs 2 mo, $p < 0.001$), mOS (18 vs 7 mo, $p = 0.002$).

Conclusions: First-line FOLFIRINOX offers promising results in patients with LA and M-BTC. It deserves prospective evaluation to further improve outcomes for advanced BTC.

Legal entity responsible for the study: Department of Oncology, Hôpital Paul Brousse.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

762P A randomized phase II trial of adjuvant chemotherapy with gemcitabine versus S-1 after major hepatectomy for biliary tract cancer: Kansai Hepato-Biliary Oncology Group (KHBO1208)

H. Terajima[1], S. Kobayashi[2], H. Nagano[3], A. Tomokuni[4], K. Gotoh[2], D. Sakai[5], E. Hatano[6], S. Seo[7], Y. Uchida[1], T. Ajiki[8], H. Satake[9], K. Kamei[10], T. Tohyama[11], T. Hirose[12], I. Ikai[13], S. Morita[14], T. Ioka[15]

[1]Department of Gastroenterological Surgery and Oncology, Kitano Hospital The Tazuke Kofu Kai Medical Research Institute, Osaka, Japan, [2]Department of Surgery, Osaka University Graduate School of Medicine, Suita, Japan, [3]Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, [4]Department of Surgery, Osaka International Cancer Institute, Osaka, Japan, [5]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan, [6]Department of Surgery, Hyogo College of Medicine, Nishinomiya, Japan, [7]Department of Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, [8]Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, [9]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [10]Department of Surgery, Kindai University Faculty of Medicine, Osakasayama, Japan, [11]Department of Hepato-Biliary-Pancreatic and Breast Surgery, Ehime University Graduate School of Medicine, Touon, Japan, [12]Department of Surgery, Otsu Red Cross Hospital, Otsu, Japan, [13]Department of Surgery, National Hospital Organization Kyoto Medical Center, Kyoto, Japan, [14]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [15]Department of Cancer Survey and Gatrointestinal Oncology, Osaka International Cancer Institute, Osaka, Japan

Background: No adjuvant chemotherapy regimens after major hepatectomy for biliary tract cancer (BTC) have been standardized due to the frequency of adverse events. Survival benefits of adjuvant gemcitabine (GEM) or S-1 (S1) chemotherapy were investigated with the recommended dose determined in our previous clinical trial (KHBO1003), with 10% dose-limited toxicity.

Methods: We performed a phase II multicenter randomized trial. The primary endpoint was 1-year recurrence-free survival (RFS), and the secondary end-points were other RFS, overall survival (OS), and others. The following 6-month adjuvant chemotherapy regimens were performed within 12 weeks after R0 or R1 major hepatectomy (hemihepatectomy or trisectionectomy) for BTC: GEM (1000 mg/m2) every 2 weeks or S1 (80 mg/m2/day) for 28 days every 6 weeks. Thirty-five patients were assigned to each arm (alpha error, 10%; beta error, 20%). P values of < 0.10 were considered to indicate a statistically significant difference.

Results: No patients were excluded for the per-protocol analysis. There were no statistically significant differences in the patient characteristics of the two arms. The 1-year RFS and the 1-year OS rates of the GEM arm were 51.4% and 80.0%, respectively, while those of the S1 arm were 62.9% and 97.1%, respectively. The 2-year RFS rate, the 1- and 2-year OS rates, and the OS curve of the S1 arm were superior to those of the GEM arm ($p = 0.0894$, $p = 0.0242$, $p = 0.0679$, and $p = 0.0606$, respectively), although the 1-year RFS rate was not significantly different ($p = 0.334$). With regard to the OS curve, the hazard ratio of the S1 group was 0.477 (90% confidence interval, 0.245-0.927).

Conclusions: The adjuvant chemotherapy with S1 may provide better survival benefits compared with that with GEM after major hepatectomy for BTC.

Clinical trial identification: NCT01815307 (March 21, 2013).

Legal entity responsible for the study: Kansai Hepato-Biliary Oncology Group.

Funding: Japan Society of Clinical Oncology Clinical Research Grant Program 2012 and 2013.

Disclosure: I. Ikai, S. Morita: Lecture fee: Taiho Pharmaceutical Co., Eli Lilly Japan K.K. T. Ioka: Research funding, Lecture fee: Taiho Pharmaceutical Co. All other authors have declared no conflicts of interest.

763P Neoadjuvant vs. adjuvant chemotherapy for cholangiocarcinoma: A propensity score matched analysis

S. Yadav[1], H. Xie[1], I.B. Riaz[1], P. Sharma[2], A. Mahipal[1], R. McWilliams[1]

[1]Department of Oncology, Mayo Clinic, Rochester, MN, USA, [2]Department of Internal Medicine, Bridgeport Hospital, Yale New Haven Health System, Bridgeport, CT, USA

Background: The role of neoadjuvant-chemotherapy (NADJ) in cholangiocarcinoma is unknown. The purpose of this study is to evaluate whether NADJ improves overall survival (OS) in cholangiocarcinoma compared to adjuvant-chemotherapy (ADJ).

Methods: Using the National Cancer Database, we identified patients who underwent surgery and chemotherapy for stage I-III cholangiocarcinoma between 2006 and 2014. Patients with metastatic disease at diagnosis or unknown chemotherapy sequence with surgery were excluded. Propensity score for NADJ was calculated by multivariate logistic regression method. Matching with patients who received ADJ was then performed at the ratio of 1:3 using nearest neighbor method with a caliper width of 0.2. Covariates included in matching were: age at diagnosis, sex, race, insurance status, Charlson score, year of diagnosis, location of tumor, tumor grade, clinical stage, and use of radiation.

Results: 1450 patients met our inclusion criteria, 299 (20.6%) received NADJ while 1151 (79.3%) received ADJ. The median age at diagnosis was 63 years. Factors associated with higher ($p < 0.05$) use of NADJ compared to ADJ were: ages <54 (35% vs. 23%), white race (91% vs. 86%), year of diagnosis 2012-2014 (48% vs. 40%),

intrahepatic tumor location (74% vs. 54%), clinical stage I (46% vs. 38%), and unknown grade of tumor (36% vs. 14%). 279 patients in NADJ group were matched to 698 patients in ADJ group, with resulting standardized mean difference of < 0.1 for all covariates. In the matched cohort, patients who received NADJ had a significantly better OS compared to those who received ADJ (HR: 0.79; 95% CI: 0.65 – 0.96, p = 0.01). The 1- and 5-year OS was 85.9% and 42.1% respectively for NADJ, while it was 85.0% and 32.7% respectively for ADJ.

Conclusions: In this large national database study, NADJ compared to ADJ improved OS in a select group of patients with cholangiocarcinoma.

Legal entity responsible for the study: Siddhartha Yadav.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

764P Advanced intrahepatic cholangiocarcinoma (iCCA) treated with arterial-directed therapies (ADT): Outcomes and safety from a multicenter Italian experience

V. Dadduzio[1], M.D. Rizzato[1], G. Ramondo[2], C. Vivaldi[3], M. Milella[4], G. Brandi[5], S. Cereda[6], S. Murgioni[1], G.G. Cardellino[7], R. Filippi[8], D. Santini[9], G. Pasquini[3], R. Intini[1], V. Vaccaro[4], A. Palloni[5], M. Reni[6], G. Musettini[3], E. Gringeri[10], C. Aliberti[2], V. Zagonel[1]

[1]Medical Oncology 1, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [2]Oncology Radiodiagnostics Department, Istituto Oncologico Veneto IRCCS, Padua, Italy, [3]U.O. Oncologia 2 Universitaria, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [4]Medical Oncology 1, Istituto Nazionale Tumori Regina Elena, Rome, Italy, [5]Oncology, Policlinico S. Orsola-Malpighi, Bologna, Italy, [6]Medical Oncology, San Raffaele Scientific Institute, Milan, Italy, [7]Oncology, Udine University and General Hospital, Udine, Italy, [8]Medical Oncology, IRCCS Istituto di Candiolo, Candiolo, Italy, [9]Oncology, Campus Bio-Medico di Roma, Rome, Italy, [10]Department of Surgery, Hepatobiliary Surgery and Liver Transplantation, Padua University Hospital, Padua, Italy

Background: Most of iCCA patients die because of hepatic progression, even in metastatic stage. Chemotherapy leads to modest increase in life expectancy; arterial-directed therapies (ADT), such as chemoembolization (TACE) or radioembolization (TARE), have been proposed to obtain local disease control, eventually leading to a survival benefit.

Methods: We conducted a multicenter retrospective study involving 8 Italian Cancer Centers to evaluate efficacy outcomes and safety of ADT in advanced iCCA. Primary endpoint was overall survival (OS) from the first ADT.

Results: 99 patients received at least one ADT from 2007 to 2017. TACE was performed in 74 patients, TARE in 25 patients. Median time from diagnosis of advanced disease to first ADT was 7.0 months. Median OS from first ADT was 11.9 months (95% CI 9.9-16.1); progression-free survival was 3.4 months (95% CI 3.2-4.0) with a disease control rate of 64% and an objective response rate of 20%. Adverse events (AE) after procedure were reported in 37 patients, more commonly low grade (G1-G2) abdominal pain (19%) and fever (18%); G3-G4 AE were reported in 11% of patients, while one fatal (G5) AE occurred due to brain hemorrhage one week after the procedure. No survival differences were observed in patients receiving more than one ADT (n.47) compared to those receiving only one procedure (n.52). OS according to procedure (TARE or TACE) was 19.1 and 10.5 months respectively (HR 0.53; 95% CI 0.32-0.88; p.031). Extrahepatic disease and Ca19.9 levels >100 kU/L were significantly associated with worse OS at univariate analysis (HR 1.77 and 2.73, respectively).

Conclusions: Patients receiving ADT had good survival outcomes when compared with historical data of systemic chemotherapy, although authors acknowledge these data could also be driven by a selection bias. Procedures were feasible and tolerable, with limited serious AEs. Notably, patients receiving more than one procedure did not gain an OS benefit compared to those receiving only one ADT. According to these retrospective data, performing ADT in presence of extrahepatic disease may be questionable. Specific prospective studies should be designed in order to confirm ADT role in iCCA.

Legal entity responsible for the study: Istituto Oncologico Veneto IRCCS.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

765P Prediction of overall survival with 2nd-line (L2OS) chemotherapy (CT) in patients with advanced biliary tract cancer (aBTC): AGEO CT2BIL cohort update and international multicenter external validations

C. Neuzillet[1], A. Casadei Gardini[2], B. Brieau[3], C. Vivaldi[4], C. Smolenschi[5], G. Brandi[6], D. Tougeron[7], R. Filippi[8], A. Vienot[9], N. Silvestris[10], A-L. Pointet[11], S. Murgioni[12], B.J-C. Rousseau[13], M. Scartozzi[14], L. Dahan[15], T. Boussaha[16], S. Crusz[17], A. Meurisse[18], A. Lievre[19], D. Vernerey[20]

[1]Medical Oncology, Henri Mondor University Hospital, Créteil, France, [2]Oncology, Istituto Tumori della Romagna I.R.S.T., Meldola, Italy, [3]Gastroenterology, Hôpital Cochin, Paris, France, [4]Oncology, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy, [5]GI Oncology, Gustave Roussy Institute, Villejuif, France, [6]Oncology, Policlinico S. Orsola-Malpighi, Bologna, Italy, [7]Hepato Gastroenterology, CHU Poitiers, Jean Bernard Hôpital, Poitiers, France, [8]Oncology, Università degli Studi di Torino, Turin, Italy, [9]Oncology, Besançon University Hospital, Besançon, France, [10]Oncology, Ospedale Oncologico "Giovanni Paolo II"- IRCCS, Bari, Italy, [11]Gastroenterology and GI Oncology, Hopital European George Pompidou, Paris, France, [12]Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [13]Medical Oncology, Centre Hospitalier Universitaire Henri-Mondor, Créteil, France, [14]Oncology, University Hospital and University of Cagliari, Cagliari, Italy, [15]Service d'HGE et d'Oncologie, CHU La Timone Enfants, Marseille, France, [16]Oncology, Centre Multidisciplinaire d'Oncologie-CePo, Lausanne, Switzerland, [17]Oncology, Barts Cancer Institute-Queen Mary University of London, London, UK, [18]Methodology and Quality of Life in Oncology Unit, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [19]Gastroenterology, CHU de Pontchaillou, Rennes, France, [20]Statistics, CHU Besançon, Hôpital Jean Minjoz, Besançon, France

Background: Benefit of CT beyond standard 1st-line (L1) gemcitabine plus cisplatin (GEMCIS) or oxaliplatin (GEMOX) in aBTC is unclear. Our aim was to identify and validate prognostic factors for L2OS in aBTC to guide patient selection for 2nd line (L2) CT.

Methods: All consecutive patients with aBTC receiving L2 CT after GEMCIS/GEMOX L1 between 2003-2016 in 28 French centers were included. The association of clinico-biological data with L2OS was investigated in univariate and multivariate Cox analyses. A simple score was derived from the multivariate model. The model and score were validated in 3 external cohorts with similar inclusion criteria (Italy, France, UK).

Results: The development cohort included 405 patients treated with L1 GEMOX (91%) or GEMCIS. 55% were men; median age was 64 years. 27% had prior surgical resection; 95% had metastatic disease. Performance status (PS) was 0/1/2 in 18%/52%/30%. Of the 251 patients with available CA19.9 at the beginning of L2, 35% had a CA19.9 ≥ 400 IU/L. Among 22 clinical parameters, 8 were associated with L2OS in univariate analysis. In multivariate analysis, 4 were independent prognostic factors: PS, reason for L1 stopping, prior surgery, peritoneal carcinomatosis (PC) (Table). Type of L2 CT regimen was not associated with L2OS. The clinical model had a C-index of 0.659, a good calibration and was validated in the 3 external cohorts (Table). Analysis of patients with complete data for the 4 clinical factors and CA19.9 (multiple imputations for missing data) showed that CA19.9 was independently associated with L2OS. A score was derived from this model.

Table: 765P Multivariate Cox Model for L2OS (HR, P-value)

	AGEO (N = 405)		ITALY (N = 288)		France (N = 70)		UK (N = 24)	
Prior surgery								
Yes No	1 1.3	0.031	1 1.4	0.013	1 1.8	0.16	1 4.8	0.045
Reason for L1 stopping								
Toxicity/ Other Progression	1 1.5	<0.001	1 1.8	<0.001	1 3.0	0.0063	1 31.9	<0.001
PS								
0 1 2	1 1.5 3.0	<0.001	1 1.2 2.1	0.001	1 2.0 6.7	<0.001	1 7.4 20.4	0.011
PC								
No Yes	1 1.3	0.018	1 1.4	0.019	1 1.0	1.0	1 15.3	0.001

Conclusions: We validated L2OS prognostic factors previously reported and identified PC as a new pejorative one in 800+ patients. Our model and score will be useful for guiding therapeutic decisions and stratifying randomization in future clinical trials.

Legal entity responsible for the study: AGEO (Association des GastroEntérologues Oncologues) academic group.

Funding: Has not received any funding.

Disclosure: C. Neuzillet: Research funding (outside the study): Celgene; Clinical trial PI: AstraZeneca. A. Casadei Gardini: Consulting, Advisory role: Eisai; Speakers' bureau: Bayer. B.J.-C. Rousseau: Advisory board: Bayer. M. Scartozzi: Consulting Advisory role, Speakers' bureau: Bayer, Amgen, Merck, Sanofi; Research funding : Bayer, Msd,

Bms, Sanofi. A. Lievre: Consulting, Advisory role: Merck, Amgen, Bayer, Ipsen, Shire; Speakers' bureau: Merck, Roche, Amgen, Bayer, Ipsen, Novartis, BMS. All other authors have declared no conflicts of interest.

766P Prognostic factors in patients with advanced biliary tract cancer (BTC) who showed durable disease control with first-line gemcitabine plus cisplatin (GemCis)

J. Hyung, C. Yoo, K-P. Kim, B.J. Kim, J.H. Jeong, H-M. Chang, B-Y. Ryoo

Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: GemCis is the standard first-line chemotherapy for patients with advanced BTC. In ABC-02 study, the BTC patients received up to 6-8 cycles of three-weekly GemCis. Currently, treatment strategy and prognostic factors of patients without progression to first-line GemCis is not well defined.

Methods: Advanced BTC patients treated with GemCis between April 2010 and February 2016 at Asan Medical Center, Seoul, Korea, were retrospectively analyzed. The patients without progression after 6-8 cycles were included in the study. Univariate and multivariate analyses were performed to identify prognostic factors for overall survival (OS).

Results: Among the 740 BTC patients in the initial screen, 231 cases (31.2%) were eligible for analysis. Median follow-up period was 23.8 months [IQR 5.1-86.3 months], the median OS from the initiation of treatment was 22.3 months [95% CI 19.0-25.7], and the median PFS was 12.5 months [95% CI 11.1-13.9]. Median age was 60 year-old (29-77) and 211 patients (91.3%) had ECOG performance status of 0 or 1 at the time of diagnosis. Objective response was achieved in 49 patients (21.2%). OS was significantly associated with number of metastatic site (>2 vs < 2: Hazard ratio [HR]=1.5, 95% CI 1.0-2.3, $p = 0.04$), best response to GemCis (stable disease vs partial response: HR = 1.9, 95% CI 1.3-2.7, $p = 0.006$). Maintenance therapy after durable disease control after at least 6 cycles of GemCis was not associated with OS ($p = 0.47$).

Conclusions: In patients who showed durable disease control to first-line GemCis, number of metastatic sites and objective response were significant poor prognostic factors. These results might help to design future clinical trials for this patient population.

Legal entity responsible for the study: Changhoon Yoo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

767P Predictive factors of outcome in patients with advanced biliary tract cancer receiving gemcitabine plus cisplatin as first-line chemotherapy

Y. Suzuki[1], M. Kan[1], G. Kimura[1], K. Umemoto[1], K. Watanabe[1], M. Sasaki[1], H. Takahashi[1], Y. Hashimoto[1], H. Imaoka[1], I. Ohno[1], S. Mitsunaga[1], M. Ikeda[1]

[1]*Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan*

Background: Gemcitabine plus cisplatin (GC) is acknowledged as standard chemotherapy for advanced biliary tract cancer (BTC). Few studies have been conducted to identify the prognostic factors in patients receiving this therapy. The purpose of this study was to identify and validate predictive factors of outcome in patients with advanced BTC receiving GC therapy.

Methods: The data of 307 patients with advanced BTC who received GC as the first-line chemotherapy at our institution from January 2007 to June 2017 were reviewed retrospectively. All patients were randomly assigned to the investigation and validation datasets at the ratio of 2:1. Multivariate analysis was conducted to identify the prognostic factors in the investigation dataset ($n = 205$) and the patients were classified, according to the prognostic factors, into three risk groups, that is, groups with a good, intermediate and poor prognosis. This classification was then applied to the validation dataset ($n = 102$).

Results: The median overall survival (OS) and 1-year survival rate in the investigation dataset were 13.0 months (95% confidence interval, 11.0-13.9) and 54.7% respectively. Multivariate analysis identified the performance status, pretreatment serum lactate dehydrogenase level and pretreatment neutrophil-to-lymphocyte ratio as independent predictive factors of the OS. The patients were classified into three groups according to the identified prognostic factors, and the outcomes were found to differ significantly among the three groups ($p < 0.01$). When this classification was applied to the validation dataset, the OS was found to differ significantly among the three risk groups ($p < 0.05$).

Conclusions: This study identified three predictive factors of outcome, which allowed patients of advanced BTC receiving GC therapy to be classified into three risk groups.

Legal entity responsible for the study: Principal Investigator: Masafumi Ikeda, M.D.

Funding: Has not received any funding.

Disclosure: H. Takahashi: Research funding: Bayer Pharmaceutical, Bristol-Myers Squibb; Honoraria: Taiho Pharmaceutical. I. Ohno: Honoraria: Taiho Pharmaceutical, Merck Serono. M. Ikeda: Research fundings: Bayer Yakuhin, Kyowa Hakko Kirin, Yakult, Taiho Pharmaceutical, Eli Lilly Japan, Ono Pharmaceutical, Eisai, AstraZeneca, Zeria Pharmaceutical, Baxter, Chugai Pharmaceutical, Bristol Myers Sqiibb, Merck Serono, Kowa, Nano Carrier, ASLAN Pharmaceuticals; Honoraria: Novartis Pharma, Bayer Yakuhin, Bristol-Myers Squibb, Abbott Japan, Eisai, Eli Lilly Japan, Taiho Pharmaceutical, Chugai Pharmaceutical, Daiichi-Sankyo, Yakult, Otsuka Pharmaceutical, and Nobelpharma. All other authors have declared no conflicts of interest.

768P Nomograms predicting survival of patients with advanced or recurrent biliary tract cancer receiving a first-line chemotherapy

N. Takahara, Y. Nakai, K.O. Saito, M. Sato, H. Ooyama, S. Kanai, T. Suzuki, T. Sato, R. Hakuta, K. Ishigaki, T. Takeda, S. Mizuno, H. Kogure, M. Tada, K. Koike

Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Background: Some clinical factors are known to be associated with the survival of patients with advanced biliary tract cancer (BTC). A comprehensive model based on these variables is necessary for prediction of an individual's survival and appropriate patient counseling.

Methods: A nomogram for predicting 1-year survival in patients with advanced BTC in the palliative chemotherapy setting was developed using clinical data from 222 patients with advanced or recurrent BTC who had received first-line systemic chemotherapy from 2006 to 2017 at The University of Tokyo Hospital (Baseline Nomogram). For 214 patients whose initial response to chemotherapy is known, another nomogram (ChemoResponse-based Nomogram) was constructed using the response to chemotherapy as additional variable. Nomogram performance in terms of discrimination and calibration ability was evaluated using the C statistic.

Results: Two different nomograms were developed and subjected to internal validation. The baseline nomogram incorporated 8 baseline clinical variables (age, sex, performance status, tumor location, disease status, CEA, CA19-9, and modified Glasgow prognostic score), whereas the chemoresponse-based nomogram was composed of 9 variables including initial response to chemotherapy evaluated by RECIST ver1.1. Internal validation revealed good performance of the two nomograms in discrimination: C statistics of 0.685 for the baseline and 0.734 for the chemoresponse-based nomogram, which showed better discrimination performance than the baseline nomogram.

Conclusions: This study suggests that individual 1-year survival probability of patients receiving first-line systemic chemotherapy for advanced or recurrent BTC can be reliably predicted by a nomogram-based method incorporating clinical variables and initial response to chemotherapy.

Legal entity responsible for the study: The ethical committee of The University of Tokyo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

769P Stromal progesterone receptor expression and long-term survival in patients with resected periampullary adenocarcinoma

G. Andersson, S. Olsson-Hau, S. Lundgren, M. Heby, B. Nodin, K. Jirstrom

Department of Clinical Sciences Lund, Division of Oncology and Pathology, Lund, Sweden

Background: Early trials have reported a beneficial effect from tamoxifen treatment in patients with unresectable pancreatic cancer, in particular in women. However, the presence and prognostic significance of female hormone receptors in pancreatic or other periampullary cancers has not yet been described.

Methods: Immunohistochemical screening of normal and malignant pancreatic tissue revealed that the predominantly expressed female hormone receptor was the progesterone receptor (PgR), in particular in the cancer-associated stroma. The impact of PgR expression on overall survival (OS) was further examined on tissue microarrays with primary tumours from a consecutive retrospective cohort of 175 patients with resected periampullary adenocarcinoma.

Results: Median follow-up time was 29.7 (range 1.9–185.1) months. Stromal PgR positivity (PgR+), allover denoted in 31% of the cases, was significantly higher in pancreatobiliary-type than in intestinal-type tumours (38.7% vs 19.0%, $p = 0.008$), with an equal distribution between sexes. Stromal PgR+ was significantly associated with a prolonged OS in KRAS-mutated tumours, whereas the opposite was seen in KRAS wild-type tumours (p for interaction =0.015). This association was particularly evident in women, with a median OS of 60.5 months for PgR+/KRAS mutated tumours and 9.9 months for PgR+/KRAS wild-type tumours (p for interaction <0.001). PgR expression was not prognostic in male patients.

Conclusions: The finding of stromal PgR expression, and its link to clinical outcome in a considerable proportion of pancreatic and other periampullary cancers is novel. The concept of tamoxifen treatment for patients with unresectable disease, in particular elderly women, should be pursued, and PgR and KRAS may be relevant biomarkers for improved patient stratification.

Legal entity responsible for the study: Karin Jirstrom.

Funding: Swedish Government Grant for Clinical Research; Lund University Faculty of Medicine and University Hospital Research Grants; Cancerfonden (CAN 2016/483); Fru Berta Kamprads Stiftelse; Vetenskapsrådet (2015-03598).

Disclosure: All authors have declared no conflicts of interest.

770P A novel immune-inflammatory score to predict survival in patients (pts) with advanced biliary tract cancer (ABTC) receiving first-line chemotherapy (1-line cht)

M. Salati, F. Caputo, A. Spallanzani, M. Rimini, F. Gelsomino, K. Andrikou, S. Cascinu
Medical Oncology, University Hospital of Modena, Modena, Italy

Background: Cht is the mainstay of treatment for ABTC with median overall survival (mOS) < 12 months. Given the palliative intent of treatment, its limited survival gain and not negligible toxicities it is of paramount importance to properly select pts. Determinants of immune-inflammation are regarded as promising prognostic factors in ABTC.

Methods: Clinical and laboratory data before starting 1-line cht were evaluated in 123 pts with unresectable locally advanced and metastatic ABTC (intrahepatic, perihilar and distal cholangiocarcinoma and gallbladder cancer) treated from 1st January 2010 to 31st July 2017 at Modena Cancer Centre. Potential prognostic factors were assessed by univariate (Cox proportional hazard univariate model) and multivariate analyses (multiple Cox proportional hazard regression with the likelihood ratio test).

Results: At univariate analysis ECOG PS > 0, metastatic disease, gallbladder cancer, no previous surgery, monocht, LDH > upper limit of normal, albumine < 3.5 gr/dl, absolute neutrophil count (ANC) > 8000/μl, lymphocyte/monocyte ratio (LMR) < 2.1, neutrophil/lymphocyte ratio (NLR) > 3, platelet/lymphocyte ratio > 160, AST > 40 IU/L, gamma-glutamyl-transpeptidase > 40 IU/L, CEA > 9.5 ng/ml, CA19-9 >700 U/L were significantly associate with shorter OS. At multivariate analysis, LMR < 2.1, NLR > 3, ANC > 8000/μl, albumine < 3.5 gr/dl retained statistical significance as poor prognostic factors. By combining these four variables, three different risk groups were identified: low-risk group (0 factors), intermediate-risk group (1-2 factors) and high-risk group (3-4 factors), with mOS of 22, 12, and 5 months respectively ($P < 0.001$). The prognostic value of the score was indipendent from treatment procedures (doublet vs monocht) and primary tumour site ($P < 0.001$).

Conclusions: We developed a cost-effective and easily-available scoring system that discriminates ABTC treated with 1-line cht into three, different, statistically significant prognostic groups. It could become a useful tool to add to established factors for improving pts' selection in daily practice.

Legal entity responsible for the study: Massimiliano Salati.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

771P "The German- Registry" of incidental gallbladder cancer and the GAIN - phase III trial: Transformation from a registry to treatment platform due to a trial in trial concept

T.O. Götze[1], V. Paolucci[2], S-E. Al-Batran[1]
[1]Institute of Clinical Cancer Research, Nordwest-Krankenhaus, Frankfurt am Main, Germany, [2]Surgical Deptartment, Ketteler- Krankenhaus, Offenbach, Germany

Background: The biggest biliary platform in Europe - the German- Registry (GR) shows significant survival benefit for radical resection (RR) in gallbladder carcinoma. But nevertheless results for T2-3 are still disappointing even after RR.

Methods: For data analysis the GR was used. Currently more than 1100 cases of incidental gallbladder carcinoma (IGBC) are registered. Based on the GR a new multicenter a neoadjuvant trail (GAIN) with the support of the DFG (grant) /AIO/CALGP/ACO has been started in 20 centers in Germany and in addition a trial in trial concept, including GAIN and the GR is planned. GAIN is a randomized multicenter phase III study for T2-3 IGBCs + resectable and borderline resectable biliary tract cancers (BTC), evaluating the role of neoadjuvant CTX with Gem/Cis in a multimodal setting in front of and after surgery vs. upfront surgery alone. If screened pts. is not eligible for curative treatment, pts. will be directly included in another 1st. line trial (trial- in- trial concept) under the direction of the GR. All IGBCs in addition will be directly registered in the GR.

Results: In the GR (n > 1100pts) in T1b- T3 cases there is a significant survival benefit for patients with IRR. Wedge resection of the liver showed good data in T1b and T2. For T3 more radical techniques showed better results. Less than 50% of T2–3 tumors in the GR have had RR.

Conclusions: There is a significant benefit after RR in T1b- T3 IGBC but the results in T2-3 are disappointing like in the whole entity of BTC. Data of current (PRODIGE 12, BILCAP) adjuvant trials are inconsistent. Therefore the multimodal concept based on a biliary network is needed. The GAIN trial is supported by the DFG and is also supported by the German AIO and the German CALGP/ACO. Due to the trial in trial concepts patients screened for GAIN but are candidates for 1st line will be directly included in another 1st line trial without time delay so the project directly closes a healthcare gap. The data of the GR were already able to change the current treatment standards for GBCA in Germany, reflected by the current S3- Guidelines. So GR will now transform to treatment platform and potentially create a new way how to treat biliary pts.

Clinical trial identification: EudraCT: 2017-004444-38; DFG Projektnumber 316590476.

Legal entity responsible for the study: Krankenhaus Nordwest gGmbH Frankfurt.

Funding: DFG (Deutsche Forschungsgemeinschaft/ German Research Foundation) DFG- Projektnumber 316590476.

Disclosure: T.O. Götze: COI: MSD, Lilly, BMS, Celgene; Shire, Bayer. All other authors have declared no conflicts of interest.

772P ARCAD-NADEGE cohort: Result of a small bowel adenocarcinomas prospective cohort

T. Aparicio[1], S. Manfredi[2], D. Tougeron[3], J. Henriques[4], O. Bouche[5], D. Pezet[6], G. Piessen[7], R. Coriat[8], A. Zaanan[9], J.L. Legoux[10], E. Terrebone[11], M. Pocard[12], J-M. Gornet[13], D. Vernerey[4], P. Afchain[14]
[1]Gastroenterology and Digestive Oncology, Hôpital Saint Louis, Paris, France, [2]Gastroenterology, CHU de Dijon, Dijon, France, [3]Gastroenterology, CHU Poitiers, Jean Bernard Hôpital, Poitiers, France, [4]Statistics, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [5]Gastroenterology, CHU de Reims - Hôpital Robert Debré, Reims, France, [6]Surgery, CHU de Clermont Ferrand, Clermont Ferrand, France, [7]Digestive Surgery, C.H.U. Claude Huriez, Lille, France, [8]Gastroenterology, Hôpital Cochin, Paris, France, [9]Gastroenterology and Digestive Oncology, Hopital European George Pompidou, Paris, France, [10]Hepato-Gastroenterolgy and Digestive Oncology, C.H.R. Orleans - La Source, Orleans, France, [11]Gastroenterology, CHU Haut Lévèque, Pessac, France, [12]Surgery, CHU Lariboisière, Paris, France, [13]Gastroenterology and Digestive Oncology, Hôpital St. Louis, Paris, France, [14]Oncology, CHU Saint Antoine, Paris, France

Background: Small bowel adenocarcinoma (SBA) is a rare tumour. Data are coming from register study or monocentric retrospective studies. The purpose of the NADEGE cohort is to describe characteristics and prognosis of SBA in unselected patients (pts) at a nationwide level.

Methods: All the pts with a SBA diagnosed from January 2009 to December 2012 were enrolled in the NADEGE cohort. The study involved 74 centres that enrolled 347 eligible pts.

Results: Pts were predominantly male (59%), median age: 63 years [23-90]. Primary locations were duodenum (60.6%), jejunum (20.7%) and ileum (18.7%). The tumour was poorly differentiated (20.9%), moderately (38.6%), well differentiated (40.5%) and not determined (7.5%). A predisposing disease was reported in 68 (19.7%) cases: Crohn disease 30 (8.6%), Lynch syndrome 24 (6.9%), familial adenomatous polyposis (FAP) 6 (1.8%), celiac disease 6 (1.8%) and Peutz-Jeghers syndrome 2 (0.6%). The tumour was metastatic at diagnostic in 122 (35.2%) pts, localized and resected in 202 (58.2%) and locally advanced in 19 (5.5%). Crohn disease was significantly associated with younger age, poor differentiation and ileum primary and Lynch syndrome with younger age, poor differentiation, early stage and duodenal primary. Adjuvant chemotherapy was performed in 61.5% pts with locally resected tumour mainly with oxaliplatin based regimen (89.9%). Palliative chemotherapy was performed in 85.1% of pts with metastases mainly with oxaliplatin based regimen (69.8%). With a median follow-up of 54 months, the 5 years overall survival (OS) rate was 87%, 78% and 55% for stage I, II, III respectively and the median survival was 12.7 months for stage IV. In pts with resected tumour multivariate analysis revealed a higher risk of death associated to poor differentiation (HR = 1.85, 95%CI 1.01-3.39, p = 0.047) and T4 (HR = 2.51, 95%CI 1.45-4.36, p = 0.001). Stage IV pts treated by chemotherapy had a better survival than pts not treated (14.3 vs 2.2 months, p = 0.0002).

Conclusions: NADEGE cohort provide data on SBA treated in a recent period. Tumours characteristics differ according to predisposing disease. FOLFOX chemotherapy is the main regimen used in adjuvant and metastatic setting. Tumour grade and T stage are prognostic factors for OS in resected tumour.

Legal entity responsible for the study: GERCOR.

Funding: ARCAD.

Disclosure: All authors have declared no conflicts of interest.

773P Impact of the number of nodes examined on survival in node negative small bowel adenocarcinoma: A SEER database analysis

M. Thiessen, P.A. Tang, R. Lee-Ying, J.G. Monzon
Medical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada

Background: Adjuvant chemotherapy (AC) may have benefit in both node negative (N-) and node positive (N+) non-metastatic small bowel adenocarcinoma (SBA). In N- cases, increased number of nodes examined (NNE) has been associated with increased survival. The objective of this analysis was to determine whether N- status is associated with lower NE at time of curative surgery compared to N+ cases, and how many NNE represents adequate sampling.

Methods: SAS 9.4 software and cases of non-metastatic SBA with complete AJCC staging (2004+) from the SEER database were used for this analysis. Age, gender, race, grade, NNE and T stage were compared between N+ and N- cases. Survival analysis

using N- cases was performed to determine which nodal cut-offs and variables best predicted survival.

Results: 613 cases of non-metastatic SBA (183 N- and 430 N+) diagnosed from 2004 to 2014 were analyzed. T stage and nodal sampling were the only two variables that differed statistically between N- and N+ cases (Table). Using the Log-rank test, a statistical separation in survival curves was identified at a minimum of > =13 NNE ($p = 0.0136$), a maximum of > =21 NNE ($p = 0.0142$), and with the greatest statistical separation at > =17 NNE ($p = 0.0003$). Out of age, gender, race, grade, > =13 NNE, > =17 NNE, > = 21 NNE, and T stage, only age, node cut-off of > =17 (HR 0.47, p=.0032) and T stage remained after stepwise selection of variables for Cox regression modelling. ROC's for Cox Regression models at 60 months, which included Age, T stage and either > = 13 NNE, > = 17 NNE, or > = 21 NNE were associated with AUC's of 0.700, 0.717 and 0.667, respectively.

Table: 773P

	Node -	Node +	p
Median Nodes Sampled	9	12	0.0008
Proportion of Cases by T Stage			
T1	10.9%	0.7%	<.0001
T2	11.5%	1.6%	<.0001
T3	60.7%	45.4%	0.0006
T4	16.9%	52.3%	<.0001

Conclusions: N- SBAs are associated with decreased nodal sampling compared to N+ SBAs. Low sampling is associated with decreased survival, possibly related to the presence of occult nodal disease. While further work is needed to determine what is considered adequate nodal sampling in N- SBA's, this analysis suggests that N- cases where less than 17 nodes have been examined have a poorer outcome.

Legal entity responsible for the study: Maclean Thiessen.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

774P The role of adjuvant therapy in resectable SBA: A different clinicians attitude with a relevant impact on outcome

G. Orsi[1], K. Andrikou[1], F. Bergamo[2], F. Nappo[3], C. Manai[2], A. Passardi[4], M. Puzzoni[5], S. Vallarelli[6], M. Libertini[7], M.L. Riggi[1], G. Pugliese[8], A. Zaniboni[7], M. Schirripa[9], L. Procaccio[3], N. Silvestris[10], M. Scartozzi[5], A. Casadei Gardini[4], V. Zagonel[2], S. Cascinu[8]

[1]Department of Oncology/Hematology, University of Modena and Reggio Emilia, Modena Cancer Center, Modena, Italy, [2]Medical Oncology Unit 1, Department of Clinical and Experimental Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy, [3]Medical Oncology 1, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [4]Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [5]University of Cagliari, Department of Medical Oncology, Cagliari, Italy, [6]Istituto Tumori "Giovanni Paolo II", Medical Oncology Unit, National Cancer Research Centre, Bari, Italy, [7]Fondazione Poliambulanza, Oncology Department, Brescia, Italy, [8]Oncologia, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [9]Medical Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [10]Istituto Tumori "Giovanni Paolo II", Medical Oncology Unit and Scientific Direction, National Cancer Research Centre, Bari, Italy

Background: Small bowel adenocarcinoma (SBA) is a rare malignancy that accounts for 1-2% of gastrointestinal tumours. We evaluated the clinico-pathological characteristics, outcomes and prognostic factors of patients who underwent surgery for SBA.

Methods: We retrospectively analysed the features and outcome parameters of 54 SBA patients from 6 italian institutions between 2005 and 2017.

Results: The primary tumour was in the duodenum, jejunum and ileum in 30 (55.6%), 18 (33.3%) and 6 (11.1%) patients, respectively. Among the 54 patients studied, adjuvant chemotherapy were performed in 35.2 % of patients with stage II and in 27.8 % of patients with stage III. Relapse rates were higher for chemonaive patients compared to treated patients (50% vs 23.5%). Median overall (OS) and progression-free survival (PFS) were 26.98 and 19.78 months, respectively. Duodenal adenocarcinoma ($p = 0.022$), lymph node metastases ($p = 0.00269$), long-term treatment with metformin ($p = 0.0095$), no adjuvant treatment ($p = 0.0006$) and PLR >0,1766 ($p = 0,0137$) were associated with poor overall survival outcomes. The factors associated with PFS were patients with older age (>75 years) ($p = 0.04$) and T4 according to TNM system ($p = 0.02$).

Conclusions: The lack of well-defined guidelines for treatment of SBA justifies the heterogeneity of therapeutic choices resulting in negative impact on patient outcomes. Thus, there is an urgent need for prognostic and predictive biomarkers to guide therapy decisions for these patients. Our results suggest that the site, lymph node metastases, metformin and PLR >0,1766 could be novel prognostic markers for SBA patients who undergo curative surgery. However, prospective studies are necessary to confirm the role of these factors and identify new potential biomarkers of treatment efficacy, that could improve the selection of the right treatment for the right patient.

Legal entity responsible for the study: Modena University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

775TiP A phase III, randomized, open-label study to compare the efficacy of tislelizumab versus chemotherapy as second-line therapy for advanced unresectable/metastatic esophageal squamous cell carcinoma (ESCC)

L. Shen[1], J.A. Ajani[2], S-B. Kim[3], E. Van Cutsem[4], B. Guo[5], J. Song[6], V. Paton[7], K. Kato[8]

[1]GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China, [2]MD Anderson Cancer Center, The University of Texas, Houston, TX, USA, [3]Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [4]Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium, [5]Medical Oncology, BeiGene (Beijing) Co., Ltd., Beijing, China, [6]Biometry, BeiGene USA, Inc., Fort Lee, NJ, USA, [7]Clinical Development, BeiGene USA, Inc., Emeryville, CA, USA, [8]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan

Background: Approximately 40% of patients (pts) with esophageal cancer are diagnosed with advanced unresectable or metastatic disease; the 5-year survival rate for advanced disease is < 5%. Inhibition of PD-1 has demonstrated antitumor activity and was generally well tolerated in pts with advanced unresectable or metastatic ESCC. Tislelizumab, a humanized IgG4 monoclonal antibody, has high affinity and specificity for PD-1. Tislelizumab was specifically engineered to minimize $F_c\Upsilon R$ binding on macrophages that, based on preclinical evidence, is believed to minimize potentially negative interactions with other immune cells. A first-in-human study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and had preliminary antitumor effects in pts with solid tumors, including ESCC. A recommended phase 3 dose of 200 mg administered IV every 3 weeks (Q3W) has been established for tislelizumab.

Trial design: This phase 3, randomized study (NCT03430843) was designed to evaluate the efficacy, safety, and tolerability of tislelizumab compared with chemotherapy for second-line treatment of advanced unresectable/metastatic ESCC. Adult pts, aged ≥18 years, with histologically or cytologically confirmed ESCC that has progressed with first-line therapy, have ≥1 measurable/evaluable lesion, and have an Eastern Cooperative Oncology score ≤1 will be enrolled. Approximately 450 pts will be randomized (1:1) to receive either tislelizumab 200 mg IV Q3W or investigator-chosen chemotherapy (paclitaxel 135–175 mg/m^2 IV Q3W or 100 mg/m^2 IV weekly for 6 weeks with 1 week of rest [Japan only], docetaxel 75 mg/m^2 or 70 mg/m^2 IV Q3W, or irinotecan 125 mg/m^2 IV Q3W). Overall survival is the primary endpoint; secondary endpoints include objective response rate, progression free survival, duration of response, and health-related quality-of-life outcomes. Safety/tolerability will be assessed by monitoring adverse events (AEs), including immune-related AEs, as well as physical examinations, vital signs, and electrocardiograms. As of 11 April 2018, 6 patients have been enrolled.

Clinical trial identification: NCT03430843.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Regina Switzer, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: BeiGene, Ltd.

Funding: BeiGene, Ltd.

Disclosure: J.A. Ajani: Honoraria, research funding: BWS, Five Prime Therapeutics, Medscape, Celgene, Taiho Pharmaceutical, Merck, Delta-Fly, Gilead. E. Van Cutsem: Consulting role, research funding: Baxter, Lilly, Roche, Servier, Amgen, Bayer, Boehringer, Celgene, MSO, Merck, Novartis, Ipsen, Roche, Sanofi. B. Guo: Employee, ownership interest: BeiGene. J. Song, V. Paton: Employee: BeiGene. K. Kato: Consulting role, speakers' bureau, research funding: Beigene, MSD, Ono Pharmaceutical, BMS, Eli Lilly, Shionogi, Merck Serono. All other authors have declared no conflicts of interest.

776TiP Global phase III study of tislelizumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma (HCC): A trial-in-progress

S. Qin[1], R.S. Finn[2], M. Kudo[3], T. Meyer[4], A. Vogel[5], M.P. Ducreux[6], T.M. Macarulla[7], G. Tomasello[8], F. Boisserie[9], J. Hou[10], C. Li[11], J. Song[12], A.X. Zhu[13]

[1]Medical Oncology, People's Liberation Army (PLA) 81 Hospital, Nanjing, China, [2]School of Medicine, University of California Los Angeles, Los Angeles, CA, USA, [3]Department of Gastroenterology and Hepatology, Kindai University School of Medicine, Osaka, Japan, [4]Medical Oncology, University College London Cancer Institute, London, UK, [5]Medical Oncology, Medizinische Hochschule Hannover, Hannover, Germany, [6]Medical Oncology, Gustave Roussy, Villejuif, France, [7]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital (HUVH), Barcelona, Spain, [8]Medical Oncology, Azienda Istituti Ospitalieri di Cremona, Cremona, Italy, [9]Clinical Science, BeiGene USA, Inc., Fort Lee, NJ, USA, [10]Immuno-Oncology, BeiGene USA, Inc., Emeryville, CA, USA, [11]Medical Oncology, BeiGene (Beijing) Co., Ltd., Beijing, China, [12]Biometry, BeiGene USA, Inc., Fort Lee, NJ, USA, [13]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA

Background: Unresectable HCC accounts for 70% of diagnosed HCC. Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity and specificity for programmed cell death receptor-1 (PD-1). Tislelizumab was specifically engineered to

minimize $F_c\gamma R$ binding on macrophages that, based on preclinical evidence, is believed to minimize potentially negative interactions with other immune cells. A phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed preliminary evidence of antitumor activity in patients with advanced solid tumors, including HCC. A recommended phase 3 dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been established for tislelizumab.

Trial design: This global, phase 3, randomized, multicenter study (NCT03412773) was designed to evaluate the efficacy and safety of tislelizumab compared with sorafenib as a potential first-line treatment of unresectable HCC. Adult patients, aged ≥18 years, with unresectable, histologically confirmed HCC, an ECOG score ≤1, Child-Pugh A classification, BCLC Stage C disease or BCLC Stage B disease that has relapsed after loco-regional therapy, and who have not received prior systemic therapy, are being enrolled. Approximately 640 patients from 100 international centers are planned to be randomized (1:1) to receive tislelizumab 200 mg IV Q3W or sorafenib 400 mg orally BID. The primary outcome of this study is overall survival (OS) of patients treated with tislelizumab compared with OS of patients treated with sorafenib; secondary outcomes include objective response rate, progression-free survival, duration of response, time to progression, and quality-of-life outcomes. Safety/tolerability assessments include monitoring adverse events (AEs), including immune-related AEs, as well as physical examinations, vital signs, and electrocardiograms. Exploratory endpoints include assessment of potential biomarkers, characterization of the tislelizumab pharmacokinetic profile in patients with HCC, and assessment of host immunogenicity to tislelizumab. As of 11 April 2018, 11 patients have been enrolled.

Clinical trial identification: NCT03412773.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Regina Switzer, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: Beigene, Ltd.

Funding: BeiGene, Ltd.

Disclosure: R.S. Finn: Consulting, Advisory role, Research funding: Pfizer, Bayer, Novartis, BMS. M. Kudo: Honrorara, Advisory role, Research funding: Chugai, Otuka, Takeda, Taiho, Sumitomo Dainippon, Daiichi Sankyo, MSD, Esiai, Bayer, Ajinomoto, Kowa, BMS, Abbvie. T. Meyer: Advisory role, Research funding: BMS, Merck, Beigene, Eisai, Bayer, BTG, Ipsen. A. Vogel: Advisory role, Research funding, Travel/accommodation/expenses, Honoraria: Novartis, MSD, BMS, Delcath Systems, Sanofi, Bayer, Ipsen, Roche. M.P. Ducreux: Ad boards, Symposiums, Research funding: Roche, Merck Serono, Amgen, Novartis, Sanofi, Bayer, Sirtex, Lilly, Servier, Ipsen, Pfizer. F. Boisserie, J. Hou, C. Li: C, J. Song: Employee: BeiGene. A.X. Zhu: Advisory role, Research funding: Eisai, BMS, Novartis, Merck, Sanofi, AstraZeneca, Exelixis, Bayer, Lilly. All other authors have declared no conflicts of interest.

777TiP A phase III, double-blind, randomized study of pamiparib versus placebo as maintenance therapy in patients with inoperable, locally advanced, or metastatic gastric cancer that responded to platinum-based first-line chemotherapy

F. Ciardiello[1], Y-J. Bang[2], J. Bendell[3], A. Cervantes[4], R. Brachmann[5], K. Zhang[6], M. Raponi[7], H. Farin[8], L. Shen[9]

[1]Medical Oncology, University of Campania "Luigi Vanvitelli", Naples, Italy, [2]Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea, [3]GI Oncology Research, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [4]Medical Oncology, Instituto de Investigación Sanitaria INCLIVA, Valencia, Spain, [5]Clinical Development, BeiGene USA, Inc., Emeryville, CA, USA, [6]Biostatistics, BeiGene USA, Inc., Emeryville, CA, USA, [7]Translational Research and Biomarkers, BeiGene USA, Inc., Emeryville, CA, USA, [8]Clinical Development, BeiGene USA, Inc., Cambridge, MA, USA, [9]Medical Oncology, Beijing Cancer Hospital, Beijing, China

Background: Gastric cancer is the fifth most common cancer, and is the third leading cause of cancer deaths worldwide. In patients with locally advanced or metastatic gastric cancer, fluoropyrimidine- and platinum-based combination chemotherapy is first-line standard of care. Despite refinement in chemotherapy regimens, outcomes are poor and median survival after first-line treatment remains low. A subset of gastric cancers exhibit platinum sensitivity and genomic instability that is characteristic of homologous recombination deficiency (HRD). Poly(ADP-ribose) polymerase proteins 1 and 2 (PARP1/2) are involved in DNA damage repair, and their inhibition is cytotoxic for cells with HRD. Pamiparib (previously known as BGB-290) is a selective PARP1/2 inhibitor that crosses the blood-brain barrier, has shown potent DNA–PARP trapping, and has demonstrated antitumor activity in preclinical models. In early phase clinical studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed preliminary antitumor activity. These studies also established 60 mg orally twice daily as the recommended pivotal dose.

Trial design: This double-blind, placebo-controlled, randomized, multicenter phase 3 study (NCT03427814) conducted in Asia, Australia, Europe, and North America is designed to compare the efficacy, safety, and tolerability of pamiparib with placebo as maintenance therapy in ~540 patients with advanced gastric cancer who have responded to first-line, platinum-based chemotherapy. Patients who are ≤8 weeks after their last platinum dose of first-line chemotherapy will be randomized 1:1 to receive either pamiparib 60 mg twice daily or placebo. Patient randomization will be stratified by genomic loss of heterozygosity status (ie, high versus low), region, and ECOG status. Radiologic assessments will be centrally evaluated per RECIST every 8 weeks after first dose. The primary endpoint is progression-free survival; key secondary endpoints include safety/tolerability, overall survival, objective response rates, and duration of response.

Clinical trial identification: NCT03427814.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Aarati Rai, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: BeiGene, Ltd.

Funding: Beigene, Ltd.

Disclosure: Y-J. Bang: Consulting role, research funding: Samyang, Beigene, AstraZeneca, MedImmune, Novartis, Genentech/Roche, MSD, Merck Serono, Bayer, GSK, BMS Pfizer, Lilly, Boeringer Ingelheim, Macrogenics, Takeda, Boston Biomedical, Five Prime, CKD, Ono, Taiho, Beigene, Curis, GreenCross. J. Bendell: Gilead, Genentech, BMS, Five Prime, Lilly, Merck, MedImmune, Celgene, EMD Serono, Taiho, H. Macrogenics, GSK, Novartis, OncoMed, Leap, TG Therapeutics, Astrazeneca, BI, Daiichi Sankyo, Bayer, Incyte, Apexigen, Roche, Koltan, SynDevRx, Forty Seven, Abbvie, StemCentrix, Array, Onyx, Sanofi, Takeda, Abbott, Eisai, Celldex, Agios, Armo, CytoMx, Nektar, Armo, Boston Biomedical, Ipsen, Merrimack, Novartis, Tarveda, Tyrogenex, Oncogenex, Marshall Edwards, Pieris, Mersana, Calithera, Blueprint, Gritstone, Evelo, Forma, Forty Seven, EMD Serono, Merus. R. Brachmann, K. Zhang, H. Farin: Employee: BeiGene: M. Raponi: Employee: BeiGene; Ownership interest: BeiGene, Clovis Oncology. All other authors have declared no conflicts of interest.

778TiP Ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive locally advanced or metastatic esophagogastric adenocarcinoma (EGA): The randomized phase II INTEGA trial (AIO STO 0217)

E. Goekkurt[1], M. Binder[2], S. Lorenzen[3], P.C. Thuss-Patience[4], S-E. Al-Batran[5], A. Hinke[6], S. Hegewisch-Becker[7], S. Nilsson[2], C. Bokemeyer[2], A. Stein[2]

[1]Hematology-Oncology Practice Eppendorf (HOPE), University Cancer Center Hamburg (UCCH), Hamburg, Germany, [2]University Cancer Center Hamburg (UCCH), University Medical Center HH-Eppendorf, Hamburg, Germany, [3]III. Medizinischen Klinik, Rechts der Isar Hospital,TUM, Munich, Germany, [4]Medizinische Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [5]Institute of Clinical Cancer Research, Nordwest-Krankenhaus, Frankfurt am Main, Germany, [6]Cancer Clinical Research Consulting, CCRC, Berlin, Germany, [7]HOPE, Hämatologisch-Onkologische Praxis Eppendorf, Hamburg, Germany

Background: Inhibition of PD-1 has demonstrated improved survival as single agent in refractory EGA compared to placebo. In 1st line HER2 negative EGA combination regimens of PD-1 inhibitors (i) with chemotherapy or CTLA4i are currently investigated. Since a survival benefit could not be shown for the addition of pertuzumab, the TOGA regimen with platinum, fluoropyrimidine and trastuzumab remains the standard of care in 1st line HER2+ EGA. Combination regimens with PD-1i +/- CTLA4i have not yet been evaluated in HER2+ EGA. Thus, the INTEGA trial will evaluate two trastuzumab and PD-1i based combinations to determine the best regimen to challenge the TOGA regimen in a phase 3 trial.

Trial design: INTEGA is a randomized exploratory phase II investigator initiated trial by the AIO esophagogastric working group with two experimental arms. Patients (pts) with previously untreated (for metastatic disease) HER2 + (IHC3+ or 2+/ISH+) EGA will be randomized to receive trastuzumab and nivolumab in combination with either mFOLFOX6 or ipilimumab (3mg/kg every 3 weeks). Treatment with nivolumab is limited to a maximum of 12 months, ipilimumab to 4 applications. Primary endpoint is 12month overall survival rate, which should be increased from 55% (TOGA regimen) to 70% in each arm. Based on a type I error of 5% and 80% power 41 pts per arm are required and with a 15% drop out rate overall 97 pts will be randomized. An early stopping rule will be applied in case of an increase in toxicity after the first 15 pts received at least two months of treatment. The trial is flanked by a large translational program including immunoprofiling to determine and correlate the respective immune response signatures with clonal dynamics. Recruitment has started in March 2018. Overall 40 German sites are planned. Conclusion: The INTEGA trial will determine the feasibility and efficacy of trastuzumab and nivolumab in combination with either mFOLFOX6 or ipilimumab in 1st line HER2+ EGA. The translational research program will shed light on the potential mode of action of these novel combinations.

Clinical trial identification: NCT03409848.

Legal entity responsible for the study: AIO-Studien-gGmbH.

Funding: BMS.

Disclosure: E. Goekkurt: Advisory board: Sanofi, Merck, BMS, MSD, Servier, Sirtex, Pfizer, Lilly; Speakers fees: Servier, MSD, BMS. M. Binder: Travel expanses: BMS, Hexal; Advisory board: Roche, BMS, MSD, Hexal, Takeda, Celgene, AbbVie; Speakers fees: Chugai, Roche, BMS, Janssen-Cilag, Hexal, Sanofi, Celgene, AstraZeneca. S. Lorenzen: Advisory board: Sanofi, Merck, BMS, MSD, Servier, Lilly, Roche; Speakers fees: Servier, Roche, BMS, Lilly. P.C. Thuss-Patience: Advisory board: Merck, Roche, Lilly, Pfizer, MSD, BMS, Nordic. S-E. Al-Batran: Advisory board, speakers fees: BMS. A. Hinke: Honoraria: Roche S. Hegewisch-Becker: Advisory board: Lilly, BMS, Merck. C. Bokemeyer: Research funding: German Cancer Aid, Sanofi, Roche, Merck, GBA Innovationfond, BMS; Honoraria: Merck, Sanofi, Roche, Bayer, BMS, Servier, AstraZeneca; Advisory board: Lilly/ImClone, Mundipharma, Hexal, Bayer Schering,

Sanofi, Merck. Travel, accommodations, expenses: Merck Serono, Sanofi, Pfizer, BMS. A. Stein: Research funding: German Cancer Aid, Sanofi, Roche, Merck, GBA Innovationfond, BMS; Advisory board: Sanofi, Amgen, Merck, Roche, BMS, MSD, Servier, Sirtex; Speakers fees: Sanofi, Merck, Roche, Servier, Bayer, Lilly. All other authors have declared no conflicts of interest.

779TiP TRIANgLE study (JCOG1510): A phase III study of tri-modality combination therapy with induction docetaxel (DOC), cisplatin (CDDP), 5-fluorouracil (FU) (DCF) vs definitive chemoradiotherapy (dCRT) for locally advanced unresectable squamous cell carcinoma (SCC) of the thoracic esophagus

H. Daiko[1], H. Hara[2], H. Ogawa[3], K. Hori[4], J. Mizusawa[5], S. Ozawa[6], M. Takagi[7], M. Tanaka[8], H. Baba[9], Y. Shirakawa[10], M. Tsuda[11], S. Nakagawa[12], H. Takeuchi[13], T. Abe[14], Y. Ito[15], T. Kojima[16], T. Kadota[5], H. Fukuda[5], K. Kato[17], Y. Kitagawa[18]

[1]Esophageal Surgery Division, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan, [3]Division of Radiation and Proton Therapy Center, Shizuoka Cancer Center, Shizuoka, Japan, [4]Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan, [5]JCOG Data Center/ Operations Office, National Cancer Center, Tokyo, Japan, [6]Department of Gastroenterological Surgery, Tokai University School of Medicine, Kanagawa, Japan, [7]Department of Gastroenterological Surgery, Shizuoka General Hospital, Shizuoka, Japan, [8]Department of Radiation Oncology, Osaka City General Hospital, Osaka, Japan, [9]Department of Gastroenterological Surgery, Graduate School of Life Sciences, Kumamoto University, Kumamoto, Japan, [10]Department of Gastroenterological Surgery, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan, [11]Department of Gastroenterological Oncology, Hyogo Cancer Center, Hyogo, Japan, [12]Department of Gastroenterological Surgery, Niigata Cancer Center Hospital, Niigata, Japan, [13]Department of Surgery, Hamamatsu University School of Medicine, Hamamatsu, Japan, [14]Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, [15]Department of Radiation Oncology, Showa University School of Medicine, Tokyo, Japan, [16]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [17]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan, [18]Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Background: Although standard treatment for locally advanced unresectable esophageal SCC (LAUEC) has been dCRT consisted of CDDP plus FU, treatment outcome is limited. In the phase II trial of induction chemotherapy (Cx) with DCF followed by conversion surgery (CS) or dCRT plus CS for patients (pts) with LAUEC, 39.6% of pts received R0 resection via CS and achieved better 3-year overall survival (OS) of 71.4% with manageable toxicity.

Trial design: Eligibility criteria include as follows; histologically proven SCC, cT4b or cT3 but highly suspicious of cT4b and/or unresectable lymph nodes metastasis (LNM) invading to adjacent organs, no distant metastasis except for supraclavicular LNM, age 20 to 75, and performance status 0-1. Pts are randomized into following two arms stratified by institution, invasion to adjacent organs (definitive versus suspicious) and supraclavicular LNM (yes versus no). Pts in arm A receive dCRT consisted of CDDP (70 mg/m^2/day, days 1 and 29) and FU (700 mg/m^2/day, days 1-4 and 29-32, civ) with concurrent radiotherapy (60 Gy/30 fr) followed by additional Cx (CDDP [80 mg/m^2/day, day 1 and 29] and FU [800 mg/m^2/day, days 1-5 and 29-33, civ]). Pts in arm B receive 3 courses of DCF (DOC [70 mg/m^2, day 1], CDDP [70 mg/m^2, day 1] and FU [750 mg/m^2, days 1–5] every 3 weeks) followed by CS if converted to be resectable, or dCRT same as Arm A if not converted to be resectable based on the radiological evaluation. Salvage surgery or endoscopic resection are acceptable in arm A (if residual, progressive, or recurring after dCRT) and in arm B (if converted to be resectable during or after dCRT). Primary endpoint is OS to confirm the superiority of arm B. We assumed 3-year OS with arm A to be 30% and expected a 12% increase for arm B. The planned sample size was calculated as a total of 230 pts (115 pts per arm) with a one-sided alpha of 5%, power of 70%, an accrual period of 4.5 years, and a follow-up period of 3 years. This trial was registered with UMIN-CTR, number UMIN000031165 and started in February 2018.

Clinical trial identification: UMIN000031165.

Legal entity responsible for the study: Japan Clinical Oncology Group: JCOG.

Funding: Japan Agency for Medical Research and Development (AMED).

Disclosure: H. Daiko, H. Ogawa, K. Hori, J. Mizusawa, S. Ozawa, M. Takagi, M. Tanaka, H. Baba, Y. Shirakawa, M. Tsuda, S. Nakagawa, H. Takeuchi, T. Abe, Y. Ito, T. Kadota, H. Fukuda: Japan Agency for Medical Research and Development (AMED), Ministry of Health, Labour and Welfare, Japan H. Hara: Japan Agency for Medical Research and Development (AMED), Ministry of Health, Labour and Welfare, Japan, Astrazeneca, Chugai, Merck Serono, MSD, Ono, Taiho, Takeda, Boehringer, Dainippon Sumitomo, Daiichi sankyo, Lilly, Pfizer, LSK Biopharma, Eisai, Incyte T. Kojima: Japan Agency for Medical Research and Development (AMED), Ministry of Health, Labour and Welfare, Japan, Shionogi, Ono, MSD, Oncolysis BioPharma, Astellas Amgen BioPharma K. Kato: Ono Pharmaceuticals, Merck and Co., Merck Serona, Shionogi Co and Ltd., Japan Agency for Medical Research and Development (AMED), Ministry of Health, Labour and Welfare, Japan Y. Kitagawa: Japan Agency for Medical Research and Development (AMED), Ministry of Health, Labour and Welfare, Japan, Kyowa hakko kirin, Takeda, Yakult honsya, Daiichi-sankyo.

780TiP Phase II trial of perioperative PD-L1 inhibition with avelumab and mDCF chemotherapy for resectable locally advanced gastric and esophago-gastric adenocarcinoma

T. Alcindor[1], A. Awan[1], T. Opu[1], J. Asselah[2], M. Vanhuyse[3], C. Mueller[4], L. Ferri[4]

[1]Medicine & Oncology, McGill University Health Centre - Glen Site, Montreal, QC, Canada, [2]Oncology, The McGill University Health Centre - Glen Site, Montreal, QC, Canada, [3]Oncology, Cedars Cancer Center, Montreal, QC, Canada, [4]Surgery, The McGill University Health Centre - Glen Site, Montreal, QC, Canada

Background: Perioperative chemotherapy improves survival in locally advanced gastric and esophago-gastric adenocarcinoma (EGA), in comparison with surgery alone. The pathologic complete response rate (pCR) is as a possible surrogate for survival and is influenced by the chemotherapy regimen given. We and others have previously described the efficacy of docetaxel/cisplatin/fluorouracil (DCF) in the perioperative management of this cancer. Research by other groups has shown equivalent efficacy and lesser toxicity of a modified DCF regimen. Given the promising activity of immune checkpoint inhibitors in these malignancies, we hypothesize that the addition of immunotherapy with avelumab, an anti-PD-L1 agent, to mDCF chemotherapy (immunochemotherapy), will result in improved outcomes. Our trial is approved by Health Canada and our hospital Research Ethics Board. It is registered as NCT03288350 (www.clinicaltrials.gov).

Trial design: Eligible patients will receive neoadjuvant therapy consisting of 4 cycles of avelumab + mDCF, followed by surgery and assessment of pathologic response. Then they will receive 4 cycles of adjuvant therapy of mDCF + avelumab. Primary endpoint is pCR. Secondary endpoints are 2-year disease-free survival rate and incidence of non-hematological grade 3-4. Exploratory translational studies are planned. We hypothesize that immunochemotherapy will yield a pCR rate of 20% in comparison with 7% for chemotherapy only (historical data). Main inclusion criteria are : diagnosis of gastric or EGA adenocarcinoma, locally advanced disease, adequate organ function, performance status 0-1, stages Ib-III. Main exclusion criteria are: other histologies, metastatic disease, use of immunosuppressants, serious autoimmune disease, daily prednisone intake $>$ 10 mg or equivalent. To validate the hypothesis with power of 0.80 and α error of 0.05, 50 participants will be needed. Enrolment has started and is following a 2-stage Simon rule : accrual will stop if no more than 1 pCR is seen in the first 16 patients ; if more than 6/50 patients show pCR, the trial will be considered successful in that the alternate hypothesis cannot be rejected.

Clinical trial identification: NCT03288350, posted September 20, 2017.

Legal entity responsible for the study: Research Institute of the McGill University Health Centre.

Funding: EMD Serono.

Disclosure: T. Alcindor: Consultant: EMD Serono, BMS, Lilly. J. Asselah: Taiho, Ipsen, Pfizer. M. Vanhuyse: BMS. All other authors have declared no conflicts of interest.

781TiP PRODIGE 29-UCGI 26(NEOPAN): A randomised trial of chemotherapy with folfirinox or gemcitabine in locally advanced pancreatic carcinoma (PC)

M.P. Ducreux[1], R. Desgrippes[2], M. Texier[3], F. Di Fiore[4], P. Vanelslander[5], O. Capitain[6], R. Guimbaud[7], J. Forestier[8], F. El Hajbi[9], P. Follana[10], A. Parzy[11], N. Baba Hamed[12], Y. Rinaldi[13], T. Brotelle[14], J-P. Pignon[3], C. Jouffroy[15], L. Dahan[16], O. Bouche[17]

[1]Gastroenterology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [2]Medical Oncology, C.H. Saint Malo, St. Malo, France, [3]Biostatistics and Epidemiology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [4]Gastroenterology, CHU Hôpitaux de Rouen-Charles Nicolle, Rouen, France, [5]Gastroenterology, Hôpital Saint Claude, Saint Quentin, France, [6]Medical Oncology, Institut de Cancerologie de l'Ouest - Centre Paul Papin, Angers, France, [7]Digestive Oncology, Centre Hospitalier Rangueil, Toulouse, France, [8]Medical Oncology, Hôpital Edouard Herriot, Lyon, France, [9]Urology and Digestive Oncology, Centre Oscar Lambret, Lille, France, [10]Medical Oncology, Centre Anticancer Antoine Lacassagne, Nice, France, [11]Digestive Pathology, Centre Francois Baclesse, Caen, France, [12]Oncology, Hôpital St. Joseph, Paris, France, [13]Oncology, Hôpital Européen, Marseille, France, [14]Onco-Hematology, Centre Hospitalier Henri Duffaut, Avignon, France, [15]R&D, UNICANCER, Paris, France, [16]Hepatogastroenterology and Oncology Department, CHU La Timone, Marseille, France, [17]Hepatogastroenterology and Oncology Department, CHU de Reims - Hôpital Robert Debré, Reims, France

Background: PC is an aggressive malignancy and the 4th cause of all cancer deaths worldwide. More than 30% of patients with PC are unresectable because of the local extension with a median overall survival (OS) of less than one year. The standard of care remains gemcitabine (gem) alone. 5FU, irinotecan, oxaliplatin (Folfirinox) is superior to gemcitabine in the treatment of metastatic PC, in terms of OS and progression-free survival (PFS).

Trial design: This phase 3, multicenter randomised study (NCT02539537) was designed to evaluate the efficacy of FOLFIRINOX versus gem in the treatment of locally advanced PC (LAPC). This study enrols patients $>$ 18 year of age, with cytologically or pathologically proven adenocarcinoma of the pancreas, who had a LAPC proven to be unresectable after multidisciplinary discussion, a performance status ECOG $<$ 2, normal hematologic, hepatic, and renal functions, adequate other vital functions; the tumour has to be measurable (RECIST criteria) and the patient has to give his informed

consent. The primary endpoint of this study is PFS; secondary endpoints include a composite index for induction treatment severe toxicity: biliary tract infection Grade3-4 + any grade 5 toxicities + induction chemotherapy interruption for toxicity, OS, time to treatment failure, quality of life, percentage of surgery with curative intent. Treatment regimens is: Arm A: gem 1000 mg/m^2 30-minute infusion, weekly for 7 weeks followed by one week rest and then weekly for 3 weeks followed by one week. Arm B: leucovorin 400 mg/m^2 D1, irinotecan 180 mg / m^2 D1, Oxaliplatin 85 mg / m^2 D1, 5 Fluorouracil 2400 mg/m^2 IV continuous infusion over 46 h (no bolus of 5FU), treatment repeated every two weeks for 4 months (12 cycles). Duration of treatment: 6 months in both arms. After this 6-month period, each center has to choose for its patients between 3 strategies: stop of treatment, maintenance chemotherapy with gem or capecitabine and radio-chemotherapy. At this time 74 among the 170 planned patients have been enrolled. The first IDMC meeting has recommended continuing the study without any change.

Clinical trial identification: EudraCT: 2014-003510-82.

Legal entity responsible for the study: UNICANCER.

Funding: French Program for Cancer Clinical Research (PHRC).

Disclosure: M.P. Ducreux: Wife employee: Sandoz. P. Follana: Advisory board, board of directors, consultant board: AstraZeneca, Novartis, Tesaro. O. Bouche: Stock owner: Amgen, Bayer, Merck, Roche; Employment: Lilly, Pierre Fabre, Novartis. All other authors have declared no conflicts of interest.

782TiP Atezolizumab + bevacizumab vs sorafenib in locally advanced or metastatic hepatocellular carcinoma: The randomised phase III study IMbrave150

M.P. Ducreux[1], A-L. Cheng[2], S. Qin[3], A.X. Zhu[4], M. Ikeda[5], T-Y. Kim[6], D-Z. Xu[7], W. Verret[8], J. Liu[7], R.S. Finn[9], P.R. Galle[10]

[1]Medical Oncology, Gustave Roussy, Villejuif, France, [2]Medical Oncology, National Taiwan University Hospital, Taipei, Taiwan, [3]Medical Oncology, People's Liberation Army Cancer Center, Nanjing, China, [4]Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA, [5]Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [6]Medical Oncology, Seoul National University College of Medicine, Seoul, Republic of Korea, [7]Roche Product Development, F. Hoffman-La Roche Ltd., Shanghai, China, [8]Product Development Oncology, Genentech, Inc., South San Francisco, CA, USA, [9]Geffen School of Medicine, University of California, Los Angeles, CA, USA, [10]I. Medical Department, University Medical Center Mainz, Mainz, Germany

Background: Advanced hepatocellular carcinoma (HCC) is a disease of high unmet medical need. Despite considerable toxicities, sorafenib (sor) is the 1L standard of care. Single-agent inhibition of PD-L1/PD-1 or VEGF signalling has only modest activity in HCC, but in a Phase Ib study of atezolizumab (atezo; anti–PD-L1) + bevacizumab (bev; anti-VEGF) combination, a response rate of 61% with a manageable safety profile (Pishvaian ESMO 2018, submitted) is observed. Clinical benefit with atezo + bev was also seen in 1L renal cell carcinoma and 1L non-small cell lung cancer (Motzer ASCO GU 2018, Reck ESMO IO 2017). The potential synergy between atezo and bev may stem from bev's additional immunomodulatory effects in the tumour microenvironment (increased DC maturation, enhanced T-cell infiltration, reduced MDSCs and Tregs in tumours) that may potentiate the efficacy of atezo in re-invigorating the anti-tumour T-cell response.

Trial design: IMbrave150 is a global, multicentre, randomised, open-label, Phase III trial enrolling 1L patients (pts) with locally advanced or metastatic and/or unresectable HCC. Key inclusion/exclusion criteria are shown in the table. Pts will be randomised 2:1 to receive atezo (1200 mg) plus bev (15 mg/kg) IV Q3W or sor (400 mg) PO BID until loss of clinical benefit or unacceptable toxicity. Crossover is not allowed. Stratification factors are ECOG PS (0 vs 1), baseline alpha fetoprotein level (< 400 vs ≥ 400 ng/mL), macrovascular invasion and/or extrahepatic spread (presence vs absence) and region (Asia excluding Japan vs rest of world). Co-primary endpoints are investigator (INV)–assessed ORR (RECIST v1.1) and OS, which will be tested in parallel. Secondary endpoints are INV-assessed PFS, DOR and time to progression (TTP; RECIST v1.1), along with independent review facility (IRF)–assessed ORR, PFS, DOR and TTP (RECIST v1.1 and HCC mRECIST). Approximately 480 pts will be enrolled globally.

Table: 782TiP Eligibility criteria

Inclusion Criteria	Exclusion Criteria
- $\geq$ 1 measurable untreated lesion (per RECIST v1.1) - Naive to prior systemic therapy for HCC - Child-Pugh class A liver function - ECOG PS 0/1 - Adequate haematologic and end-organ function	- Co-infection of HBV and HCV - Pts with untreated varices with bleeding or high risk for bleeding - History of autoimmune disease or immune deficiency - Inadequately controlled arterial hypertension

Clinical trial identification: NCT03434379.

Editorial acknowledgement: Medical writing assistance for this abstract was provided by Steffen Biechele, PhD, of Health Interactions.

Legal entity responsible for the study: F. Hoffmann-La Roche AG.

Funding: F. Hoffmann-La Roche AG.

Disclosure: M.P. Ducreux: Employee: Sandoz; Honoraria: Roche/Genentech, Novartis, Ipsen, Lilly, Amgen, Servier, Merck Serono Ltd; Consulting, Advisory role: Bayer, Sirtex Medical, Lilly, Servier, Ipsen, Roche/Genentech, Amgen, Novartis, Sanofi, and Merck Serono Ltd; Research funding: Roche/Genentech, Pfizer, Merck Serono Ltd. A-L. Cheng: Consulting, Advisory role: Bayer Schering Pharma, Merck Serono Ltd, Bristol-Meyers Squibb, Onxeo, Novartis, Eisai, Ono Pharmaceutical. Speakers' bureau for Novartis; Research funding: Sanofi. A.X. Zhu: Consulting, Advisory role: AstraZeneca, Bayer, Merck, Bristol-Meyers Squibb, Eisai, Novartis, Sanofi, Exelixis, Lilly; Research funding: Lilly, Bayer, Bristol-Meyers Squibb, Novartis, Merck. M. Ikeda: Consulting, Advisory role: NanoCarrier, Bayer Yakuhin, Eisai, Kyowa Hakko Kirin, Novartis, Shire, MSD, Bristol-Myers Squibb Japan, Teijin Pharma, Daiichi Sankyo; Honoraria: Taiho Pharmaceutical, Novartis, Bayer Yakuhin, Bristol-Myers Squibb Japan, Abbott Japan, Eisai, Lilly Japan, Chugai Pharma, Daiichi Sankyo, Otsuka, Yakult Honsha, Nobelpharma, Chugai Pharma, Dainippon Sumitomo Pharma, Teijin Pharma; Research funding: Taiho Pharmaceutical, Bayer Yakuhin, Kyowa Hakko Kirin, Yakult, Lilly Japan, Ono Pharmaceutical, Eisai, AstraZeneca, Zeria Pharmaceutical, Chugai Pharma, Bristol-Myers Squibb, Merck Serono, Kowa, NanoCarrier, Aslan Pharmaceuticals, Novartis, Takara Bio, Baxalta/Shire. D-Z. Xu; J. Liu: Employee: F. Hoffmann-La Roche Ltd. W. Verret: Employee: Roche/Genentech. R.S. Finn: Consulting, Advisory role: Pfizer, Bayer, Novartis, Bristol-Meyers Squibb, Merck, Eisai, Lilly, Roche/Genentech. Research funding: Pfizer, Bayer, Novartis, Eisai, Lilly, Merck, Bristol-Meyers Squibb. P.R. Galle: Consulting, Advisory role: Bayer, Lilly, AstraZeneca, Bristol-Meyers Squibb; Speakers' bureau: Bayer, Sirtex Medical; Travel, accommodations, expenses: Bayer; Honoraria: Bayer, Sirtex Medical, Lilly, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Blueprint Medicines; Research funding: Bayer. All other authors have declared no conflicts of interest.

783TiP CA209-9DX: phase III, randomized, double-blind study of adjuvant nivolumab vs placebo for patients with hepatocellular carcinoma (HCC) at high risk of recurrence after curative resection or ablation

M.J. Jimenez Exposito[1], M. Akce[2], J.L. Montero Alvarez[3], E. Assenat[4], L.A. Balart[5], A.D. Baron[6], T. Decaens[7], A. Heurgue-Berlot[8], A.O. Martin[9], S.W. Paik[10], V. Poulart[11], A.S. Sehbai[12], N. Takemura[13], J-H. Yoon[14]

[1]Clinical Development – Oncology, Bristol-Myers Squibb, Princeton, NJ, USA, [2]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA, [3]Gastroenterology, Hospital Universitario Reina Sofia, Cordoba, Spain, [4]Medical Oncology, CHU de Montpellier - Hospital Saint Eloi, Montpellie, France, [5]Internal Medicine, Tulane Medical Center, Tulane University health Sciences Center, New Orleans, LA, USA, [6]Medical Center, California Pacific, San Francisco, CA, USA, [7]Clinique Universitaire d'Hépato-gastroentérologie, CHU Grenoble Alpes, Grenoble, France, [8]Department of Hepato-Gastroenterology, Centre Hospitalier Universitaire Reims, Reims, France, [9]Digestive System Service, Universidad Autonoma de Madrid (UAM) - Hospital Universitario La Paz, Madrid, Spain, [10]Gastroenterology, Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea, [11]Biostatistics, Bristol-Myers Squibb, Braine-l'Alleud, Belgium, [12]Hematology/Oncology, Pinnacle Research Group, Llc, Anniston, AL, USA, [13]Gastroenterological Surgery, Tokyo National Center for Global Health and Medicine, Tokyo, Japan, [14]Gastroenterology, Seoul National University Hospital, Seoul, Republic of Korea

Background: Despite significant improvements in the treatment of early HCC, curative therapies remain associated with high recurrence rates (≈70% at 5 y) (EASL. J Hepatol 2018), and therefore, adjuvant therapies are needed. Nivolumab (NIVO) has demonstrated durable tumor responses and a manageable safety profile in patients (pts) with advanced HCC, regardless of HCC etiology (CheckMate-040 study) (El-Khoueiry, et al. Lancet 2017). Additionally, NIVO has shown clinical benefit as adjuvant therapy in melanoma (CheckMate-238 study) (Weber, et al. NEJM 2017). This phase 3, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of adjuvant NIVO in pts with HCC who are at high risk of recurrence after curative hepatic resection or ablation, a population for whom no effective therapies are currently available.

Trial design: The trial will include 530 pts aged $\geq$18 y with a first diagnosis of HCC (any etiology) who are at high risk for HCC recurrence after curative resection or ablation, and who have well-preserved liver function (Child-Pugh score 5 or 6), randomized (1:1) to receive NIVO (480 mg intravenous Q4W) or placebo (PBO). Additional eligibility criteria include Eastern Cooperative Oncology Group performance status of 0 or 1, no evidence of tumor metastasis, no prior therapy for HCC (including loco-regional therapies), and no liver transplant. Pts will be treated until recurrence per blinded independent central review (BICR) assessment, unacceptable toxicity, or withdrawal, or for up to 1 y total duration. Survival follow-up will continue for up to 5 y. The primary endpoint is to compare recurrence-free survival, per BICR assessment. Secondary endpoints include overall survival and time to recurrence (defined as time from randomization to first documented disease recurrence). The trial will be open for enrollment in 20 countries worldwide and is currently recruiting.

Clinical trial identification: NCT03383458.

Editorial acknowledgement: Professional medical writing assistance and editorial assistance was provided by Andrea Hammons PhD, and Christine Craig of PPSI (a PAREXEL company), funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Meyers Squibb.

Funding: Bristol-Meyers Squibb.

Disclosure: M.J. Jimenez Exposito: Employee, stock owner, stock interest: Bristol-Myers Squibb. L.A. Balart: Research grants, advisor: Merck & Co., Inc. A. Heurgue-Berlot: Personal fees: Gilead, Abbvie, MSD, outside the submitted work. V. Poulart: Employee: Bristol-Myers Squibb. J-H. Yoon: Grants: Bayer HealthCare Pharmaceuticals, outside the submitted work. All other authors have declared no conflicts of interest.

784TiP Phase III KEYNOTE-585 study of chemotherapy (Chemo) + pembrolizumab (Pembro) vs chemo + placebo as neoadjuvant/adjuvant treatment for patients (Pts) with gastric or gastroesophageal junction (G/GEJ) cancer

Y-J. Bang[1], E. Van Cutsem[2], C.S. Fuchs[3], A. Ohtsu[4], J. Tabernero[5], D.H. Ilson[6], W.J. Hyung[7], V.E. Strong[8], T.O. Goetze[9], T. Yoshikawa[10], L.H. Tang[11], P.M.T. Hwang[12], D. Adelberg[12], K. Shitara[4]

[1]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [2]Gastroenterology/Digestive Oncology, University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium, [3]Medical Oncology, Yale Cancer Center, New Haven, CT, USA, [4]Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan, [5]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [6]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [7]Surgery, Yonsei Cancer Hospital, Yonsei University Health System, Seoul, Republic of Korea, [8]Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [9]Institute of Clinical Cancer Research, Institute of Clinical Cancer Research, UCT University Cancer Center, Frankfurt, Germany, [10]Gastrointestinal Surgery, Kanagawa Cancer Center, Kanagawa, Japan, [11]Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [12]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA

Background: Pembro is FDA-approved for the treatment of pts with recurrent locally advanced or metastatic G/GEJ adenocarcinoma whose disease has progressed on or after $\geq$2 prior therapies and whose tumors express PD-L1 (combined positive score $\geq$1). Combining chemo with pembro in the neoadjuvant/adjuvant setting may benefit pts with locally advanced, resectable G/GEJ cancer. KEYNOTE-585 (NCT03221426) is a phase 3, randomized, double-blind study of chemo + pembro vs chemo + placebo as neoadjuvant/adjuvant treatment for locally advanced resectable G/GEJ cancer.

Trial design: Eligibility criteria are age $\geq$18 years; previously untreated, resectable G/GEJ adenocarcinoma (pts with Siewert type 1 tumors are eligible if initial treatment is planned perioperative chemo and resection), with no evidence of metastatic disease; planned surgery after preoperative chemo; adequate organ function; ECOG performance status 0/1; and no active autoimmune disease. Pts will be randomly assigned 1:1 to receive chemo + pembro (arm 1) or chemo + placebo (arm 2). Pts will receive neoadjuvant (preoperative) chemo + pembro every 3 weeks (Q3W) for 3 cycles or chemo + placebo Q3W for 3 cycles followed by surgery, then adjuvant chemo + pembro Q3W for 3 cycles or chemo + placebo Q3W for 3 cycles, then monotherapy with pembro or placebo Q3W for 11 cycles; overall treatment is up to 17 cycles. Chemo is cisplatin 80 mg/m^2 IV on day 1 + either capecitabine 1000 mg/m^2 orally twice daily $\times$ 14 days or 5-fluorouracil (5-FU) 800 mg/m^2 IV daily $\times$ 5 days (investigator's choice). Pembro 200 mg IV is given on day 1. Adjuvant monotherapy is pembro (arm 1) or placebo (arm 2). In a separate safety cohort, 5-FU 2600 mg/m^2 IV + docetaxel 50 mg/m^2 IV + oxaliplatin 85 mg/m^2 IV + leucovorin 200 mg/m^2 IV (FLOT) is being studied as a potential chemo option. Primary end points are overall survival, event-free survival per central review, and rate of pathologic complete response (no invasive disease and histologically negative nodes). Adverse events are graded and monitored for up to 90 days after treatment. Pts will be followed up for survival status. Planned enrollment is 860 pts.

Clinical trial identification: NCT03221426. Study start date was October 9, 2017.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Sarita Shaevitz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA).

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: Y-J. Bang: Consultancy: AstraZeneca, Novartis, Genentech/Roche, MSD, Pfizer, Bayer, BMS, Eli Lilly, Merck Serano, FivePrime, Taiho, Ono, ADC Therapeutics, GreenCross, Samyang Biopharm; Research funding (to institution): AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serano, Bayer, GSK, BMS, Pfizer, Eli Lilly, Boeringer-Ingelheim, MacroGenics, Boston Biomedical, FivePrime, CKD Pharma, Ono, Otsuka, Taiho, Takeda, BeiGene, Hanmi, Green Cross, Curis, Daiichi Sankyo, Astellas. E. Van Cutsem: Advisory board member: Bayer, Lilly, Roche; Servier Research funding: Amgen, Bayer, Boehringer, Celgene, Lilly, MSD, Merck, Novartis, Epsen, Roche, Sanofi, Servier. C.S. Fuchs: Advisory board member: Eli Lilly, Entrinsic Health, Genentech, Merck, Sanofi, Five Prime Therapeutics, Merrimack, Bayer, Agios, Taiho, Kew, Bain; Capital leadership: CytomX. A. Ohtsu: Research funding: BMS Consultant: Celgene. J. Tabernero: Advisory board member: Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho, Takeda. D.H. Ilson: Advisory board member: Pieris, AstraZeneca, Astellas, BMS, Pfizer, Bayer, Lilly, Roche, Oncolys, Merck. W.J. Hyung: Stock ownership: Hutom; Advisory board member: Ethicon; Research funding: Medtronics T.O. Goetze: Advisory board member: MSD, Lilly, Shire, Celgene, Bayer, BMS; Speakers' bureau: Lilly; Travel expenses: BMS, Lilly. T. Yoshikawa: Advisory board member: Novartis, MSD Oncology, Chugai Pharma; Research funding: Novartis, Chugai Pharma, Taiho Pharmaceutical, Yakult; Honoraria: Pharmaceutical, Abbott Nutrition, Takeda, Daiichi Sankyo, Ajinomoto, Ono Pharmaceutical, Nihonkayaku, Johnson & Johnson, Medtronic, Olympus, Lilly. P.M.T. Hwang: Employee, Stock ownership: Merck. D. Adelberg: Employee: Merck. K. Shitara: Advisory board member: Astellas Pharma, Lilly, Bristol-Myers Squibb, Takeda, Pfizer, Ono Pharmaceutical; Research funding: Dainippon Sumitomo Pharma, Lilly, MSD, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharma, Ono Pharmaceutical; Honoraria: Novartis, AbbVie, Yakult. All other authors have declared no conflicts of interest.

785TiP Phase III KEYNOTE-590 study of chemotherapy + pembrolizumab versus chemotherapy + placebo as first-line therapy for patients (Pts) with advanced esophageal or esophagogastric junction (E/EGJ) cancer

K. Kato[1], M.A. Shah[2], P.C. Enzinger[3], J. Bennouna[4], L. Shen[5], A. Adenis[6], J-M. Sun[7], B.C. Cho[8], M. Ozguroglu[9], T. Kojima[10], V. Kostorov[11], C. Hierro[12], Y. Zhu[13], S. Shah[13], P. Bhagia[13], T. Doi[14]

[1]Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [2]Internal Medicine-Medical Oncology, Weill Cornell Medicine/ New York Presbyterian Hospital, New York, NY, USA, [3]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [4]Medical Oncology, University Hospital of Nantes, Nantes, France, [5]GI Oncology, Beijing Cancer Hospital, Beijing, China, [6]Medical Oncology, Institut du Cancer de Montpellier, Montpellier, France, [7]Hematology/Oncology, Samsung Medical Center, Seoul, Republic of Korea, [8]Oncology, Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea, [9]Medical Oncology, Istanbul University, Cerrahpasa School of Medicine, Istanbul, Turkey, [10]Gastroenternology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa-shi, Japan, [11]Outpatient Chemotherapy Department, Leningrad Regional Oncology Dispensary, St. Petersburg, Russian Federation, [12]Medical Oncology, Vall dHebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [13]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [14]Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: In the phase 1b KEYNOTE-028 study, pembrolizumab monotherapy demonstrated manageable safety and durable antitumor activity in heavily pretreated pts with PD-L1–positive advanced esophageal carcinoma. KEYNOTE-590 (ClinicalTrials.gov, NCT03189719) is a phase 3, randomized, double-blind, multicenter study of cisplatin and 5-fluorouracil plus pembrolizumab vs cisplatin and 5-fluorouracil plus placebo in pts with previously untreated advanced E/EGJ carcinoma.

Trial design: Eligibility criteria are age $\geq$18 years; locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or metastatic Siewert type 1 adenocarcinoma of the EGJ; no prior therapy for advanced disease; measurable disease per RECIST v1.1; ECOG performance status 0/1; adequate organ function; no autoimmune disease; no active infection; and provision of tissue sample for evaluation of PD-L1 expression and gene expression profiling. Pts will be randomly assigned 1:1 to receive cisplatin 80 mg/m^2 IV every 3 weeks (Q3W) (capped at 6 doses) plus 5-fluorouracil 800 mg/m^2 continuous IV on days 1-5 Q3W plus pembrolizumab 200 mg IV Q3W or cisplatin 80 mg/m^2 IV Q3W (capped at 6 doses) plus 5-fluorouracil 800 mg/m^2 continuous IV on days 1-5 Q3W plus placebo Q3W IV. Pts will continue treatment for up to 2 years. Crossover from one treatment arm to another is not permitted. Coprimary end points are overall survival and progression-free survival per RECIST v1.1 by blinded independent central review in all pts and in pts with PD-L1–positive tumor expression (combined positive score $\geq$10%). Secondary end points include objective response rate per RECIST v1.1, duration of response, safety, and health-related quality of life. Response will be assessed using computed tomography (preferred) or magnetic resonance imaging every 9 weeks by central imaging review per RECIST v1.1. Adverse events (AEs) will be graded per NCI CTCAE v4.0 and monitored for at least 30 days (90 days for serious AEs) after the last dose of study treatment. Pts will be followed up for survival status. Planned enrollment is approximately 700 pts.

Clinical trial identification: NCT03189719. The study start date was July 25, 2017.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Sarita Shaevitz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: K. Kato: Advisory board member: MSD, Ono, Beigene; Research funding: MSD, Ono, Shionogi, Merck Serono M.A. Shah: Research funding: Merck, Roche, Boston Biomedical P.C. Enzinger: Advisory board member: Merck, Astellas, Five Prime, Lilly, Celgene, Beigene J. Bennouna: Advisory board member: Roche, Boehringer Ingelheim, AstraZeneca, Shire, MSD; Honoraria: Roche, Boehringer Ingelheim, AstraZeneca, Shire, MSD. A. Adenis: Advisory board member: Bayer, BMS, Servier; Research funding: Bayer, BMS, Merck, Sanofi, Pfizer; Honoraria: Bayer, BMS, Sanofi; Travel expenses: BMS, Merck, Bayer. J-M. Sun: Advisory board member: Boehringer Ingelheim, Research funding: AstraZeneca. B.C. Cho: Advisory board member: AstraZeneca, Roche, Boehringer Ingelheim, Yuhan, BMS, MSD, Novartis

Speakers' bureau: AstraZeneca, BMS, MSD, Novartis; Research funding: Bayer, AstraZeneca, Yuhan, Novartis; Honoraria: AstraZeneca, Roche, Boehringer Ingelheim, Yuhan, BMS, MSD, Novartis. M. Ozguroglu: Advisory board member: Astellas, Janssen Honoraria: Janssen. T. Kojima: Honoraria: Oncolys Biopharma Other-Patents, Royalties; Other Intellectual Property: Ono Pharmaceutical, MSD, Shionogi Pharma, Oncolys BioPharma, Astellas Amgen BioPharama. V. Kostorov, T. Doi: Advisory board member: Novartis, MSD, Lilly Japan, Chugai Pharma, Kyowa Hakko Kirin, Daiichi Sankyo, Amgen Research funding: Taiho, Novartis, Merck Serono, Astellas Pharma, MSD, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Lilly, Sumitomo Group, Chugai Pharma, Bayer, Kyowa Hakko Kirin, Daiichi Sankyo, Celgene. Y. Zhu, P. Bhagia: Employee: Merck. S. Shah: Employee, Stock owner: Merck. All other authors have declared no conflicts of interest.

786TiP Prospective multicenter feasibility study of laparoscopic sentinel basin dissection after endoscopic submucosal dissection for early gastric cancer

K.W. Ryu[1], B.W. Eom[1], H.M. Yoon[1], Y-W. Kim[2], J.S. Min[3], G.S. Cho[4], I. Cho[4], Y.J. Lee[5], J-H. Park[5], H. Hur[6], Y.K. Park[7], O. Jeong[7], M.R. Jung[7], J.H. Lee[8], J.Y. An[8]

[1]Center for Gastric Cancer, National Cancer Center, Gyeonggi-do, Republic of Korea, [2]Graduate School of Cancer Science and Policy, National Cancer Center, Gyeonggi-do, Republic of Korea, [3]Department of Surgery, Dongnam Institute of Radiological and Medical Sciences, Cancer Center, Busan, Republic of Korea, [4]Department of Surgery, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea, [5]Department of Surgery, Gyeongsang National University, Jinju, Republic of Korea, [6]Department of Surgery, Ajou University School of Medicine, Suwon, Republic of Korea, [7]Department of Surgery, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea, [8]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: Although standard radical gastrectomy is recommended after non-curative resection of endoscopic submucosal dissection for early gastric cancer, in most cases, no residual tumor and no lymph node metastasis was revealed after surgery. Lymph node metastasis can be evaluated using sentinel basin dissection, however, there was no evidence that sentinel lymph node concept can be applied after endoscopic resection.

Trial design: This trial is an investigator-initiated, multicenter prospective phase II trial. Patients who underwent endoscopic submucosal dissection for clinical stage T1N0M0 gastric cancer and the resections were proven as non-curative were eligible. Qualified investigators who completed the prior phase III trial (Senorita I) are exclusively allowed to participate in this study. Intraoperative endoscopic submucosal injection of a standardized dual tracer was administered to normal mucosa nearby the scar, and sentinel basins were detected using gamma-probe and dissected. Then, standard laparoscopic gastrectomy with lymphadenectomy was performed. Sample size was calculated based on inferior confidence interval of detection rate of 95%, and estimated accrual was 237. The primary and secondary end-points were detection rate and sensitivity of sentinel basin, respectively. This study is expected to evaluate the feasibility of laparoscopic sentinel basin dissection after endoscopic submucosal dissection. If the feasibility is identified, multicenter phase III trial will be started comparing laparoscopic sentinel node navigation surgery versus laparoscopic standard gastrectomy in early gastric cancer after endoscopic resection.

Clinical trial identification: NCT03123042; registered April 21st, 2017.

Legal entity responsible for the study: Sentinel Node Oriented Tailored Approach (SENORITA) Study Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

787TiP A phase III study of adjuvant docetaxel, capecitabine and oxaliplatin triplet vs capecitabine and oxaliplatin doublet in patients with curatively resected stage IIIB or IV(M0) (AJCC 6th ed) gastric adenocarcinoma (TRIUMPH, KCSG ST14-05)

M-H. Ryu[1], D.Y. Zang[2], K-W. Lee[3], B.Y. Shim[4], M.H. Lee[5], S.Y. Rha[6], Y-K. Kang[1]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Division of Hematology and Oncology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea, [4]Medical Oncology, St. Vincent's Hospital, Suwon, Republic of Korea, [5]Internal medicine, Inha University Hospital, Incheon, Republic of Korea, [6]Internal Medicine, Yonsei Cancer Center, Seoul, Republic of Korea

Background: In stage IIIB or IV(M0) (by AJCC 6th edition) gastric cancer (GC), recurrence rate is higher than 50% even with curative D2 surgery and current standard adjuvant chemotherapy with capecitabine and oxaliplatin (XO) or S-1. Accordingly, more effective treatment is needed to reduce recurrence rate in these far advanced GCs. Our previous phase II study of adjuvant chemotherapy in stage IIIB or IV(M0) GC (Yoon S, et al. Gastric Cancer. 2017;20:182) suggested that docetaxel-containing triplet was safe and might be better in terms of recurrence-free survival (RFS) when compared with historic data of fluoropyrimidine plus platinum or fluoropyrimidine alone. Based on this background, a phase III randomized study to evaluate adjuvant docetaxel, capecitabine and oxaliplatin (DXO) triplet vs current standard XO in patients (pts) with curatively resected stage IIIB or IV(M0) GC has been initiated (NCT01935778).

Trial design: Since October 2013, pts with curatively resected stage IIIB or IV(M0) gastric or gastroesophageal junction adenocarcinoma have been recruited from 6 sites in Korean Cancer Study Group (KCSG). Other key eligibility criteria include ECOG performance status 0-1, age of 20-75 years, D2 surgery, and adequate organ functions. Three to 8 weeks after surgery, pts are randomized 1:1 in open label to adjuvant DXO arm vs XO arm. Stratification factors for randomization include pathologic stage (IIIB vs IV(M0)) and extent of gastrectomy (total vs subtotal). In DXO arm, pts receive docetaxel 60 mg/m^2 i.v. on day 1, capecitabine 800 mg/m^2 p.o. twice daily on days 1-14, and oxaliplatin 100 mg/m^2 i.v. on day 1, every 3 weeks for 6 cycles; in XO arm, pts receive capecitabine 1000 mg/m^2 p.o. twice daily on days 1-14, and oxaliplatin 130 mg/m^2 i.v. on day 1, every 3 weeks for 8 cycles. Primary endpoint is 3-year RFS rate. Secondary endpoints include overall survival and safety. With power of 80% and two-sided α level of 5%, 183 events are required to detect 15% difference in 3-year RFS rate, i.e., 50% in DXO arm vs 35% in XO arm (HR = 0.66). With 10% of drop-out rate, target enrollment is 286 subjects.

Clinical trial identification: NCT01935778.

Legal entity responsible for the study: Asan Medical Center.

Funding: Boryung.

Disclosure: M-H. Ryu: Consultant, Honoraria: DAE HWA Pharmaceutical, Bristol-Myers Squibb, Ono pharmaceutical. K-W. Lee: Research funding: Macrogenics, MSD, Green Cross Crop., ASLAN Pharmaceuticals, AstraZeneca/MedImmune, Five Prime Therapeutics, LSK BioPharma, Merck KGaA, Array BioPharma, Pharmacyclics, Pfizer, ONO Pharmaceuticals. M.H. Lee: Research funding: CJ Healthcare, Yuhan. Y-K. Kang: Consultant: Ono, BMS, Taiho, Roche, Lilly, Blueprint, Taiho, Daehwa, LSK Biopharma. All other authors have declared no conflicts of interest.

788TiP ACELARATE: A randomised phase III, open label, clinical study comparing NUC-1031 with gemcitabine in patients with metastatic pancreatic carcinoma

D. Harrison Palmer[1], P.J. Ross[2], P. Silcocks[1], W. Greenhalf[3], O. Faluyi[4], Y.T. Ma[5], J. Wadsley[6], C. Rawcliffe[1], J. Neoptolemos[7], J.W. Valle[8], H. Wasan[9], N. Starling[10], K. Patel[11], J. Bridgewater[12]

[1]Liverpool Cancer Trials Unit, University of Liverpool, Liverpool, UK, [2], Guy's and St Thomas' NHS Foundation Trust, London, UK, [3]Liverpool Experimental Cancer Medicine Centre, University of Liverpool, Liverpool, UK, [4]Medical Oncology, Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK, [5]Medical Oncology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [6]Medical Oncology, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK, [7]Department of General Surgery, University of Heidelberg, Heidelberg, Germany, [8]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [9]Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK, [10]Medical Oncology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [11]Medical Oncology, Churchill Hospital, Oxford, UK, [12]Oncology, University College London Hospitals, London, UK

Background: Pancreatic ductal adenocarcinoma (PDAC) is predicted to be the second leading cause of cancer-related death by 2030 (Rahib et al, 2014). The overall 5-year survival rate is currently less than 7%. Gemcitabine is used for patients who are not suitable for combination therapy, but the response is poor at less than 10% (Conroy et al, 2011). Gemcitabine efficacy is limited due to intrinsic or acquired resistance mechanisms associated with transport, activation and breakdown. NUC-1031, a phosphoramidate transformation of gemcitabine, is designed to overcome the three key resistance mechanisms responsible for a poor survival prognosis to gemcitabine. In a Phase I study, NUC-1031 was well tolerated and demonstrated anti-tumour activity across a wide range of advanced cancers, including PDAC (Blagden et al, ASCO 2015). This ongoing Phase III study is designed to compare NUC-1031 with gemcitabine as first-line treatment in patients with PDAC who are unsuitable for combination chemotherapy.

Trial design: First-line patients with metastatic PDAC are being randomised to either NUC-1031 (825 mg/m^2) or gemcitabine (1000 mg/m^2) on days 1, 8 and 15 of a 28-day cycle until disease progression. Patients unsuitable for combination chemotherapy with a PS of 0-2 are eligible. Over 125 patients have been randomised across more than 20 centres. To detect a hazard ratio of 0.705 between the two arms, 270 events must be obtained from 328 patients, assuming a median survival of 6 months in the control (gemcitabine) arm. The primary outcome measure is overall survival. Secondary outcome measures include progression free survival, objective response rate, disease control rate, quality of life and safety. Translational research will explore the use of biomarkers for predictive benefit of NUC-1031 over gemcitabine.

Clinical trial identification: ISRCTN16765355.

Legal entity responsible for the study: Clatterbridge Cancer Centre NHS Foundation Trust.

Funding: NuCana Biomed Ltd.

Disclosure: D. Harrison Palmer, W. Greenhalf: Research grant, travel bursary: Nucana Biomed Ltd. J. Wadsley: Honoraria: AstraZeneca, Sanofi-Genzyme, Eisai, Bayern, celgene, Lilly, Novartis. Consultancy, Advisory: AstraZeneca, Sanofi-Genzyme,

Eisai, Bayer, Celgene, Lilly, Novartis; Research funding: AstraZeneca, Sanofi-Genzyme. J. Neoptolemos: Travel grant: Nucana Biomed Ltd. J.W. Valle, H. Wasan: Research funding: Nucana Biomed Ltd. All other authors have declared no conflicts of interest.

789TiP HALO 109-301: Phase III, randomized, double-blind, placebo-controlled study of pegvorhyaluronidase alfa (PEGPH20) + nab-paclitaxel/gemcitabine (AG) in patients with previously untreated hyaluronan (HA)-high stage IV pancreatic ductal adenocarcinoma (PDA)

E. Van Cutsem[1], P.G. Corrie[2], M.P. Ducreux[3], D. Sigal[4], V. Sahai[5], D-Y. Oh[6], A. Bullock[7], Y-J. Bang[6], A.D. Baron[8], A. Hendifar[9], C-P. Li[10], P. Philip[11], M. Reni[12], M. Zalupski[13], L. Zheng[14], C. Berman[15], D. Chondros[15], M.A. Tempero[16]

[1]Department of Digestive Oncology, University Hospital Gasthuisberg-University of Leuven and KU Leuven, Leuven, Belgium, [2]Cancer Division, Cambridge University Hospitals NHS Foundation Trust - Addenbrooke's Hospital, Cambridge, Cambridgeshire, UK, [3]GI Oncology Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [4]Department of Medical Oncology, Scripps Clinic, La Jolla, CA, USA, [5]Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI, USA, [6]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [7]Department of Hematology-Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA, [8]Division of Hematology/Oncology, California Pacific Medical Center, San Francisco, CA, USA, [9]Department of Oncology, Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [10]Department of Medicine, Taipei Veterans General Hospital, Taipei City, Taiwan, [11]Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA, [12]Department of Oncology, Ospedale San Raffaele, Milan, Italy, [13]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA, [14]Department of Oncology, Johns Hopkins University, Baltimore, MD, USA, [15]Clinical Development, Halozyme Therapeutics, Inc., San Diego, CA, USA, [16]San Francisco Pancreas Center, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

Background: Poor outcome in PDA is associated with high stromal HA content (HA-high). In vitro, PEGPH20 degrades tumor HA and may increase access and efficacy of tumor therapies. In a Phase 2 study, PEGPH20 + standarddose nabpaclitaxel/gemcitabine (PAG) improved PFS over chemotherapy alone (AG) in tumors retrospectively identified as HA-high. In this Phase 3 study, we investigate the efficacy and safety of PAG vs AG in patients with HA-high, previously untreated, Stage IV PDA. There are 2 primary endpoints: PFS and OS. Secondary endpoints are objective response rate, duration of response, and safety.

Trial design: Patients $\geq$18 years with untreated HA-high, Stage IV PDA and ECOG PS 0–1 are eligible. Exclusion criteria include a history of thromboembolic events (TEs) or cerebrovascular accident. Patients ($N \leq 570$) are randomized 2:1 to PAG (PEGPH20=3.0 μg/kg + A = 125 mg/m^2 + G = 1000 mg/m^2) or AG (A = 125 mg/m^2 + G = 1000 mg/m^2) and stratified by region (North America/Europe/Other). HA-high status is prospectively determined by the RxDx Assay and scoring methodology codeveloped by Ventana Medical Systems, Inc., and Halozyme Therapeutics, Inc. The assay identifies HA in the extracellular matrix, with PDA defined as HA-high when the HA score is $\geq$ 50% based on HA staining. Treatment is provided in 4-week cycles (3 weeks on treatment, 1 week off) until disease progression, unacceptable toxicity, death, or consent withdrawal. PEGPH20 or placebo are dosed twice-weekly (Cycle 1) then weekly ($\geq$Cycle 2); AG is dosed weekly (all cycles). Dexamethasone is used before and after PEGPH20 to reduce PEGPH20-related musculoskeletal symptoms, and enoxaparin prophylaxis is administered subcutaneously once daily at 1 mg/kg to minimize TEs. Tumor response is independently assessed per RECIST v1.1. Adverse events are graded per NCI CTCAE v4.03. An independent data monitoring committee is overseeing the safety data. The trial was initiated in 2016, is open at $>$ 200 study sites across $>$20 countries, and is expected to complete by 2020.

Clinical trial identification: EudraCT 2015-004068-13; NCT02715804.

Editorial acknowledgement: Medical writing assistance was provided by Tamsin Williamson at Paragon, Knutsford, UK.

Legal entity responsible for the study: Halozyme Therapeutics, Inc.

Funding: Halozyme Therapeutics, Inc.

Disclosure: E. Van Cutsem: Sponsored clinical trials Investigator: Halozyme P.G. Corrie, M.P. Ducreux, D. Sigal, D.-Y. Oh, A. Bullock, Y.-J. Bang, A.D. Baron, A. Hendifar, C.-P. Li, P. Philip, M. Reni, M. Zalupski, L. Zheng, M.A. Tempero: Sponsored clinical trials Investigator: Halozyme Therapeutics, Inc. V. Sahai: Consultant, Scientific advisory board: Halozyme. C. Berman, D. Chondros: Employee: Halozyme Therapeutics, Inc.

790TiP A phase II clinical investigation of BPM31510-IV (ubidecarenone) in patients with advanced pancreatic cancer

A.A. Niewiarowska[1], D.M. Lucius[2], R. Sarangarajan[3], N.R. Narain[4], R. Ramanathan[5], P. Ritch[6], J. Strauss[7], M. Kundranda[8], D. Propper[9]

[1]Hematology, Vita Medical Associates, Bethlehem, PA, USA, [2]Clinical Operations, BERG, LLC, Framingham, MA, USA, [3]Biosystems, BERG, LLC, Framingham, MA, USA, [4]Biosystems, Analytics, & Precision Medicine, BERG, LLC, Framingham, MA, USA, [5]Oncology, Mayo Clinic Cancer Center, Scottsdale, AZ, USA, [6]Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA, [7]Oncology, Mary Crowley Medical Research Center, Dallas, TX, USA, [8]Gastrointestinal Medical Oncology, Medical Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ, USA, [9]Oncology, St. Bartholomew's Hospital, London, UK

Background: BPM31510-IV is an ubidecarenone containing intravenous nanodispersion targeting the metabolic machinery in cancer, shifting bioenergetics from lactate dependency towards mitochondrial OxPhos and reversing the Warburg effect. BPM31510-IV enables delivery of ubidecarenone preferentially into cancer cell mitochondria, generating reactive oxygen species and activation of apoptosis. In a phase I study, BPM31510-IV was well-tolerated as a monotherapy, and in combination with gemcitabine, with an established maximum tolerated dose (MTD) of 110mg/kg and thus, formed the basis for the Phase 2 investigation.

Trial design: In this study eligible patients (aged $\geq$ 18 y) relapsed/refractory to standard treatment for advanced metastatic pancreatic cancer and meeting inclusion/exclusion criteria receives either two 72 hr infusions of 110mg/kg BPM31510-IV or in combination with gemcitabine (1000 mg/m^3 over 30 min, weekly x 3 weeks every 28 days). Tumor response is evaluated at wk 10, and then every 8 wks. This study occurs in two parts: Part 1 is designed to enroll 10 patients in the BPM31510-IV (monotherapy arm) and 10 patients in the BPM31510-IV plus gemcitabine (combination therapy arm) with intent to enroll an additional 15 patients (Part 2) into the applicable treatment arm(s). Endpoints will include overall response rate in both groups along with overall survival, progression-free survival, and time to progression. Additionally, patient reported Quality of Life using the validated FACT-HEP as well as tumor response measured by CA 19-9 levels will be combined with multi-omic molecular profiling to assess adaptive molecular responses. An exploratory objective of this study is to comprehensively perform multi-omic profiling for identification of biomarker panels for patient stratification for later stages of clinical development.

Clinical trial identification: NCT02650804.

Editorial acknowledgement: Khampaseuth Thapa. BERG, LLC.

Legal entity responsible for the study: BERG, LLC.

Funding: BERG, LLC.

Disclosure: A.A. Niewiarowska, R. Ramanathan, P. Ritch: Research sponsorship: BERG, LLC. D.M. Lucius: Employee, stock owner: BERG, LLC. R. Sarangarajan: Co-founder, employee, stock options owner: BERG, LLC. N.R. Narain: Co-founder, president & CEO, stock options owner: BERG, LLC. J. Strauss: Research sponsorship: BERG, LLC; Stock & other ownership: Abbott, Abbvie, Bristol-Myers Squibb, Intuitive surgical, Merck. M. Kundranda: Research sponsorship: BERG, LLC; Honoraria: Bayer. D. Propper: Research sponsorship: BERG, LLC; Consulting, advisory role: BMS; Speaker's bureau: Merck; Travel, accommodations, expenses: Celgene.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii271–viii302, 2018
doi:10.1093/annonc/mdy284

GENITOURINARY TUMOURS, PROSTATE

791O Updated results of GETUG-12, a phase III trial of docetaxel-based chemotherapy in high-risk localized prostate cancer, with a 12-year follow-up

K. Fizazi[1], A. Carmel[2], F. Joly[3], R. Delva[4], G. Gravis[5], F. Rolland[6], F. Priou[7], J-M. Ferrero[8], N. Houede[9], L. Mourey[10], C. Theodore[11], I. Krakowski[12], J-F. Berdah[13], M. Baciuchka Palmaro[14], B. Laguerre[15], A. Flechon[16], A. Ravaud[17], M. Brihoum[18], S. Culine[19], G. Le Teuff[2]

[1]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [2]Statistics, Gustave Roussy, Villejuif, France, [3]GINECO & Centre Francois Baclesse Caen, Caen, France, [4]Medical Oncology Department, Centre Paul Papin, Angers, France, [5]Medical Oncology, Institute Paoli Calmettes, Marseille, France, [6]Medical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [7]Medical Oncology, CHD Vendee - Hopital Les Oudairies, La Roche Sur Yon, France, [8]Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France, [9]Medical Oncology Departmentical Oncology Department, Institut de Cancérologie du Gard, Nimes, France, [10]Medical Oncology, Institut Universitaire du Cancer -Toulouse- Oncopole, Toulouse, France, [11]Medical Oncology, Hopital Foch, Suresnes, France, [12]Medical Oncology & Supportive Care, Institute Bergonié, Bordeaux, France, [13]Medical Oncology, Oncovar, Hyeres, France, [14]Medical Oncology, Hopital Nord, Marseille, France, [15]Medical Oncology, Centre Eugene - Marquis, Rennes, France, [16]Medical Oncology, Centre Léon Bérard, Lyon, France, [17]Medical Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France, [18]Clinical Research, UNICANCER, Kremlin-Bicêtre, France, [19]Medical Oncology, Hôpital St. Louis, Paris, France

792O A randomized phase II study of cabazitaxel (CAB) vs (ABI) abiraterone or (ENZ) enzalutamide in poor prognosis metastatic castration-resistant prostate cancer (mCRPC)

K.N. Chi[1], S. Taavitsainen[2], N. Iqbal[3], C. Ferrario[4], M. Ong[5], D. Wadhwa[6], S.J. Hotte[7], G. Lo[8], B. Tran[9], A. Azad[10], L. Wood[11], J.R. Gingerich[12], S. North[13], C.V. Pezaro[14], D. Ruether[15], S.S. Sridhar[16], M. Annala[17], J. Bacon[2], A.W. Wyatt[2]

[1]Medical Oncology, BC Cancer - Vancouver Centre, Vancouver, BC, Canada, [2]Urologic Sciences, University of British Columbia, Vancouver, BC, Canada, [3]Oncology, Saskatoon Cancer Centre University of Saskatchewan, Saskatoon, SK, Canada, [4]Medical Oncology, Jewish General Hospital McGill University, Montreal, QC, Canada, [5]Medical Oncology, Ottawa Hospital Cancer Centre, Ottawa, BC, Canada, [6]Medical Oncology, BC Cancer - Kelowna Centre, Kelowna, BC, Canada, [7]Medical Oncology, Juravinski Cancer Centre, Hamilton, ON, Canada, [8]Medical Oncology, Durham Regional Cancer Centre, Oshawa, ON, Canada, [9]Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia, [10]Medical Oncology, Monash Health, Melbourne, Australia, [11]Medical Oncology, QEII Health Sciences Centre, Halifax, NS, Canada, [12]Medical Oncology, CancerCare Manitoba, Winnipeg, MB, Canada, [13]Medical Oncology, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, [14]Oncology, Eastern Health, Box Hill, Australia, [15]Medical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada, [16]Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [17]Department of Urologic Sciences, Vancouver Prostate Centre-Vancouver General Hospital, Vancouver, BC, Canada

793PD **Preliminary results from TRITON2: A phase II study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations**

W. Abida[1], A.H. Bryce[2], N.J. Vogelzang[3], R.J. Amato[4], I. Percent[5], J.D. Shapiro[6], R. McDermott[7], A. Hussain[8], A. Patnaik[9], D. Petrylak[10], C.J. Ryan[11], T. Stanton[12], J. Zhang[13], A.D. Simmons[14], D. Despain[15], M. Collins[16], T. Golsorskhi[17], H.I. Scher[1], S. Chowdhury[18]

[1]Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Hematology/Oncology, Mayo Clinic, Phoenix, AZ, USA, [3]Medical Oncology, Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA, [4]Oncology, UT Health Science Center, Houston, TX, USA, [5]Medical Oncology, Florida Cancer Specialists, Port Charlotte, FL, USA, [6]Medical Oncology, Cabrini Hospital, Malvern, Australia, [7]Genito-Urinary Oncology, Adelaide and Meath Hospital (Incorporating the National Children's Hospital), Dublin, Belgard Square North, Ireland, [8]Department of Medicine, University of Maryland Greenebaum Cancer Center, Baltimore, MD, USA, [9]Medical Oncology, University of Chicago Comprehensive Cancer Center, Chicago, IL, USA, [10]Medical Oncology, Yale University, Yale Cancer Center, New Haven, CT, USA, [11]Department of Medicine, University of Minnesota, Minneapolis, MN, USA, [12]Medical Oncology, St. Joseph Health Cancer Center, Santa Rosa, CA, USA, [13]Genitourinary Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA, [14]Translational Medicine, Clovis Oncology, Inc., Boulder, CO, USA, [15]Biostatistics, Clovis Oncology, Inc., Boulder, CO, USA, [16]Study Operations, Clovis Oncology, Inc., Boulder, CO, USA, [17]Clinical Development, Clovis Oncology, Inc., Boulder, CO, USA, [18]Medical Oncology, Guy's Hospital and Sarah Cannon Research Institute, London, UK

794PD **Prospective comprehensive genomic profiling (CGP) of 3,343 primary and metastatic site prostate tumors**

S.M. Ali[1], J. Chung[1], N. Dewal[2], L.M. Gay[3], Y. He[2], E.S. Sokol[2], S.Z. Millis[2], J.K. Killian[2], A.B. Schrock[1], S.K. Pal[4], V.A. Miller[2], J.S. Ross[2], N. Agarwal[5]

[1]Clinical Development, Foundation Medicine, Inc., Cambridge, MA, USA, [2]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA, [3]Pathology, Foundation Medicine, Cambridge, MA, USA, [4]Medical Oncology, City of Hope, Duarte, CA, USA, [5]Oncology/Internal Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA

795PD Genomic profiling of circulating tumour DNA (ctDNA) and tumour tissue for the evaluation of rucaparib in metastatic castration-resistant prostate cancer (mCRPC)

S. Chowdhury[1], R. McDermott[2], J.M. Piulats[3], J.D. Shapiro[4], I. Mejlholm[5], D. Morris[6], P. Ostler[7], A. Hussain[8], I. Dumbadze[9], E.R. Goldfischer[10], E. Pintus[11], A. Benjelloun[12], M.E. Gross[13], S. Tejwani[14], G. Chatta[15], A. Font[16], A. Loehr[17], A.D. Simmons[18], S.P. Watkins[19], W. Abida[20]

[1]Medical Oncology, Guy's Hospital and Sarah Cannon Research Institute, London, UK, [2]Genito-Urinary Oncology, AMNCH Adelaide and Meath Hospital, Dublin, Ireland, [3]Medical Oncology, Instituto Catalan de Oncologia, Barcelona, Spain, [4]Medical Oncology, Cabrini Hospital, Malvern, Australia, [5]Oncology, Vejle Sygehus, Vejle, Denmark, [6]Oncology, Urology Associates Clinical Research, Nashville, TN, USA, [7]Clinical Oncology, Mount Vernon Cancer Centre, Northwood, UK, [8]Department of Medicine, University of Maryland Greenebaum Cancer Center, Baltimore, MD, USA, [9]Urology, The Urology Group, Cincinnati, OH, USA, [10]Urology, Premier Medical Group of the Hudson Valley, Poughkeepsie, NY, USA, [11]Medical Oncology, Frimley Health NHS Foundation Trust, Slough, UK, [12]Medical Oncology, Centre Hospitalier Universitaire Dr-Georges-L.-Dumont, Moncton, NB, Canada, [13]Department of Medicine, University of Southern California, Los Angeles, CA, USA, [14]Medical Oncology, Henry Ford Health System, Detroit, MI, USA, [15]Genitourinary Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA, [16]Medical Oncology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [17]Translational Medicine, Clovis Oncology, Inc., Boulder, CO, USA, [18]Translational Medicine, Clovis Oncology, Boulder, CO, USA, [19]Clinical Science, Clovis Oncology, Inc., Boulder, CO, USA, [20]Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

796PD Detection of circulating tumor DNA in de novo metastatic castrate sensitive prostate cancer

W.J. Struss, G. Vandekerkhove, M. Annala, K.N. Chi, M.E. Gleave, A. Wyatt

Department of Urologic Sciences, Vancouver Prostate Centre-Vancouver General Hospital, Vancouver, BC, Canada

797PD LATITUDE study: PSA response characteristics and correlation with overall survival (OS) and radiological progression-free survival (rPFS) in patients with metastatic hormone-sensitive prostate cancer (mHSPC) receiving ADT+abiraterone acetate and prednisone (AAP) or placebo (PBO)

N. Matsubara[1], K.N. Chi[2], M. Ozguroglu[3], A. Rodriguez Antolin[4], S. Feyerabend[5], L. Fein[6], B.Y. Alekseev[7], G. Sulur[8], A. Protheroe[9], S. Li[10], S.D. Mundle[11], P. De Porre[12], N. Tran[13], K. Fazazi[14]

[1]Division Oncology and Hematology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [2]Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, [3]Medical Oncology, University of Istanbul Cerrahpasa Medical Faculty, Istanbul, Turkey, [4]Urology, University Hospital 12 de Octubre, Madrid, Spain, [5]Urology, University of Tübingen, Tübingen, Germany, [6]Clinical Research in Oncology, Institute of Oncology Rosario, Rosario, Argentina, [7]Medical Sciences, Herzen Cancer Research Institute, Moscow, Russian Federation, [8]WC Clinical Oncology, Janssen R&D US, Los Angeles, CA, USA, [9]Medical Oncology, Churchill Hospital University of Oxford, Oxford, UK, [10]R&D, Janssen Research & Development, Los Angeles, CA, USA, [11]Global Medical Affairs, Janssen Research & Development, Raritan, NJ, USA, [12]BE Clinical Oncology, Janssen R&D BE, Beerse, Belgium, [13]Clinical Oncology, Janssen R&D, Los Angeles, CA, USA, [14]Medical Oncology, Institut Gustave Roussy, Villejuif, France

798PD **In-depth assessment of metastatic prostate cancer with high tumour mutational burden**

N. Mehra[1], J. van Riet[2], M. Smits[1], H. Westdorp[3], M. Gorris[3], T. van Ee[3], M. van der Doelen[4], I. van Oort[4], M. Sedelaar[4], J. Textor[3], E. Cuppen[5], K. Grunberg[6], M.J.L. Ligtenberg[7], W. Zwart[8], A. Bergman[9], H.J.G. van de Werken[2], J. Schalken[10], I.J.M. de Vries[3], M.P. Lolkema[11], W.R. Gerritsen[1]

[1]Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [2]Department of Cancer Computational Biology Center / Urology, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Department of Tumour Immunology, Radboud Institute for Molecular Life Sciences, Nijmegen, Netherlands, [4]Urology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [5]Center for Molecular Medicine, University Medical Center Utrecht / Hartwig Medical Foundation / Center for Personalized Cancer Treatment, Utrecht, Netherlands, [6]Department of Pathology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [7]Department of Pathology / Human Genetics, Radboud University Medical Center Nijmegen, Nijmegen, Netherlands, [8]Oncode Institute / Division of Oncogenomics, Netherlands Cancer Institute (NKI-AVL), Amsterdam, Netherlands, [9]Division of Oncogenomics and Internal Medicine, Netherlands Cancer Institute (NKI-AVL), Amsterdam, Netherlands, [10]Laboratory of Experimental Urology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [11]Medical Oncology, Erasmus University Medical Center / Center for Personalized Cancer Therapy, Rotterdam, Netherlands

799PD **Phase I dose-escalation study of fractionated dose 177Lu-PSMA-617 for progressive metastatic castration resistant prostate cancer (mCRPC)**

S.T. Tagawa[1], S. Vallabhajosula[2], Y. Jhanwar[2], A. Hackett[1], C. Oromendia[3], M.J. Naiz[4], S.J. Goldsmith[2], D.M. Nanus[5], H. Beltran[5], A.M. Molina[1], B. Faltas[1], J. Sreekumar[1], J. Babich[2], K. Ballman[3], N.H. Bander[4]

[1]Hematology and Medical Oncology, Weill Cornell Medical College, New York, NY, USA, [2]Radiology, Weill Cornell Medical College, New York, NY, USA, [3]Department of Healthcare Policy & Research, Weill Cornell Medical College, New York, NY, USA, [4]Urology, Weill Cornell Medical College, New York, NY, USA, [5]Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York, NY, USA

800P **The prognostic value of the proportion and subtype patterns of intraductal carcinoma of the prostate in patients with *de novo* metastatic prostate cancer: A propensity score matching study**

J. Zhao, J. Liu, G. Sun, P. Shen, J. Chen, X. Zhang, H. Zhang, Z. Liu, Y. Bao, Y. Yang, P. Zhao, K. Shu, H. Zeng

Department of Urology, Institute of Urology, West China Hospital, SiChuan Univer, West China Hospital, Sichuan University, Chengdu, China

Background: Intraductal carcinoma of the prostate (IDC-P) is an adverse prognosticator of prostate cancer (PCa). However, the role of IDC-P proportion and architectural patterns in patient outcome remain unclear.

Methods: Data of 644 *de novo* metastatic PCa (mPCa) patients between 2010-2017 were retrospectively analyzed. IDC-P was identified from 12-core prostate biopsy. IDC-P proportion were calculated. IDC-P were classified into two architectural patterns according to the 2016 WHO classification: pattern-1 (loose cribriform or micropapillary) and pattern-2 (solid or dense cribriform). Propensity-score matching (PSM) was conducted to balance the baseline characteristics between patients with and without IDC-P. Kaplan-Meier curves and COX regression were utilized in survival analysis. The endpoints were castration-resistant PCa free survival (CFS) and overall survival (OS).

Table: 800P The CFS for patients of different IDC-P groups and patients without IDC-P after propensity-score matching

A. The survival outcomes for *de novo* mPCa patients of different IDC-P groups

IDC-P group	CASE	Median CFS (95%CI)	Log-rank test				
			Group 0	Group 1	Group 2	Group 3	Group 4
Group 0	180 (50.0%)	17.8 (15.3-20.3)	-	0.663	0.019	0.104	0.000
IDC-P-Group 1	41 (11.4%)	18.0 (12.7-23.2)	0.663	-	0.194	0.264	0.001
IDC-P-Group 2	58 (16.1%)	14.2 (10.1-18.3)	0.019	0.194	-	0.785	0.014
IDC-P-Group 3	22 (6.1%)	11.9 (6.0-17.8)	0.104	0.264	0.785	-	0.080
IDC-P-Group 4	59 (16.4%)	8.4 (6.7-10.1)	0.000	0.001	0.014	0.080	-
IDC-P group	**CASE**	**Median OS (95%CI)**	**Log-rank test**				
			Group 0	**Group 1**	**Group 2**	**Group 3**	**Group 4**
Group 0	180 (50.0%)	68.8 (58.9-78.7)	-	0.655	0.098	0.028	0.000
IDC-P-Group 1	41 (11.4%)	Not reached	0.655	-	0.569	0.201	0.049
IDC-P-Group 2	58 (16.1%)	45.9 (29.7-62.1)	0.098	0.569	-	0.530	0.061
IDC-P-Group 3	22 (6.1%)	39.7 (25.1-54.3)	0.028	0.201	0.530	-	0.441
IDC-P-Group 4	59 (16.4%)	29.9 (20.7-39.2)	0.000	0.049	0.061	0.441	-

B. The survival outcomes for *de novo* mPCa patients of different risk group

Risk group	CASE	Median CFS (95%CI)	Log-rank test		
			Group 1 or 0	Group 2 or 3	Group 4
Favorable-risk: Group 1 or 0	221 (61.4%)	17.8 (15.5-20.1)	-	0.009	0.000
Intermediate-risk: Group 2 or 3	80 (22.2%)	14.1 (10.3-17.9)	0.009	-	0.007
Poor-risk: Group 4	59 (16.4%)	8.4 (6.7-10.1)	0.000	0.007	-
Risk group	**CASE**	**Median OS (95%CI)**	**Log-rank test**		
			Group 1 or 0	**Group 2 or 3**	**Group 4**
Favorable-risk: Group 1 or 0	221 (61.4%)	72.6 (63.8-72.6)	-	0.027	0.000
Intermediate-risk: Group 2 or 3	80 (22.2%)	43.2 (35.2-51.1)	0.027	-	0.080
Poor-risk: Group 4	59 (16.4%)	29.9 (20.7-39.2)	0.000	0.080	-

CFS: CRPC-free survival; OS: Overall survival; IDC-P: Intraductal carcinoma of the prostate; CI: Confidence interval; mPCa: metastatic prostate cancer

Results: Totally, 180/644 (28.0%) patients harboured IDC-P. IDC-P ≥10% (CFS: HR: 2.27, p < 0.001; OS: HR: 2.63, p < 0.001) and IDC-P pattern-2 (CFS: HR: 1.98, p < 0.001; OS: HR: 2.11, $p = 0.003$) were independently associated with worse prognosis in the post-PSM cohort. Based on these two risk factors, all men could be classified into five groups with significant differences in survival (Table 1). Patients in Group 0 (Without IDC-P) and IDC-P-Group 1 (IDC-P < 10% AND IDC-P pattern-1) had favorable mCFS (18.0- vs. 17.8-Mo, $p = 0.663$) and mOS (68.8-Mo vs. Not reached, $p = 0.655$), while men of IDC-P-Group 4 (IDC-P ≥ 10% AND IDC-P pattern-2) harboured the worst outcomes (mCFS: 8.4-Mo; mOS: 29.9-Mo). IDC-P-Group 2 (IDC-P < 10% AND IDC-P pattern-2; mCFS: 14.2-Mo; mOS: 45.9-Mo) and IDC-P-Group 3 (IDC-P ≥ 10% AND IDC-P pattern-1; mCFS: 11.9-Mo; mOS: 39.7-Mo) had intermediate prognosis.

Conclusions: IDC-P proportion ≥10% and pattern-2 were two unfavorable prognosticators for mPCa. Pathological reporting criterion based on IDC-P could further improve the prediction of patient outcome and optimize treatment decision.

Legal entity responsible for the study: Department of Urology, Institute of Urology, West China Hospital, Sichuan University.

Funding: This work was supported by the National Natural Science Foundation of China (NSFC 81672547, 81402110, and 81272820); Science and Technology Support Program of Sichuan Province (2015SZ0142); The 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University.

Disclosure: All authors have declared no conflicts of interest.

801P Bone metabolism biomarkers (BMB) in hormone sensitive prostate cancer (HSPC): Results from SWOG S1216, a phase III trial of androgen deprivation therapy (ADT) +/- orteronel

P.N. Lara[1], E. Mayerson[2], E. Gertz[3], C. Tangen[2], A. Goldkorn[4], M. van Loan[3], M. Hussain[5], S. Gupta[6], J. Zhang[7], P. Twardowski[8], D.I. Quinn[9], N.J. Vogelzang[10], I. Thompson[11], N. Agarwal[12]

[1]Hem-Onc/Internal Medicine, University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA, [2]SWOG Statistical Center, FHCRC, Seattle, WA, USA, [3]ARS/USDA, UC Davis, Davis, CA, USA, [4]Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA, [5]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [6]Medicine, University of Minnesota, Minneapolis, MN, USA, [7]Medical Oncology, Moffitt Comprehensive Cancer Center, Tampa, FL, USA, [8]Medical Oncology, City of Hope, Duarte, CA, USA, [9]Translation and Clinical Science Program / Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [10]Oncology, US Oncology Research c/o Comprehensive Cancer Crts of NV, Las Vegas, NV, USA, [11]Urology, Christus Health, San Antonio, TX, USA, [12]Oncology/ Internal Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA

Background: BMB are independently prognostic for survival in men with metastatic castration resistant PC. It is unclear whether prognostic or predictive value of BMB applies to an earlier HSPC state. We prospectively assessed BMB in men enrolled in S1216, a phase III trial of ADT +/- orteronel with an ultimate goal to identify HSPC patient (pt) subsets defined by BMB that have differential survival outcomes. Here we report initial results of baseline BMB from S1216 & their relationship to clinical variables.

Methods: Bone resorption [C-telopeptide(CTx) & Pyridinoline (PYD)] & formation markers [C-terminal collagen propeptide (CICP) & bone alkaline phosphatase (BAP)] were measured. Elevated BMB was defined as above median or in upper quartile for each BMB. Men were grouped as having all four, 1-3, or no BMB elevated. Frequency tables of BMB distribution across pt subsets were generated. To

account for multiple comparisons, a p-value of < 0.001 was considered potentially significant.

Results: Of 1,313 men, 799 had baseline BMB. Pt characteristics [median (range) or n (%)]: age 67y (19-92); PSA 29 ng/dL (2-6710); Gleason >7: n = 479 (64%); bone mets: 604 (76%); bisphos/denosumab: 44 (5.5%); Zubrod PS 0: 547 (68%); & minimal disease extent: 389 (49%). Median BMB: CTx 0.46 ng/mL (0.03-12.2); PYD 1.68 nmol/L (0.35-17.5); CICP 116 ng/mL (0.25-3360); BAP 1.66 u/L (0-1001). At least one BMB was > median in 87% & in top quartile in 57%. In 604 w/ bone mets, 540 had at least 1 BMB > median while distribution of BMB elevation >median differed significantly w/ in groups defined by PSA ($p < 0.0001$), Gleason score ($p = 0.0001$), PS ($p < 0.0001$) & disease extent ($p < 0.0001$). For example, in 292 with PSA>29, 30% had all 4 BMB elevated; in those with PSA < 29, only 6% had all 4 elevated. BMB distribution in all men did not differ within race/ethnicity, age, & bisphos/denosumab groupings. Trends were similar when BMB upper quartile was used.

Conclusions: In men with HSPC initiating ADT, at least one BMB was elevated in 87%. Differences in BMB distribution were seen within pre-defined subsets, with BMB elevation tracking with higher tumor grade, disease burden & lower PS. Assessment of BMB association with patient outcomes is planned.

Clinical trial identification: SWOG S1216; NCT01809691.

Legal entity responsible for the study: SWOG.

Funding: NIH/NCI grants CA180888, CA180819; and Millennium Pharmaceuticals (Takeda Oncology Company) NIH.

Disclosure: All authors have declared no conflicts of interest.

802P Comparative efficacy and cost-effectiveness of maximum androgen blockade (MAB), docetaxel with androgen deprivation therapy (ADT), and ADT alone for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in China

W. Jiang[1], S. Qu[2], Y. Liu[2], X. Yao[3], M. Liu[4]

[1]Department of Urology, Fujian Medical University Union Hospital, Fuzhou, China, [2]Real-World Insights, IQVIA, Shanghai, China, [3]Health Economics & Outcome Research, Sanofi, Shanghai, China, [4]Department of Pharmacy, Fujian Medical University Union Hospital, Fuzhou, China

Background: The study aims to compare the efficacy and cost-effectiveness of maximum androgen blockade (MAB), docetaxel with androgen deprivation therapy (Doce-ADT), and ADT alone for the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) from healthcare system perspective in China.

Methods: English and Chinese databases were systematically searched for head-to-head randomized controlled trials among the 3 therapies up to January 30th 2018. The network meta-analysis was conducted for overall survival (OS) and progression-free survival (PFS). A Markov model with a lifetime survival projection was adopted for economic evaluation. The quality-adjusted life years (QALYs), direct medical costs and incremental cost-effectiveness ratios (ICERs) were reported. One-way and probabilistic sensitivity analyses (PSA) were used to test the robustness of the results.

Results: Nine RCTs involving 5861 patients were included: 1181 (20%) patients with Doce-ADT, 1463 (25%) patients with MAB, and 3217 (55%) patients with ADT alone. The hazard ratios for PFS and OS were 0.625 (95% CI: 0.565-0.690) and 0.782 (95% CI: 0.700-0.876) respectively for Doce-ADT versus ADT-alone; 0.823 (95% CI: 0.701-0.961) and 0.867 (95% CI: 0.790-0.949) for MAB versus ADT alone; and 0.764 (95% CI: 0.630-0.916) and 0.904 (95% CI: 0.778-1.046) for Doce-ADT vs. MAB. The cost-effectiveness analysis showed that Doce-ADT, MAB and ADT alone were associated with 5.03, 4.56 and 4.02 QALYs, at an average cost of RMB 423,109, 397,440 and 326,771 per patient, respectively. [GM/1] Therefore, Doce-ADT was cost-effective with an ICER of RMB 95,247 and RMB 54,095 per QALY gained compared with MAB and ADT alone, respectively. MAB was cost-effective with an ICER of RMB 131,617 per QALY gained compared with ADT alone. Sensitivity analyses confirmed the results.

Conclusions: As the first study comparing the three therapies treating mHSPC patients in China, the study suggests that Doce-ADT is likely to be the best option from both clinical outcomes and economic evaluation perspectives, followed by MAB.

Legal entity responsible for the study: IQVIA.

Funding: This study was funded by Sanofi China.

Disclosure: All authors have declared no conflicts of interest.

803P Randomized trial of androgen deprivation therapy (ADT) + enzalutamide (Arm A) versus ADT + bicalutamide (Arm B) in metastatic hormone sensitive prostate cancer (mHSPC)

U.N. Vaishampayan[1], L. Heilbrun[2], P. Monk[3], G. Sonpavde[4], S. Tejwani[5], E.I. Heath[6], J. Fontana[2], S. Chinni[2]

[1]Oncology, Karmanos Cancer Institute, Detroit, MI, USA, [2]Oncology, Karmanos Cancer Center, Detroit, MI, USA, [3]Oncology, Ohio State University, Columbus, OH, USA, [4]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [5]Oncology, Henry Ford Hospital, Detroit, MI, USA, [6]Oncology, Karmanos Cancer Center, Detroit, MI, USA

Background: The addition of abiraterone or docetaxel has shown overall survival (OS) benefit in mHSPC. There is adequate rationale for clinical efficacy of enzalutamide and ADT combination in mHSPC. We compared the combination of enzalutamide (Arm A) or bicalutamide (Arm B), each with ADT in mHSPC.

Methods: The primary endpoint was the seven month PSA remission (SMPR), with PSA nadir of < 4 ng/ml, as this is an accepted surrogate for overall survival (OS) outcomes. Secondary endpoints were toxicities, biochemical and radiologic progression free survival (PFS), and OS. Stratification was by presence of bone pain (yes/no) and race; (AA or other). PSA was monitored monthly for first 7 months and then every 3 months. Metastatic site biopsies were mandatory pretherapy and optional post therapy.

Results: 71 men; 29 African American (AA),41 Caucasian and 1 Asian were enrolled. The median age was 67 years (range 46-87 years) and median baseline PSA was 56.3 ng/ml in Arm A (4.2- 10,431 ng/ml) and 60 (4.9-12,030 ng/ml) in Arm B. 26 pts (39%) had bone pain and 37(52%) had extensive disease. Predominant grade 3+ adverse events on Arm A were: Hypertension (13%), infection (7%), and syncope (7%) and on Arm B were: Hypertension (21%), Fatigue (7%), and Hematuria (7%). No seizures were noted. PSA nadir < 4ng/ml at month 7 was achieved in 29/31 (94%) pts in arm A and 16/24 (67%) pts in arm B. 53% on arm A and 43% on Arm B continue to maintain PSA< 4 ng/ml. 4 (11%) deaths have occurred on enzalutamide arm as compared to 13 (37.1%) deaths on Arm B. Among AA patients, SMPR was 100% on Arm A and 46% on Arm B. 53 (75%) biopsy samples had tumor tissue available. TMPRSS-ERG fusion gene and CXCR4 expression and androgen biosynthetic enzyme levels were determined in metastatic biopsies. Patients with low copy number of ERG had an increased likelihood of SMPR (19/20 or 95%) as compared to high copy number (14/20 or 70%).

Conclusions: Early enzalutamide use in mHSPC improved PSA remission rates and has the potential to subsequently improve OS outcomes High ERG copy number was associated with decreased SMPR. This is the first randomized trial to report efficacy results of the combination of ADT and enzalutamide compared with ADT and bicalutamide in mHSPC.

Legal entity responsible for the study: Karmanos Cancer Center.

Funding: Astellas Inc.

Disclosure: U.N. Vaishampayan: Research support, consulting: Astellas Inc. P. Monk, G. Sonpavde, S. Chinni: Research support: Astellas Inc. All other authors have declared no conflicts of interest.

804P Health-related quality of life (HRQoL) after progressive disease (PD) in SPARTAN: A phase III trial of apalutamide (APA) versus placebo (PBO) in men with nonmetastatic castration-resistant prostate cancer (nmCRPC)

E.J. Small[1], D. Cella[2], K. McQuarrie[3], F. Saad[4], B.A. Hadaschik[5], J.N. Graff[6], H. Uemura[7], S. Oudard[8], M.K. Yu[9], S. Hudgens[10], A. Lopez-Gitlitz[9], B. Rooney[11], M. Morris[12], M.R. Smith[13]

[1]Hematology/Oncology, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA, [2]Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [3]Patient Reported Outcomes, Janssen Global Services, Horsham, PA, USA, [4]Urology, Centre Hospitalier de l'Universite de Montréal, Montréal, QC, Canada, [5]Urology, University of Duisburg-Essen, German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, and Ruprecht-Karls University Heidelberg, Heidelberg, Germany, [6]Hematology/Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA, [7]Urology & Renal Transplantation, Yokohama City University Medical Center, Yokohama, Japan, [8]Immunothérapie et Traitement Antiangiogénique en Pathologie Cancérologique, Hopital European George Pompidou, Paris, France, [9]Clinical Oncology, Janssen Research & Development, Los Angeles, CA, USA, [10]Quantitative Science, Clinical Outcomes Solutions, Tucson, AZ, USA, [11]Clinical Oncology, Janssen Research & Development, High Wycombe, UK, [12]Quantitative Science, Clinical Outcomes Solutions, Folkestone, UK, [13]Hematology/Oncology, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA

Background: Compared with PBO, APA prolongs the median metastasis-free survival (MFS) by > 2 y (HR = 0.30; 95% CI, 0.24-0.36), and provids a 55% reduction in the risk of symptomatic progression (Sx PD) (HR = 0.45; 95% CI, 0.32-0.63) in patients (pts) with nmCRPC (SPARTAN study, Smith MR, et al. NEJM 2018), with no decline in HRQoL in either treatment group up to the time of developing distant metastases (Mets). Here, we report pt HRQoL following PD.

Methods: 1207 pts (median age, both arms: 74 y) with nmCRPC were randomized 2:1 to APA (240 mg QD) or PBO. ADT was continued in all pts. HRQoL was assessed using

Table: 804P PRO group mean scores

	APA			PBO		
	Baseline	**Before Mets**	**After Mets[a]**	**Baseline**	**Before Mets**	**After Mets[a]**
All pts, n	797	772	157	396	384	184
Group mean (SE)						
FACT-P FACT-G	117.2 (0.7) 84.1 (0.4)	117.4 (0.7) 83.9 (0.5)	112.5 (1.9) 80.7 (1.3)	116.6 (1.0) 83.4 (0.7)	116.6 (1.0) 83.2 (0.7)	114.5 (1.6) 81.8 (1.1)
	Baseline	**Before Sx PD**	**After Sx PD[a]**	**Baseline**	**Before Sx PD**	**After Sx PD[a]**
Sx PD subgroup, n	64	64	30	63	63	30
Group mean (SE)						
FACT-P FACT-G	115.2 (2.5) 84.4 (1.9)	117.0 (2.4) 84.2 (1.7)	108.6 (3.7) 78.6 (2.9)	117.8 (2.0) 85.2 (1.5)	114.5 (2.2) 82.6 (1.7)	105.6 (4.3) 75.3 (3.4)

[a]Includes pts with and without subsequent approved treatment for metastatic CRPC. SE, standard error.

the pt-reported outcome (PRO) questionnaire Functional Assessment of Cancer Therapy-Prostate (FACT-P). Following development of Mets, pts in the 2 arms received similar treatments, and PROs were collected at 4, 8, and 12 mo. Sx PD was defined as 1) development of a skeletal-related event; 2) initiation of new systemic anticancer treatment due to pain progression or worsening of disease-related symptoms; or 3) development of clinically significant symptoms due to loco-regional tumor progression requiring surgery or radiation. Descriptive statistics were performed for all FACT-P subscales.

Results: Group mean PRO scores after PD were available from 341 pts and from 60 pts after Sx PD (Table). These PRO scores were similar for APA vs PBO up to 12 mo after PD. While APA delayed time to Sx PD, once Sx PD was reached there were similar numeric decreases from baseline across FACT-P subdomains up to 12 mo after Sx PD.

Conclusions: Relative to PBO, pts treated with APA had a longer MFS, with no decline in HRQoL through the time of Mets, and similar HRQoL after Mets. Sx PD was delayed with APA vs PBO and was associated with a decline in HRQoL in both groups. Thus, HRQoL decline for pts treated with APA was delayed because of a longer time to Sx PD.

Clinical trial identification: NCT01946204.

Editorial acknowledgement: This study was funded by Janssen Research & Development. Writing assistance was provided by Ann Tighe, PhD, of PAREXEL, and was funded by Janssen Global Services, LLC.

Legal entity responsible for the study: Janssen Research & Development.

Funding: Janssen Research & Development.

Disclosure: D. Cella: Consultant: AbbVie, Astellas, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Inc, Evidera, GlaxoSmithKline, Helsinn, Ipsen, Janssen Research & Development, Novartis; President: FACIT.org. F. Saad: Grants, Personal fees, Non-financial support: Janssen, Astellas, Sanofi, Bayer. B.A. Hadaschik: Grants: German Cancer Aid, German Research Foundation, Profound Medical; Grants Janssen, Uromed; Personal fees: Janssen, Astellas, Bayer, Uromed; Non-financial support: Janssen, Astellas, Bayer. J.N. Graff: Grants: Janssen, Sanofi, Astellas, Merck Bristol-Myers Squibb; Personal fees: Janssen, Sanofi, Astellas, Bayer, Dendreon. H. Uemura: Personal fees: Janssen, Astellas, Takeda, Sanofi, Bayer, and Astra-Zeneca. S. Oudard: Personal fees: Janssen, Sanofi, Astellas, Bayer, Merck. S. Hudgens: Consulting fees: Janssen. K. McQuarrie, M.K. Yu, A. Lopez-Gitlitz, B. Rooney: Employee: Janssen Research & Development; Stock owner: Johnson & Johnson. M. Morris: Consulting fees: Janssen. M.R. Smith: Grants: Janssen; Personal fees: Janssen, Astellas, Bayer. All other authors have declared no conflicts of interest.

805P A phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic (M0) castration-resistant prostate cancer (CRPC): Results of PROSPER by age and region

K. Fizazi[1], M. Hussain[2], F. Saad[3], N. Shore[4], U. De Giorgi[5], E. Efstathiou[6], U. Ferreira[7], P. Ivashchenko[8], K. Madziarska[9], M. Al-Adhami[10], K. Modelska[11], D. Phung[12], J. Steinberg[13], C.N. Sternberg[14]

[1]Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, Villejuif, France, [2]Robert H. Lurie Comprehensive Cancer Center, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA, [3]Urology, University of Montreal Hospital Center (CHUM), Montreal, QC, Canada, [4]Urology, Carolina Urologic Research Center, Myrtu Beach, SC, USA, [5]Uro-Gynecology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Piero Maroncelli, Italy, [6]Genitourinary Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [7]Urologic Oncology, State University of Campinas (Unicamp), Cidade Universitária Zeferino Vaz - Barão Geraldo, Brazil, [8]Urology, Kyiv City Clinical Hospital #3, Kiev, Petra Zaporozhtza, Ukraine, [9]Department and Clinic of Nephrology and Transplantation Medicine, Wroclaw Medical University, Wroclaw, Poland, [10]Biostatistics, Pfizer Inc., Groton, CT, USA, [11]Medical Oncology, Pfizer Inc., San Francisco, CA, USA, [12]Biostatistics, Astellas Pharma, Inc, Leiden, Netherlands, [13]Medical Oncology, Astellas Pharma, Inc., Northbrook, IL, USA, [14]Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy

Background: Men with M0 CRPC are at high risk of developing metastatic (M1) CRPC. The goal of M0 CRPC treatment is to delay M1 disease progression, delay additional antineoplastic therapies, and ultimately prolong survival and maintain quality of life. In the primary analysis of PROSPER, ENZA improved metastasis-free survival (MFS) in men with M0 CRPC. Here we report results in subgroups of patients (pts) by age and region.

Methods: Eligible men with M0 CRPC, prostate-specific antigen (PSA) doubling time $\leq$ 10 mo and PSA $\geq$ 2 ng/mL at screening continued androgen deprivation therapy and were randomized 2:1 to ENZA 160 mg or PBO. The primary endpoint was MFS. Secondary endpoints included time to PSA progression, time to first use of new antineoplastic therapy, overall survival, and safety.

Results: 1401 men were enrolled with a median age of 74 y (standard deviation, 7.8 y). Baseline characteristics were generally similar across regions and age groups (Table). Baseline use of bone-targeting agents was higher in North America compared with the other 2 regions. A greater proportion of pts aged $\geq$ 75 y had and ECOG PS of 1 than pts aged $<$ 75 y. In all men, ENZA reduced the risk of metastasis or death by 71% (HR,

Table: 805P

	Overall (N = 1401)	Age $<$ 75 y (n = 756)	Age $\geq$ 75 y (n = 645)	Europe (n = 690)	Rest of world (n = 507)	North America (n = 204)
Baseline characteristics						
Age category, no. (%) $<$ 65 y 65 to $<$ 75 y $\geq$ 75 y	190 (14) 566 (40) 645 (46)	190 (25) 566 (75) 0	0 0 645 (100)	100 (15) 285 (41) 305 (44)	57 (11) 200 (40) 250 (49)	33 (16) 81 (40) 90 (44)
ECOG PS, no. (%) 0 1	1129 (81) 270 (19)	668 (88) 87 (12)	461 (72) 183 (28)	555 (80) 134 (19)	401 (79) 105 (21)	173 (85) 31 (15)
Use of bone-targeting agent, no. (%) Yes	153 (11)	77 (10)	76 (12)	74 (11)	36 (7)	43 (21)
PSA doubling time, median (range), mo	3.7 (0.4-71.8)	3.5 (0.6-28.9)	4.0 (0.4-71.8)	3.9 (0.4-71.8)	3.5 (0.4-10.0)	3.7 (0.5-14.7)
PSA doubling time $<$ 6 mo, no. (%)	1076 (77)	596 (79)	480 (74)	510 (74)	411 (81)	155 (76)
Efficacy						
MFS HR (95% CI) P value	0.29 (0.24-0.35) $<$ 0.0001	0.25 (0.20-0.33) $<$ 0.0001	0.35 (0.26-0.47) $<$ 0.0001	0.24 (0.18-0.32) $<$ 0.0001	0.32 (0.23-0.43) $<$ 0.0001	0.41 (0.25-0.66) $<$ 0.0001

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

0.29; 95% CI, 0.24-0.35; P < 0.0001). The risk reduction with ENZA use was similar across all subgroups (Table). Safety results were generally similar among all subgroups, except that more pts in the group aged ≥ 75 y reported adverse event as the primary reason for discontinuation (13% with ENZA vs 10% with PBO) than in the overall pt population (9% with ENZA vs 6% with PBO), and more pts in North America reported falls (15%) than in Europe (7%) or rest of world (10%).

Conclusions: In men with M0 CRPC and rapidly rising PSA, ENZA treatment resulted in a clinically meaningful and statistically significant reduction of developing metastases or death. Results were consistent across subgroups of pts by age and geographic region.

Clinical trial identification: NCT02003924.

Editorial acknowledgement: Medical writing and editorial support, funded by Pfizer Inc., and Astellas Pharma, Inc., was provided by Stephanie Vadasz, Ph.D., and Shannon Davis of Ashfield Healthcare Communications.

Legal entity responsible for the study: Pfizer, Inc. and Astellas Pharma, Inc.

Funding: Pfizer, Inc. and Astellas Pharma, Inc.

Disclosure: K. Fizazi: Honoraria, consultant: Amgen, Astellas, Bayer, Clovis, CureVac, Janssen, Orion, Sanofi. M. Hussain: Honoraria: Sanofi, OncLive; Travel expenses: Sanofi; Institutional research funding: AstraZeneca, Pfizer, Bayer, Genentech. F. Saad: Honoraria, institutional research funding, consultant: Janssen, Sanofi, Astellas, Bayer, Pfizer. N. Shore: Consultant: Amgen, Astellas, Bayer, Dendreon, Fleming, Janssen, Medivation, Tolmar; Participated in speakers' bureaus: Janssen, Bayer, Dendreon. U. De Giorgi: Honoraria, consultant: Astellas, Bristol-Myers Squibb, Ipsen, Janssen, Pfizer, Novartis, Sanofi. E. Efstathiou: Honoraria, research funding, advisory boards: Janssen, Sanofi, Tolmar, Pfizer, Medivation, Astellas, Bayer, AstraZeneca. M. Al-Adhami, K. Modelska: Employees: Pfizer Inc. D. Phung, J. Steinberg: Astellas, Inc. C.N. Sternberg: Honoraria, institutional research funding: Pfizer, Astellas, Sanofi, Janssen, Bayer, Clovis Oncology, Ferring. All other authors have declared no conflicts of interest.

806P Relationship between apalutamide (APA) exposure and metastasis-free survival (MFS) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) from SPARTAN

M.R. Smith[1], C. Perez-Ruixo[2], O. Ackaert[2], D. Ouellet[3], C. Chien[3], H. Uemura[4], D. Olmos[5], P.N. Mainwaring[6], J.Y. Lee[7], M.K. Yu[8], J-J. Perez-Ruixo[2], E.J. Small[9]

[1]Hematology/Oncology, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA, [2]R&D, Janssen Research & Development, Antwerp, Belgium, [3]R&D, Janssen Research & Development, Spring House, PA, USA, [4]Urology & Renal Transplantation, Yokohama City University Medical Center, Yokohama, Japan, [5]Prostate Cancer Clinical Research Unit, CNIO - Spanish National Cancer Center, Madrid, Spain, [6]Medical Oncology, Centre for Personalised Nanomedicine, University of Queensland, Brisbane, Australia, [7]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [8]Clinical Oncology, Janssen Research & Development, Los Angeles, CA, USA, [9]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA

Background: The phase 3 SPARTAN study evaluated the efficacy and safety of APA vs placebo (PBO) in men with high-risk nmCRPC. Because dose reductions/interruptions for the management of AEs that occur during treatment can affect drug efficacy, this analysis sought to understand the relationship of APA pharmacokinetic exposure and the primary end point of SPARTAN, MFS.

Methods: 1207 pts were randomized in a 2:1 ratio to APA 240 mg/d or PBO. APA levels, and that of its active metabolite N-desmethyl APA (NAPA), were measured by a validated LC/MS/MS assay. APA and NAPA exposures were quantified as the area under the concentration–time curve at steady state (AUC_{24}) at the average daily dose received, up to the MFS event. Exposure levels were evaluated as quartiles or continuous variables. Univariate and multivariate Cox regression models evaluated the relationship between APA/NAPA exposure and MFS and were adjusted by pre-specified stratification factors (prostate-specific antigen doubling time, bone-sparing agent use, locoregional disease status) and other potential prognostic factors (age, ECOG PS).

Results: 1206 pts were included in the analysis. AEs led to dose reduction/interruption in 33% vs 19% of APA and PBO pts, respectively, with average daily dose of 225 mg (APA) vs 229 mg (PBO) in pts with dose reduction/interruption. Mean (coefficient of variation [CV]%) PK exposure levels measured as AUC_{24} for APA and NAPA, respectively, were 117 (24 CV%) μg·h/mL and 155 (17 CV%) μg·h/mL for APA-treated pts without dose reductions/interruptions, and 112 (24 CV%) μg·h/mL and 148 (18 CV%) μg·h/mL for those with dose reductions/interruptions. MFS benefit was similar across the range of APA/NAPA exposures. In univariate and multivariate Cox regression models, no significant differences in the exposure-MFS relationship were observed for APA and NAPA.

Conclusions: 240 mg/d APA provided efficacious drug exposure for the majority of pts, including those who required dose reductions/interruptions due to AEs. The MFS benefit was similar across the range of APA exposure. Dose reductions/interruptions due to AEs did not reduce the efficacy of APA.

Clinical trial identification: NCT01946204.

Editorial acknowledgement: Writing assistance was provided by Brian Haas, PhD, of PAREXEL, and was funded by Janssen Global Services, LLC.

Legal entity responsible for the study: Janssen Research & Development.

Funding: Janssen Research & Development.

Disclosure: M.R. Smith: Grants: Janssen; Personal fees: Janssen, Astellas, Bayer. C. Perez-Ruixo, O. Ackaert, D. Ouellet, C. Chien, M.K. Yu, J-J. Perez-Ruixo: Employee: Janssen Research & Development; Stock owner: Johnson & Johnson. H. Uemura: Personal fees: Janssen, Astellas, Takeda, Sanofi, Bayer, Astra-Zeneca. D. Olmos: Grants: Janssen, Astellas, Bayer, Sanofi, Genentech, Astra-Zeneca, Bayer, outside the submitted work. P.N. Mainwaring: Personal fees: XING Technologies P/L, Ipsen, Janssen, Merck, Novartis, Pfizer, Roche; Grants: Merck; Pending patent: XING Technologies P/L: All other authors have declared no conflicts of interest.

807P Prolonged urinary and bowel symptom control in men with non-metastatic castration-resistant prostate cancer (nmCRPC) treated with enzalutamide: Results from the PROSPER study

B. Tombal[1], M. Hussain[2], D. Penson[3], G. Attard[4], C.N. Sternberg[5], D. Phung[6], R. Morlock[7], K. Modelska[8], K. Ramaswamy[9], C. Ivanescu[10], F. Saad[11]

[1]Department of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [2]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA, [3]Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA, [4]Medical Oncology, The Institute of Cancer Research and The Royal Marsden, Surrey, UK, [5]Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy, [6]Data Science, Astellas Pharma Inc, Leiden, Netherlands, [7]Health Economics and Outcomes Research, Astellas Pharma Inc, Northbrook, IL, USA, [8]Medical Oncology, Pfizer Inc., San Francisco, CA, USA, [9]Oncology, Pfizer Inc., New York, NY, USA, [10]Advisory Analytics, IQVIA, Hoofddorp, Netherlands, [11]Urology, Centre Hospitalier de l'Université de Montréal/CRCHUM, Montreal, QC, Canada

Background: The PROSPER trial (NCT02003924) showed a clinically and statistically significant improvement in metastasis-free survival (HR 0.292 [95% CI 0.241, 0.352], p < 0.0001) with enzalutamide (ENZ; n = 933) versus placebo (PBO; n = 468) in asymptomatic men with nmCRPC and prostate-specific antigen doubling time ≤10 months. All men without prior orchiectomy continued androgen deprivation therapy. We assessed the impact of ENZ on prostate cancer symptoms (PCS) and health-related quality of life (HRQoL).

Methods: PCS and HRQoL were assessed at baseline (BL) and subsequently every 16 weeks, using the EORTC Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) and the EuroQol 5-domain 5-level (EQ-5D-5L). Clinically meaningful symptom worsening in PCS scores was defined using thresholds derived as 1/2 standard deviation at BL. Clinically meaningful deterioration in EQ-5D-5L visual analogue scale was defined using the pre-established threshold of 7. Time to first confirmed (at two consecutive visits) and unconfirmed (one visit) deterioration in QLQ-PR25 and EQ-5D-5L scores were assessed using Kaplan-Meier estimates and Cox models.

Results: Completion rates were high for patients (pts) remaining on study (>85% for all visits). BL scores were similar between arms and showed low symptom burden (including urinary and bowel symptoms) and high HRQoL. The proportion of pts reporting either no change or improvement in HRQoL and PCS scores at week 49 was higher with ENZ (67 − 87%) than PBO (62 − 81%). Over the course of treatment, ENZ significantly delayed worsening of symptoms including urinary and bowel symptoms/function (Table). In contrast, ENZ significantly increased the risk of worsening of hormonal treatment related symptoms compared to PBO (Table).

Conclusions: In addition to delayed disease progression in the PROSPER trial, ENZ prolonged urinary and bowel symptom control and delayed decline in HRQoL scores versus PBO.

Clinical trial identification: NCT02003924.

Editorial acknowledgement: Editorial assistance was provided by Lauren Smith from Complete HealthVizion, funded by Astellas Pharma Inc and Pfizer Inc, the co-developers of enzalutamide.

Legal entity responsible for the study: Astellas Pharma Inc and Pfizer Inc.

Funding: This study was funded by Astellas Pharma Inc and Pfizer Inc, the co-developers of enzalutamide.

Disclosure: B. Tombal: Personal fees: Astellas, during the conduct of the study; Grants: Bayer, Janssen, Sanofi, Ferring; Personal fees: Bayer, Janssen, Sanofi, Ferring, Amgen; Non-financial support: Ferring, outside the submitted work. M. Hussain: Other: Genentech/Roche, Abbvie, Bayer, Onclive, Pfizer, PCCTC, AstraZeneca, outside the submitted work; Patent pending: Systems and methods for tissue imaging, Method of treating cancer, Dual inhibition of MET and VEGF; Applicant/Proprietor Exelexis, Inc. D. Penson: Grants, personal fees: Astellas, Medivation, during the conduct of the study; Grants, personal fees: Dendreon, outside the submitted work. G. Attard: Personal fees, non-financial support: Astellas, Medivation, Pfizer, during the conduct of the study; Personal fees: Janssen-Cilag, Veridex, Takeda Sanofi-Aventis Janssen, Roche, Ventana Millenium Pharmaceuticals, Abbott Laboratories, Essa Pharmaceuticals, Bayer Healthcare Pharmaceuticals; Non-financial support: Roche/Ventana, Abbott Laboratories, Essa Pharmaceuticals, Bayer Healthcare Pharmaceuticals, Janssen; Grants: Janssen; AstraZeneca, Arno Therapeutics, Innocrin Pharma; Other: The Institute of Cancer Research (ICR), outside the submitted work. C.N. Sternberg: Oher: Bristol-Myers Squibb, Novartis, Janssen, Bayer, Eisai, MSD, Lilly, Clovis Oncology, Ferring, Pfizer, Astellas Pharma, Sanofi, Ipsen, AstraZeneca, outside the submitted work. D. Phung: Other from Astellas, outside the submitted work. R. Morlock: Personal fees: Astellas, during the conduct of the study; Personal fees: Abbot Medical Optics, Ironwood, Genentech, outside the submitted work. K. Modelska: Other: Pfizer,

Table: 807P

Instrument/scale	Baseline scores				Time to deterioration or symptom worsening	
	ENZ (n = 933)		PBO (n = 468)		Confirmed	Unconfirmed
	n	Mean (SD)	n	Mean (SD)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
QLQ-PR25						
PRAID*	144	20.37 (27.91)	67	24.38 (33.63)	NE	NE
PRBOW*	884	5.14 (8.39)	439	4.65 (7.70)	0.72 (0.59, 0.89)‡	0.80 (0.67, 0.95)‡
PRHTR*	884	14.92 (12.50)	439	15.79 (13.30)	1.29 (1.02, 1.63)‡	1.30 (1.08, 1.59)‡
PRSAC†	884	11.86 (20.05)	439	11.77 (20.63)	0.98 (0.77, 1.24)	1.04 (0.83, 1.31)
PRSFU†	49	53.40 (23.44)	24	48.26 (26.35)	NE	NE
PRURI*	884	20.69 (17.55)	439	20.02 (17.68)	0.58 (0.46, 0.72)‡	0.72 (0.60, 0.87)‡
EQ-5D-5L						
EQ-VAS†	884	76.17 (16.92)	439	77.53 (15.97)	0.75 (0.63, 0.90)‡	0.83 (0.71, 0.97)‡

*Higher scores represent higher level of symptoms/more pain; †Higher scores represent higher level of functioning/better quality of life; ‡Statistically significant at 0.05. Results for the EORTC-QLQ-PR25 PRSFU and PRAID were not estimated because of the low sample size and small number of events. CI=confidence interval; ENZ=enzalutamide; EQ-5D-5L=EuroQol 5-domain 5-level questionnaire; EQ-VAS=EuroQol visual analogue scale; NE=not estimated; PBO=placebo; PRAID=incontinence aids; PRBOW=bowel symptoms/function; PRHTR=hormonal treatment-related symptoms; PRSAC=sexual activity; PRSFU=sexual functioning; PRURI=urinary symptoms and problems; QLQ-PR25=EORTC Quality of Life Questionnaire-Prostate 25; SD=standard deviation.

outside the submitted work. K. Ramaswamy: Other: PfizerInc, during the conduct of the study; Other: Johnson & Johnson, outside the submitted work. C. Ivanescu: Employee: QuintilesIMS, funding statistical analyses (for this work under consultancy contract): Astellas. F. Saad: Grants, personal fees: Astellas, Janssen, during the conduct of the study; Grants, personal fees: Sanofi, Bayer, outside the submitted work.

808P Non-metastatic castration-resistant prostate cancer (nmCRPC): Meta-analysis of efficacy and safety with novel hormonal agents apalutamide and enzalutamide

D.V.P. Almeida[1], C.Z. de Oliveira[2], R.C. Mariano[1], F.R. Kater[1], M.C.L.A. Souza[1], V.C. Ruiz-Schutz[3], R. Yamamura[1], R. Saraiva De Carvalho[1], F.C. Maluf[1], A.K. Morgans[4], S. Srinivas[5], S. Gupta[6], T. Dorff[7], E.Y. Yu[8], F.A. Schutz[1]

[1]Medical Oncology, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil, [2]Biostatistcs, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil, [3]Internal Medicine, Universidade de São Paulo, São Paulo, Brazil, [4]Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [5]Department: Medicine - Med/Oncology, Stanford University, Stanford, CA, USA, [6]Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA, [7]Medical Oncology, City of Hope, Duarte, CA, USA, [8]Medical Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Androgen deprivation therapy (ADT) is the cornerstone treatment of prostate cancer. However, androgen independent status inevitably develops over time, leading to the castration resistant prostate cancer (CRPC) phenotype. Several treatments, including chemotherapy agents and novel hormonal agents, have been shown to improve outcome of patients with metastatic CRPC (mCRPC). Recently, two randomized controlled trials (RCT) demonstrated increased metastasis free survival (MFS) with apalutamide (SPARTAN Trial) and enzalutamide (PROSPER Trial) in nmCRPC patients, but failed to demonstrate a statistically significant increase in overall survival (OS).

Methods: A meta-analysis at trial level was performed including published data from SPARTAN and PROSPER trials. Efficacy data was investigated and retrieved to calculate hazard-ratio (HR) for OS and MFS, with 95% CI. The safety profile was investigated for fatal adverse events (FAEs) and the relative risk (RR) calculated, with 95% CI. Random-effects or fixed-effects models were performed on the basis of the heterogeneity of included studies. A p-value <0.05 was considered statistically significant.

Results: A total of 2,602 patients were included for efficacy (intention-to-treat [ITT] population) and 2,596 for safety analysis (per-protocol population). 1736 patients received novel hormonal agents (806 apalutamide and 930 enzalutamide) and 866 placebo. Efficacy analysis confirmed improved MFS (HR 0.29; 95% CI, 0.25-0.33; $p < 0.0001$) and also demonstrated a significant increase in OS (HR 0.76; 95% CI, 0.59-0.76; $p = 0.03$). Safety analysis showed an increased risk of FAEs (HR 5.24; 95% CI, 1.89-14.55) with apalutamide and enzalutamide, however this should be interpreted with caution due to the much longer exposure time to the experimental arm compared to placebo.

Conclusions: This meta-analysis reinforces the benefit of MFS and demonstrated a significant increase in OS with novel hormonal agents apalutamide and enzalutamide in patients with nmCRPC. Further analysis will be necessary to determine the breakdown of treatment-related versus –unrelated deaths.

Legal entity responsible for the study: Daniel Vargas Pivato de Almeida.

Funding: Has not received any funding.

Disclosure: A.K. Morgans: Honoraria: Sanofi, Janssen, Genentech, AstraZeneca. S. Srinivas: Data and Safety Monitoring Committee: Pfizer; Advisory Board: Jansen. T. Dorff: Advisory board: Janssen; Promotional speaker: Exelixis, Prometheus; Consulting: Bayer, EMD Serono. E.Y. Yu: Honoraria: Janssen. F.A. Schutz: Site Principal investigator: Roche, BMS, MSD, Astra Zeneca; Speaker's bureau: Sanofi, AstraZeneca, Bayer, Janssen, Astellas, BMS, Pfizer, Roche; Advisory board: Bayer, Janssen, Astellas, Novartis, Roche, MSD. All other authors have declared no conflicts of interest.

809P Statin use and outcome in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated in the TROPIC trial

D. Lorente[1], G.A. De Velasco Oria[2], J. Carles[3], S. Gillessen[4], K. Fizazi[5], A. Joshua[6], M. Eisenberger[7], O. Sartor[8], J.S. de Bono[9]

[1]Medical Oncology, Hospital Universitario La Fe, Valencia, Spain, [2]Medical Oncology, University Hospital 12 de Octubre, Madrid, MA, Spain, [3]Medical Oncology, Vall Hebron Institute of Oncology, Barcelona, Spain, [4]Division of Cancer Sciences, University of Manchester and the Christie, Manchester, UK and Division of Medical Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, University of Bern, Switzerland, [5]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [6]Medical Oncology, The Kinghorn Cancer Centre, Darlinghurst, Australia, [7]Medical Oncology, Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, MD, USA, [8]Tulane Cancer Center, Tulane Medical School, New Orleans, LA, USA, [9]Prostate Targeted Therapy Group & Drug Development Unit, The Institute of Cancer Research (ICR), London, UK

Background: Statins have been shown to block DHEAS uptake by prostate cancer cells by competitively binding to SLCO2B1, an organic anionic intracellular transporter. Use of statins by prostate cancer pts has been associated with longer time to progression (TTP) during ADT in the hormone-sensitive setting (Harshman, JAMA Oncol 2015).

Methods: We evaluated the impact of statin use in PFS and OS in mCRPC patients treated with cabazitaxel or mitoxantrone in the TROPIC phase III trial. Kaplan-Meier, univariable (UV) and multivariable (MV) cox-regression models were constructed to evaluate the association between use of statins and overall survival (OS), PSA progression-free survival (PSA-PFS) and radiographic PFS (rPFS). Covariates included in the multivariable model are listed in the table.

Results: 755 pts were included in the analysis. 138 (18.6%) pts received statins: atorvastatin (53 pts, 38.4%), simvastatin (56 pts, 40.6%), rosuvastatin (14 pts, 10.1%), pravastatin (9 pts, 6.5%), lovastatin (4 pts, 2.9%) and fluvastatin (2 pts; 1.4%). 72 pts (52.2%) were allocated to the mitoxantrone arm and 66 pts (47.8%) to the cabazitaxel arm of the trial. Statin use was associated with longer median OS (15.8 vs 13.4m; HR: 0.74; $p = 0.01$) but no difference in PSA-PFS (4.8 vs 4.6m; HR: 0.98; $p = 0.824$) or rPFS (8.3 vs 7.2m; HR: 0.94; $p = 0.661$) was observed. Statin use was associated with a longer time on prior hormone-therapy (5.3 vs 3.7 yrs; $p < 0.001$). In MV cox-regression models, the impact of statin use in survival was independent of treatment arm (cabazitaxel vs mitoxantrone) and other prognostic factors (Table).

Table: 809P Multivariable Cox-Regression OS Analysis

Variable	HR (95%CI)	p-value
Statin Use	0.79 (0.62-0.99)	0.048
Treatment Arm	0.66 (0.55-0.79)	< 0.001
Baseline PSA	1 (1-1)	0.394
Baseline Hb	0.89 (0.85-0.93)	< 0.001
Baseline ALP	1 (1-1)	0.009
Visceral Metastases	1.36 (1.11-1.68)	0.003
ECOG PS	1.67 (1.43-1.96)	< 0.001

Conclusions: Use of statins by pts treated in the TROPIC trial was associated with a longer OS, independent of treatment arm and other prognostic variables. Further analyses will elucidate the role of statins in mCRPC.

Clinical trial identification: EudraCT: 2006-003087-59; NCT00417079.

Legal entity responsible for the study: David Lorente / Prostate Targeted Therapy Group.

Funding: The TROPIC trial was funded by Sanofi Aventis. No specific funding was received for the development of the current abstract.

Disclosure: All authors have declared no conflicts of interest.

810P Abiraterone acetate plus prednisone and LHRH therapy versus abiraterone acetate plus prednisone while sparing LHRH therapy in patients with progressive, metastatic and chemotherapy-naïve, castration-resistant prostate cancer: Results from the SPARE-trial (NCT02077634)

C. Ohlmann[1], Z. Roger[2], C. Rüssel[3], E. Hellmis[4], H. Suttmann[5], M. Janssen[6], A. Hübner[7], J. Dahm[8], J. Gleißner[9], M. Scheffler[10], S. Feyerabend[11], J. Telle[12], J. Klier[13]

[1]Urology, Malteser Krankenhaus Bonn, Bonn, Germany, [2]Urology, Praxis für Urologie Pankow, Berlin, Germany, [3]Urology, Praxisgemeinschaft für Urologie, Borken, Germany, [4]Urology, Urologikum Duisburg, Duisburg, Germany, [5]Urology, Urologikum Hamburg, Hamburg, Germany, [6]Urology, Saarland University Medical Center, Hamburg, Germany, [7]Urology, WK Nord GmbH & Co. KG, Rostock, Germany, [8]Urology, PandaMED - ÜBAG, Wuppertal, Germany, [9]Urology, DGU Wuppertal, Wuppertal, Germany, [10]Urology, Gemeinschaftspraxis für Urologie, Zwickau, Germany, [11]Urologic Oncology, Studienpraxis Urologie, Nürtingen, Germany, [12]Urology, Urologische Praxis Würzburg, Würzburg, Germany, [13]Urology, Praxis, Cologne, Germany

Background: The value of continuation of luteinizing hormone-releasing hormone (LHRH) therapy in castration-resistant prostate cancer (CRPC) remains controversial and clear evidence is lacking. Especially upon treatment with the life-prolonging cytochrome P450 17-alpha-hydroxylase/$C_{17,20}$ lyase (Cyp17)-inhibitor, abiraterone, which in combination with prednisone, has the ability to further suppress testosterone serum levels over LHRH therapy alone, continuation of LHRH therapy seems to be negligible. The aim of the SPARE trial therefore was to explore the role of continuation of LHRH therapy when starting treatment with abiraterone acetate plus prednisone (AA+P) in patients with asymptomatic or mildly symptomatic, chemotherapy-naïve CPRC.

Methods: Patients were randomized to receive continuing LHRH therapy versus LHRH withdrawal at the time of starting abiraterone AA+P therapy (NCT02077634). The primary endpoint was rate of rPFS at month 12. Secondary endpoints included PSA response rate, objective response, time to PSA progression and safety.

Results: Altogether, 68 patients were randomized. Median age was 75 (60-86) years with a median PSA at baseline of 23.9 (0.17-1680) ng/ml. Results of the secondary endpoints were evaluated.

Table: 810P

	LHRH+AA+P	AA+P	HR (p-value)
Patients (n)	34	33	
Median age (range)	74 (60-86) years	76 (60-86) years	
Median baseline PSA (range)	31.9 (0.17-313.2) ng/ml	20.59 (1.97-1680) ng/ml	
PSA-decline ≥50%	23/34 (67.6%)	24/33 (72.7%)	
Median treatment duration (d)	266	420	1.667 (0.197)*
Time to PSA progression (d)	288	336	1.733 (0.188)*

*study was not powered for these endpoints.

Conclusions: The results of the exploratory study show that AA + P without continuation of LHRH therapy leads to considerable PSA response rates and longer time to PSA progression. The currently assessed efficacy is comparable to the results of the COU-AA-302 trial, hypothesising that continuation of LHRH therapy may not be necessary upon treatment with AA + P. Results on the primary endpoint and the safety profile are pending and are currently being evaluated.

Clinical trial identification: NCT02077634.

Legal entity responsible for the study: Saarland University.

Funding: Janssen-Cilag.

Disclosure: C. Ohlmann: Research funding: Janssen-Cilag. All other authors have declared no conflicts of interest.

811P Association of grade ≥3 neutropenia (NP) with outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel

A. Meisel[1], R. de Wit[2], S. Oudard[3], O. Sartor[4], F. Stenner-Liewen[5], Z. Shun[6], A. Ozatilgan[7], M. Eisenberger[8], J.S. de Bono[9]

[1]Internal Medicine - Hematology and Oncology, Stadtspital Ward; Department of Nuclear Zurich, University Hospital of Zurich; Institute of Pharmaceutical Sciences, Federal Institute of Technology, Zurich, Switzerland, [2]Medical Oncology, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Service d'Oncologie Médicale, Georges Pompidou European Hospital, Rene Descartes University, Paris, France, [4]Medicine and Urology, Tulane Cancer Center, New Orleans, LA, USA, [5]Department of Oncology, University Hospital of Basel, Basel, Switzerland, [6]Biostatistics, Sanofi, Bridgewater, NJ, USA, [7]Global Medical Oncology, Sanofi, Cambridge, MA, USA, [8]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD, USA, [9]Division of Clinical Studies, Drug Development Unit, Royal Marsden NHS Foundation Trust/The Institute of Cancer Research, Sutton, UK

Background: Subset analysis of trials investigating taxanes in patients with mCRPC suggest an association between Grade ≥3 NP and disease outcomes. In the Phase 3 PROSELICA trial (NCT01308580), NP was more common in patients receiving cabazitaxel 25 mg/m^2 (C25) vs cabazitaxel 20 mg/m^2 (C20) - 73% vs 42%, respectively. Post hoc analyses of PROSELICA examined the relationship between incidence of NP, survival and response.

Methods: PROSELICA assessed the non-inferiority of C20 (n = 598) vs C25 (n = 602) in terms of overall survival (OS) in men with mCRPC. Prophylactic granulocyte colony-stimulating factor was given to patients with Grade ≥3 NP. OS and progression-free survival (PFS) were analyzed using Kaplan-Meier (KM) estimates and Cox proportional hazard models. Nominal p values were determined by log-rank tests. Prostate-specific antigen response rate (PSArr; defined as proportion of patients with a > 50 % PSA decline from baseline) was analyzed in the eligible population using KM estimates with Chi^2 tests and odds ratios. OS, PFS and PSArr were correlated with Grade ≥3 NP occurrence and baseline neutrophilia (neutrophils ≥7000 G/l) by univariate analysis.

Results: In the intent-to-treat (ITT) population, development of Grade ≥3 NP was associated with better PSArr, PFS and OS ($p < 0.001$; Table). The positive association was observed in both treatment arms and in poor-risk patients with baseline neutrophilia.

Table: 811P

Population	Outcome	Grade ≥3 NP	No Grade ≥3 NP	Hazard ratio/Odds ratio	p value
ITT population (n = 1200)	OS, months (mo)	15.1	12.4	0.78	0.0002
	PFS, mo	3.7	2.8	0.79	0.0001
	PSArr, % n = 1079	44.1	25.5	2.3	<0.0001
C25 (n = 602)	OS, mo	15.3	12.2	0.77	0.009
	PFS, mo	3.5	3.5	0.84	0.07
	PSArr, % n = 538	46.2	34.5	1.6	0.015
C20 (n = 598)	OS, mo	14.6	12.6	0.78	0.006
	PFS, mo	4.2	2.3	0.75	0.0008
	PSArr, % n = 541	40.7	21.3	2.5	<0.0001
Neutrophilia (n = 174)	OS, mo	12.8	7.5	0.63	0.004
	PFS, mo	4.1	2.1	0.66	0.008
	PSArr, % n = 156	43.8	16.9	3.8	0.0002

Conclusions: Post hoc assessment of Grade ≥3 NP in PROSELICA was associated with improved survival and response to cabazitaxel independent of dose. These results are consistent with data obtained in the Phase 3 TAX327 (docetaxel) and TROPIC (cabazitaxel) trials. Funded by Sanofi.

Clinical trial identification: NCT01308580.

Editorial acknowledgement: Editorial assistance was provided by Danielle Lindley of Meditech Media Ltd, funded by Sanofi.

Legal entity responsible for the study: Sanofi.

Funding: Sanofi.

Disclosure: Meisel: Advisor: Astellas, Roche, Celgene, Novartis, Vifor, Sanofi, Amgen, Merck; Expert testimony: Sanofi; Research funding: Bayer (himself), Merck (institution); Expenses: Amgen, Astellas, Sanofi, Servier, Roche, Boehringer Ingelheim; Intellectual property: Merck. R. de Wit: Consultancy, Speaker fees: Sanofi. S. Oudard: Consultancy, Advisory role, Honoraria, Expense: Sanofi, Astellas, Janssen, and Ipson; Research funding: Sanofi; Speakers bureau: Sanofi, Janssen. O. Sartor: Advisor: Bellicum Pharmaceuticals, Dendreon; Advisor, Expenses: Bayer, Johnson & Johnson, Medivation, Oncogenex, Sanofi, Tokai Pharmaceuticals, AstraZeneca, Progenics; Funding (Institute): Bayer, Johnson & Johnson, Sanofi, Dendreon, Endocyte, Innocrin Pharma, Progenics. F. Stenner-Liewen: Consultancy, Advisory role, Research, expenses: Sanofi. S. Guillonneau, A. Ozatilgan: Employee: Sanofi. M. Eisenberger: Honoraria, Consultancy, Advisory role: Sanofi, Pfizer, Astellas; Research: Sanofi; Expenses: Sanofi, Pfizer. J.S. de Bono: Honoraria: Sanofi; Advisor: Sanofi, AstraZeneca, GSK, Genentech, Roche, Merck; Speakers bureau: AstraZeneca/MedImmune; Research funding (Institute): AstraZeneca/MedImmune, GSK, Sanofi, Merck Sharp & Dohme, Genmab, Genentech; Patent on abiraterone acetate with prednisone.

812P Post hoc responder analysis of health-related quality of life (HRQL) in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel in the phase III PROSELICA and FIRSTANA trials

A. Thiery Vuillemin[1], K. Fizazi[2], O. Sartor[3], S. Oudard[4], D. Bury[5], S. Guillonneau[6], A. Ozatilgan[7], M. Eisenberger[8], J.S. de Bono[9]

[1]Medical Oncology, Centre Hospitalier Régional Universitaire, Besancon, France, [2]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [3]Medicine and Urology, Tulane Cancer Centre, New Orleans, LA, USA, [4]George Pompidou European Hospital, René Descartes University, Paris, France, [5]Real World Evidence/Global Clinical Outcomes, Sanofi US, Cambridge, MA, USA, [6]Biostatistics, Sanofi, Chilly-Mazarin, France, [7]Global Medical Oncology, Sanofi US, Cambridge, MA, USA, [8]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD, USA, [9]Division of Clinical Studies Drug Development Unit, Royal Marsden NHS Foundation Trust/The Institute of Cancer Research, Sutton, UK

Background: PROSELICA (NCT01308580) assessed the non-inferiority of cabazitaxel 20 mg/m^2 (C20) vs 25 mg/m^2 (C25) in patients (pts) with mCRPC post docetaxel, while FIRSTANA (NCT01308567) investigated whether C20 and C25 were superior to docetaxel 75 mg/m^2 (D75) in chemotherapy-naive mCRPC. This analysis evaluated the impact of cabazitaxel on HRQL in both trials.

Methods: Alongside pain and analgesic score, HRQL was assessed using the Functional Assessment of Cancer Therapy Prostate (FACT-P) questionnaire. The analysis focused on FACT-P (clinically meaningful improvement or deterioration of total score [TS]) among responders.

Results: Pt baseline characteristics are shown in the table. In PROSELICA, 57.2% and 59.4% of pts receiving C20 and C25 had FACT-P TS improvements; in FIRSTANA, 63.5%, 62.3% and 57.7% of pts receiving C20, C25 and D75 had FACT-P TS improvements. In FACT-P responders, FACT-P TS improvements occurred as early as Cycle (C) 1 (mean change from baseline: PROSELICA C20 10.4, n = 264; C25 10.6, n = 266; FIRSTANA C20 11.7, n = 206; C25 11.7, n = 202; D75 9.0, n = 195); these were largely maintained. For pts with a pain response in PROSELICA, FACT-P TS improvements occurred as early as C1 (C20 6.8, n = 71; C25 11.1, n = 81) and were maintained until C8 (C20 10.6, n = 43; C25 9.6, n = 44). In FIRSTANA, FACT-P TS improvements in pts with a pain response were seen as early as C1 or C2 (C1: C20 15.5, n = 41; C25 12.5, n = 41; D75, 7.9, n = 32) and maintained until C9 (C20 9.0, n = 27; C25 10.5, n = 26; D75 16.4, n = 20). In pts with a tumor or PSA response, HRQL was maintained for all treatment arms in both studies. Additional results for clinical responder subgroups and FACT-P subscales will be presented.

Conclusions: More than half of the pts experienced HRQL improvements, which were maintained. Pts with a pain response experienced HRQL improvements. Funding: Sanofi.

Clinical trial identification: PROSELICA: NCT01308580. FIRSTANA: NCT01308567.

Editorial acknowledgement: Editorial assistance was provided by Mark Cockerill of MediTech Media Ltd, funded by Sanofi.

Legal entity responsible for the study: Sanofi.

Funding: Sanofi.

Disclosure: A. Thiery Vuillemin: Employee: AstraZeneca; Consultancy, advisory role: Novartis, Sanofi, Astellas, Pfizer, Janssen, Ipsen, Pfizer; Research funding: Pfizer; Travel, accommodation and expenses: Novartis, Sanofi, Pfizer. K. Fizazi: Honoraria: Janssen, Sanofi, Astellas, Takeda; Consultancy, Advisory role: Janssen Oncology, Bayer, Astellas, Sanofi, Orion Pharma GmbH, Curevac, AstraZeneca, ESSA, Genentech; Travel, accommodation and expenses: Amgen. O. Sartor: Advisor: Bellicum Pharmaceuticals, Dendreon; Advisor and expenses: Bayer, Johnson & Johnson, Medivation, Oncogenex, Sanofi, Tokai Pharmaceuticals, AstraZeneca, Progenics; Institute: funding: Bayer, Johnson & Johnson, Sanofi, Dendreon, Endocyte, Innocrin Pharma, Progenics. S. Oudard: Consultancy, advisory role, honoraria, expenses: Sanofi, Astellas, Janssen, Ipson; Research funding: Sanofi; Speakers bureau: Sanofi, Janssen. D. Bury: Contractor: Sanofi; Employee: Artech. S. Guillonneau, A. Ozatilgan: Employee: Sanofi. M. Eisenberger: Honoraria, Consultancy, Advisory role: Sanofi, Pfizer, Astellas; Research: Sanofi; Expenses: Sanofi, Pfizer. J.S. de Bono: Honoraria: Sanofi; Advisor: Sanofi, AstraZeneca, GSK, Genentech, Roche, Merck; Speakers' bureau: AstraZeneca/MedImmune; Research funding (institute): AstraZeneca/MedImmune, GSK, Sanofi, Merck Sharp & Dohme, Genmab, Genentech; Patent on abiraterone acetate with prednisone.

813P Treatment of metastatic castration-resistant prostate cancer (mCRPC); Survival by type of progression at initiation of treatment

D.G. Robbrecht[1], R.J. van Soest[2], I.F. Tannock[3], S. Oudard[4], B. Tombal[5], M. Eisenberger[6], F. Mercier[7], R. de Wit[1]

[1]Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, [2]Urology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, [3]Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [4]Immunothérapie et Traitement Antiangiogénique en Pathologie Cancérologique, Hopital European George Pompidou, Paris, France, [5]Urology, Cliniques Universitaires St. Luc, Brussels, Belgium, [6]Medical Oncology, Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, MD, USA, [7]Stat Process, Sanofi, Charlotte, Nc, France

Background: The usual sequence of progression events in mCRPC patients treated with new hormonal agents is known: PSA progression, followed by radiological progression and finally pain progression (Ryan, NEJM 2013; Beer, NEJM 2014). Although pain was associated with poor overall survival (OS) in the TAX 327 (Berthold, Clin Cancer Res 2008) and CALGB trials (Halabi, JCO 2008), the influence of type of progression on outcomes is not well documented in phase III trials with chemotherapy. Here, we investigated the impact of type of progression on OS in mCRPC patients receiving docetaxel-based chemotherapy.

Methods: Data from the phase III study VENICE evaluating docetaxel 75mg/m^2 q3w ± aflibercept (Tannock, Lancet Oncol 2013) was used as a training dataset. At randomization, group 1 (G1) had PSA progression only (n = 231), G2 had radiological progression (± PSA) but no pain (n = 348), and G3 had pain (± PSA, ± radiological) (n = 447). The TAX327 definition for pain was used: Mean present pain intensity $\geq$ 2 and/or mean analgesic score $\geq$ 10 within 7 days prior to randomization (Tannock, NEJM 2004). The impact of type of progression on OS was evaluated in a multivariate Cox regression analysis with backward elimination (5% level), stratified for ECOG performance status (0-1 vs 2) and treatment arm.

Results: In the VENICE trial median OS was 28.6 months for G1, 26.3 months for G2 and 16.9 months for G3. Hazard ratios [95% CI] for death were 1.14 [0.92-1.41] in G2

Table: 812P

Baseline characteristics	FIRSTANA			PROSELICA	
	D75 (n = 391)	C20 (n = 389)	C25 (n = 388)	C20 (n = 598)	C25 (n = 602)
Median age, years (range)	69.0 (41–87)	68.0 (44–90)	68.5 (42–85)	68.0 (45–89)	69.0 (45–88)
ECOG PS, n (%)					
0–1	374 (95.7)	370 (95.1)	376 (96.9)	539 (90.1)	540 (89.7)
2	17 (4.3)	19 (4.9)	12 (3.1)	59 (9.9)	62 (10.3)
Mean PSA, ng/mL (SD)	252.8 (625.2)	213.2 (434.2)	257.9 (578.8)	451.5 (881.0)	444.0 (834.0)
Median present pain intensity, score (range)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	1.0 (0.0–5.0)	2.0 (0.0–5.0)
Median FACT-P TS (range)	107.4 (41.1–152.0)	107.1 (47.2–151.0)	105.7 (40.1–148.8)	102.8 (37.0–152.8)	101.6 (33.9–150.9)

C20, cabazitaxel 20 mg/m^2; C25, cabazitaxel 25 mg/m^2; D75, docetaxel 75 mg/m^2; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FACT-P TS, Functional Assessment of Cancer Therapy Prostate Total Score; PSA, prostate-specific antigen; SD, standard deviation.

and 2.13 [1.75 - 2.59] in G3 compared to G1. In multivariate analysis, pain at randomization was the strongest predictor of poor OS: HR 1.71, 95% CI 1.39-2.11, vs PSA progression only. Other significant prognostic factors included older age, high alkaline phosphatase, short duration of first androgen deprivation therapy, low hemoglobin level and high neutrophil-lymphocyte ratio. Docetaxel led to ≥ 50% decline in PSA in 67.5%, 80.5% and 77% in G1, G2 and G3 respectively.

Conclusions: The type of progression at initiation of first-line chemotherapy in mCRPC is prognostic. Patients with pain at initiation of chemotherapy had a median OS of ~1 year shorter than those having PSA progression only. Validation of these results by an independent dataset (TAX 327) is ongoing. Results will be presented at ESMO.

Legal entity responsible for the study: Sanofi.

Funding: Sanofi.

Disclosure: R.J. van Soest: Honoraria: Astellas, Sanofi, Janssen. I.F. Tannock: Data monitoring reimburse: Janssen, Roche. S. Oudard: Personal fees: Sanofi, Janssen, Astellas. B. Tombal: Advisor, investigator: Sanofi-aventis; Janssen Pharmaceuticals, Inc., Takeda, Astellas, Pharma, Inc., Kyocyt. M. Eisenberger: Consultancy: Sanofi. F. Mercier: Research funding: Sanofi. R. de Wit: Consultant: Sanofi, Merck, Roche; Speaker fees: Merck. All other authors have declared no conflicts of interest.

814P Platinum-based therapy in men with metastatic castration resistant prostate (mCRPC) with or without DNA repair defects: A multicentre retrospective analysis

S. Gillessen[1], S. Schmid[2], H. Beltran[3], D.V.P. Almeida[4], N. Mehra[5], P. Lavaud[6], R. Morales Barrera[7], D. Pignataro[8], E. Castro Marcos[9], V. Conteduca[3], E. Efstathiou[10], H.M.L. Le[11], C.V. Pezaro[12], H. Suzuki[13], A. Zivi[14], D. Klingbiel[15], A.G. Omlin[16]

[1]Division of Cancer Sciences, University of Manchester and the Christie, Manchester, UK and Division of Medical Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, University of Bern, Switzerland, [2]Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, Switzerland, [3]Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York, NY, USA, [4]Oncology, Hospital São Jose - Beneficencia Portuguesa de São Paulo, São Paulo, Brazil, [5]Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Surrey, Netherlands, [6]Department of Medical Oncology, IGR - Insitut Gustave Roussy, Villejuif, France, [7]Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [8]Medical Oncology, Azienda Ospedaliera Universitaria San Luigi Gonzaga, Orbassano, Italy, [9]Prostate Cancer Unit, CNIO- Spanish National Cancer Center, Madrid, Spain, [10]Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [11]Medical Oncology, Guy's and St.Thomas Hospital, London, United Arab Emirates, [12]Oncology, Eastern Health, Box Hill, Australia, [13]Urology, Toho University Sakura Medical Center, Tokio, Japan, [14]Oncology, Ospedale dell'Angelo, Mestre, Venice, Italy, [15]Swiss Group for Clinical Cancer Research Coordinating Center, SAKK, Bern, Switzerland, [16]Medical Onocolgy and Haematology, Kantonsspital St. Gallen, St. Gallen, Switzerland

Background: Platinum compounds have been tested in a larger number of mostly small to medium sized clinical trials in molecularly unselected prostate cancer patients (pts). Advances in castration-resistant prostate cancer (CRPC) molecular profiling have shown that a significant proportion of pts harbor DNA repair defects, which may serve as predictive markers for sensitivity to platinum agents. Our aim was to evaluate the antitumour activity of platinum agents in a contemporaneous mCRPC cohort with or without DNA repair defects.

Methods: International, multicenter retrospective database project in 14 centers worldwide. Pts with mCRPC treated with a platinum agent were included. Pts with primary pure small cell carcinoma and/or insufficient outcome data were excluded. For antitumour activity PSA levels at baseline, after 4-, 8- and 12-weeks of therapy (tx) were analyzed as well as soft tissue response and duration of platinum-based chemotherapy. Overall survival (OS) was analyzed by Kaplan Meier method.

Results: A total of 167 pts have been included in this analysis, 33 (20%) received platinum monotherapy, 134 (80%) a platinum combination therapy. Carboplatin was used in 140 (84%), cisplatin in 26 (16%) of pts. Combination tx with etoposise was used in 45 (27%), paclitaxel in 35 (21%) and docetaxel in 28 (17%) of pts. At start of platinum tx median age was 68 years, median PSA 78 ug/l, median ALP 185 U/l, median hemoglobin 103 g/l. The metastatic sites at start of platinum therapy were: bone 84%, lymph node 59% and visceral 60%. Outcome data by DNA repair defect status are summarized in the table.

Table: 814P

Outcome of platinum based tx	DNA repair defects: assessed, present N = 40	DNA repair defects: assessed, not present N = 42	DNA repair defects not assessed N = 85
	N (%)	N (%)	N (%)
PSA decline ≥50%	13/32 (41)	8/23 (35)	24/73 (33)
Soft tissue response (PR/CR)	9/32 (28)	7/29 (24)	16/48 (33)
median time on platinum tx: months (m), interquartile range (IQR)	2.5m (IQR 1.8-5.9)	2.8m (IQR 1.4 – 4.6)	3.5m (IQR 1.4 – 4.6)
OS from start of platinum therapy (m, IQR)	9.1m (IQR 4.8 – NR)	11m (IQR 6.7-22)	12m (IQR 7-29)

Conclusions: In this retrospective analysis of a contemporary cohort of men with mCRPC and poor prognostic characteristics platinum-based treatment seems to have significant anti-tumor activity irrespective of DNA repair status. Comparison of subgroups is limited by small sample size. Updated analyses will be presented.

Legal entity responsible for the study: Ethical Committee St. Gallen.

Funding: Has not received any funding.

Disclosure: S. Gillessen: Advisory boards (compensated): IDMC, AAA International, Active Biotech AB IDMC, Astellas Pharma, Bayer, Bristol-Myers Squibb, Clovis, Curevac, Dendreon Corporation, Ferring, Innocrin Pharmaceuticals, Janssen Cilag, MaxiVAX SA, Millennium Pharmaceuticals, Orion, Roche, Sanofi Aventis Group; Advisory boards (uncompensated): Astellas Pharma, Bayer, ESSA Pharmaceuticals Corp., Nectar, ProteoMediX, Sanofi; Speakers Bureau (compensated): Janssen, Novartis; Speakers bureau (uncompensated): Astellas Pharma, Janssen, Sanofi Aventis Group; Patent pending patent application for a method for biomarker WO 2009138392 A. H. Suzuki: Steering Committee: ACIS (ARN-509); Lead Principle Investigator: ARASENS (ODM-201); Advisory board: AstraZeneca, Bayer, Janssen, Nihon Medi-Physics, Kissei; Research funding: Takeda, Bayer, Astellas, Daiichi-Sankyo, Pfizer, Nihon Kayaku Ono; Honoraria: Astellas, AstraZeneca, Daiichi Sankyo, Janssen, Pfizer, Novartis, Sanofi, Takeda. A.G. Omlin: Advisory role (compensated, institutional): AstraZeneca, Astellas, Bayer, Janssen, Molecular Partners, MSD, Pfizer, Roche, Sanofi Aventis; Research support (institutional): TEVA, Janssen; Travel support: Astellas, Bayer, Janssen, Sanofi, Aventis. All other authors have declared no conflicts of interest.

815P Symptomatic skeletal related events (SSE) and SSE-free-survival in real world castration-resistant prostate cancer (CRPC) patients: Results from CAPRI

M. Kuppen[1], H.M. Westgeest[2], A.J.M. van den Eertwegh[3], J. Van Moorselaar[4], N. Mehra[5], I. van Oort[6], A.C.M. van den Bergh[7], J.L. Coenen[8], K.K.H. Aben[9], R. Somford[10], J. Lavalaye[11], A. Bergman[12], C.A. Uyl-de Groot[13], W.R. Gerritsen[5]

[1]Institute for Medical Technology Assessment, Erasmus School of Health Policy and Management, Rotterdam, Netherlands, [2]Medical Oncology, Amphia Ziekenhuis, Breda, Netherlands, [3]Medical Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [4]Urology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [5]Medical oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [6]Urology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [7]Radiation oncology, UMCG, Groningen, Netherlands, [8]Medical Oncology, Isala Klinieken, Zwolle, Netherlands, [9]IKNL, Comprehensive Cancer Centre, Nijmegen, Netherlands, [10]Urology, Canisius Wilhelmina Ziekenhuis, Nijmegen, Netherlands, [11]Nuclear Medicine, Antonius Ziekenhuis, Nieuwengein, Netherlands, [12]Division of Internal Medicine (MOD) and Oncogenomics, Division of Internal Medicine (MOD) and Oncogenomics, Amsterdam, Netherlands, [13]Institute of Health Policy & Management, Institute for Medical Technology Assessment, Erasmus University, Rotterdam, Netherlands

Background: Bone metastases are common in CRPC patients and these patients (pts) are at risk for symptomatic skeletal related events (SSE). Bone directed therapy and early initation of a life-prolonging drug (LPD) therapy can prevent or prolong time to SSEs. The objective is to evaluate whether delay in LPD has adverse outcome in CRPC pts and a shorter SSE-free interval.

Methods: CAPRI is an investigator-initiated, observational study in 20 hospitals in the Netherlands. All treated CRPC pts are retrospectively included in subgroups based on type of first line treatment: LPD (docetaxel, abiraterone, enzalutamide or radium-223) or non-LPD (other drugs as anti-androgens, prednisone). SSEs are defined as the occurrence of either radiotherapy (RT) to the bone, surgery to the bone, pathological fracture or spinal cord compression (SCC).

Results: 1,618 pts were included in this analysis. Median follow-up was 26 months (IQR 15-39). 466 (29%) were treated with LPD (mostly docetaxel 15%) and 1,152

(71%) with non-LPD (mostly bicalutamide 62%) in first line. In the non-LPD subgroup, LPD was postponed in 712 patients. The LPD subgroup had frequent bone metastases, worse ECOG and, higher LDH, ALP and PSA at the start of first line therapy. 36% of all patients experienced a SSE during follow-up (32% RT to the bone, 4% surgery to the bone, 4% pathological fracture and 6% SCC). There was a small difference in total SSEs between subgroups (39% for LPD vs 35% for non-LPD, $p = 0.064$). Median SSE-free survival was 13.0 vs 21.2 months for LPD and non-LPD respectively (HR 1.626, $p = 0.007$). Correction for prognostic factors showed that type of first line therapy (LPD/non-LPD) was not associated with SSE-free survival (HR 1.021, $p = 0.817$). Worse ECOG and presence of bone metastases were significant predictors for worse SSE-free survival.

Conclusions: Approximately 40% of CRPC-patients developed a SSE during follow-up. Worse patient and disease characteristics probably influenced timing of LPD. These factors were also related with worse SSE-free survival. Delay in the initiation of a LPD at castration-resistant state does not appear to influence outcome related to time-to-SSE.

Clinical trial identification: The CAPRI study is registered in the Dutch Trial Registry as NTR3591.

Legal entity responsible for the study: Institute for Medical Technology Assessment, Erasmus University Rotterdam.

Funding: The CAPRI registry was funded by Sanofi-Aventis Netherlands B.V., Janssen-Cilag B.V., Astellas Pharma B.V., and Bayer B.V. The funding organizations had no role in the design and conduct of the study, collection, management, analysis, interpretation of the data, and preparation, review, or approval of the abstract.

Disclosure: A.J.M. van den Eertwegh: Study grant, travel expenses ASCO: Sanofi. Speaker fee, advisory board: Astellas. J. Van Moorselaar: Receipt of grants/research supports: Astellas, Ferring, Ipsen; Honoraria, consultation fees: Amgen, Astellas, AstraZeneca, Bayer, Janssen, Sanofi-Genzyme. I. van Oort: Conflict of interest: Astellas, Janssen, Sanofi, Bayer. J.L. Coenen: Advisory board: Sanofi. A. Bergman: PI of one of the IIS sponsored by Sanofi. W.R. Gerritsen: Speaker fees: Astellas, Bavarian Nordic, Bristol-Myers Squibb, MSD, Janssen-Cilag; Advisory boards: Amgen, Astellas, Bayer, Bristol-Myers Squibb, Curevac, Dendreon, Janssen-Cilag, Merck (MSD), Morphosys, Sanofi; Ad hoc consultancy: Aglaia Biomedical Ventures, Psioxus Therapeutics. All other authors have declared no conflicts of interest.

816P Androgen decline and outcome in castration resistant prostate cancer (mCRPC) patients treated with docetaxel (Doc), prednisone +/- bevacizumab (B)

C.J. Ryan[1], S. Dutta[2], W. Kelly[3], M.J. Morris[4], M-E. Taplin[5], S. Halabi[6]

[1]Division of Hematology, Oncology and Transplantation, Masonic Cancer Center, Minneapolis, MN, USA, [2]Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, USA, [3]Medicine, Thomas Jefferson University, Philadelphia, PA, USA, [4]Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [5]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [6]Biostatistics and Bioinformatics, Duke University, Durham, NC, USA

Background: Androgen levels are associated with overall survival (OS) in mCRPC. Doc impairs microtubules and has AR inhibitory effects. This analysis evaluates change in androgen levels (Testosterone (T), Androstenedione (A) and DHEA (D) and outcome in Doc-treated mCRPC patients.

Methods: Data from 1,050 men treated on CALGB 90401 with Doc, prednisone and either B or placebo were used. Pre-treatment, 6 week and progression serum assays for T, A and D were performed via tandem Liquid Chromatography-Mass Spectrometry (LC-MS/MS). Ratio of change in androgen (6 week value /baseline value) was calculated. Decline was further evaluated as high or low ($>$ or $<$ median decline for all patients). The logistic regression and proportional hazards models were used to assess the prognostic significance of changes in T, A, and D in predicting PSA response, PFS and OS adjusting for known prognostic factors.

Results: Median values for baseline T, A, and, D were 1.0, 13.5 and 8.1, ng/dL respectively, while androgen levels at 6 weeks were 0.64, 7.0 and 6.8, ng/dL respectively. At 6 weeks a decline in all three androgens was observed. The ratio of 6weeks/baseline in T, A and D were 0.93, 0.56 and 0.86, respectively. There was interaction between levels of T decline and treatment arm (p-value=0.047). Among 291 patients with high levels of T decline, those who also received B were more likely to experience a $\geq 50\%$ decline in PSA (87%) compared to those who did not receive B (67%,). Associations between androgen decline and PFS were NS. In multivariable analysis adjusting for prognostic factors, the hazard ratio (HR) for OS demonstrated that decline in T at 6-weeks/baseline was associated with longer OS, HR 1.02 (95% CI 1.01 ,1.03 $p = 0.001$). Median OS for low T change (ratio $>=0.93$) is 20.9 mos vs 26.3 mos for high T change (<0.93).

Conclusions: Patients treated with Doc who experience a greater drop in T on therapy experience a significantly longer OS and higher rate of PSA decline but no effect on PFS. B and androgen decline may confer interacting beneficial effects. Data are consistent with the favorable prognostic significance of higher serum androgens in the CRPC setting and reflecting the potential effect of Doc on AR signalling.

Clinical trial identification: NCT00110214.

Legal entity responsible for the study: Alliance for Clinical Trials in Oncology.

Funding: National Cancer Institute: R21 CA195424-01, U10CA180821, U10CA180882.

Disclosure: C.J. Ryan: Consulting fees: Sanofi. All other authors have declared no conflicts of interest.

817P Cabazitaxel treatment in metastatic castration-resistant prostate cancer (mCRPC) clinical trials compared to usual care in CAPRI: An observational study in the Netherlands

H.M. Westgeest[1], M. Kuppen[2], A.J.M. van den Eertwegh[3], J. Van Moorselaar[4], N. Mehra[5], I. van Oort[6], A.C.M. van den Bergh[7], J.L. Coenen[8], K.K.H. Aben[9], R. Somford[10], R. de Wit[11], A. Bergman[12], J. Lavalaye[13], C.A. Uyl-de Groot[14], W.R. Gerritsen[5]

[1]Medical Oncology, Amphia Ziekenhuis, Breda, Netherlands, [2]Institute for Medical Technology Assessment, Erasmus School of Health Policy and Management, Rotterdam, Netherlands, [3]Medical Oncology, VU Medical Center, Amsterdam, Netherlands, [4]Urology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [5]Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [6]Urology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [7]Radiation Oncology, UMCG, Groningen, Netherlands, [8]Medical Oncology, Isala Klinieken, Zwolle, Netherlands, [9]IKNL, Netherlands Comprehensive Cancer Organisation, Utrecht, Netherlands, [10]Urology, Canisius Wilhelmina Ziekenhuis, Nijmegen, Netherlands, [11]Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, [12]Division of Internal Medicine (MOD) and Oncogenomics, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [13]Nuclear Medicine, Antonius Ziekenhuis, Nieuwengein, Netherlands, [14]Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, Netherlands

Background: Cabazitaxel (CAB) has been shown in the TROPIC trial to improve overall survival (OS) in mCRPC patients after docetaxel (DOC). However clinical trial populations may not reflect the real world population. The objective is to compare patient characteristics and outcome of CAB within clinical trials and in standard of care (SOC) from data extracted from the CAPRI registry.

Methods: CRPC pts treated with CAB directly after DOC, before 1-1-2017, either within a clinical trial or as SOC were retrospectively identified and followed to 1-1-2018. For multivariable analyses, missing values were imputed by multiple imputation using the Monte Carlo Markov Chain method.

Results:

Table: 817P Baseline characteristics at start cabazitaxel (baseline period defined as 42 days before to 7 days after start of cabazitaxel).
Total percentages may not equal 100 because of rounding.

	Cabazitaxel 1st line post-docetaxel (n = 173)		
	Usual care (n = 109)	Trial (n = 64)	p-value
Age (years) Median (IQR) ≥75 years (%)	68 (64-72) 17	67 (64-72) 13	0.502
Period on ADT (months) Median (IQR)	25 (18-37)	30 (19-45)	0.091
ALP (U/L) Median (IQR) Missing (%)	222 (100-360) 18	192 (97-366) 11	0.799
PSA (ug/L) Median (IQR) Missing (%)	200 (65-567) 12	209 (79-500) 8	0.711
Hemoglobin (mmol/L) Median (IQR) Missing (%)	7.1 (6.3-7.8) 17	7.7 (6.7-8.1) 11	0.029
LDH (U/L) Median (IQR) Missing (%)	328 (252-504) 26	268 (209-397 14)	0.010
ECOG performance (%) 0 1 >1 Missing	16 49 9 27	23 56 3 17	0.186
Visceral disease (%) No Yes Missing	29 19 52	45 11 44	0.038
Opioid use (%) No Yes Missing	23 28 50	41 27 33	0.140
Symptoms (%) No Yes Missing	6 78 16	17 72 11	0.033
Docetaxel cycles Median (IQR) Missing (%)	7 (5-10) 1	10 (7-10) 3	0.002
Time since last docetaxel dose (months) Median (IQR) <6 months (valid %) Missing (%)	2.2 (0.9-4.7) 86 5	3.9 (2.0-6.0) 74 5	0.001

From a total of 3,616 pts in the CAPRI database, we identified 356 pts treated with CAB, of which 173 pts were treated directly post-DOC. Trial pts had less symptoms and visceral disease, lower LDH, higher hemoglobin, received more DOC cycles and had a longer treatment-free interval since last DOC (see Table). The median number of CAB cycles was higher in trials compared to SOC (5 vs 4, p = 0.031). Median OS was 13.6 vs 9.6 months for trial pts and SOC, respectively (HR 0.73, p = 0.07). PSA response (≥ 50% decline) was 27 vs 11%, respectively (p = 0.210). However, after correction for prognostic factors, trial participation did not retain statistical significance (HR 0.94, p = 0.73), but longer period on ADT, lower LDH and absence of visceral metastases were significant for better OS. In addition, lower PSA and absence of symptoms had a trend for better OS.

Conclusions: The OS in the trial subgroup is in agreement with the OS of the TROPIC trial in a contemporary real world setting. However, the SOC pts had a trend for worse OS which may be explained by worse prognostic factors at CAB initiation. Accordingly, pts whose disease has progressed post-DOC should be carefully selected for treatment to ensure optimal outcomes.

Clinical trial identification: The CAPRI study is registered in the Dutch Trial Registry as NTR3591.

Legal entity responsible for the study: Institute for Medical Technology Assessment, Erasmus University Rotterdam.

Funding: The CAPRI registry was funded by Sanofi-Aventis Netherlands B.V., Janssen-Cilag B.V., Astellas Pharma B.V., and Bayer B.V. The funding organizations had no role in the design and conduct of the study, collection, management, analysis, interpretation of the data, and preparation, review, or approval of the abstract.

Disclosure: A.J.M. van den Eertwegh: Study grant: Sanofi; Travel expenses, speaker fee, advisory board: Astellas. J. Van Moorselaar: Grants/research supports: Astellas, Ferring, Ipsen; Honoraria, consultation fees: Amgen, Astellas, AstraZeneca, Bayer, Janssen, Sanofi-Genzyme I. van Oort: Astellas, Janssen, Sanofi, Bayer. J.L. Coenen: Advisory board: Sanofi R. de Wit: Sanofi, Merck, Roche. A. Bergman: PI of one IIS sponsored by Sanofi. W.R. Gerritsen: Speaker fees: Astellas, Bavarian Nordic, Bristol-Myers Squibb, MSD, Janssen-Cilag; Advisory boards: Amgen, Astellas, Bayer, Bristol-Myers Squibb, Curevac, Dendreon, Janssen-Cilag, Merck (MSD), Morphosys, Sanofi; Ad hoc consultancy: Aglaia Biomedical Ventures, Psioxus Therapeutics. All other authors have declared no conflicts of interest.

818P Post hoc analysis of the effect of baseline characteristics on treatment duration in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel in the compassionate use (CUP)/ expanded access programs (EAP) and CAPRISTANA registry

Z. Malik[1], A. Pichler[2], G. Di Lorenzo[3], U. De Giorgi[4], S. Hitier[5], E. Ecstein-Fraisse[6], A. Ozatilgan[7], J. Carles[8]

[1]The Clatterbridge Cancer Centre, NHS Foundation Trust, Wirral, UK, [2]Department of Hematology and Oncology, Regional Hospital Hochsteiermark, Leoben, Austria, [3]Genitourinary Cancers Section, AOU Feder, University of Naples Federico II, Naples, Italy, [4]Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [5]Biostatistics & Programming, Sanofi, Chilly-Mazarin, France, [6]Medical Evidence Generation, Sanofi, Paris, France, [7]Global Medical Oncology, Sanofi, Cambridge, MA, USA, [8]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: Cabazitaxel is approved for patients with mCRPC, post docetaxel. The CUP (CABAZ_C_05005) and EAP (NCT01254279) provided access to cabazitaxel before commercial availability and assessed real-world safety. CAPRISTANA (CABAZC 06092), a prospective, observational study, evaluated the routine clinical use of cabazitaxel. In this analysis we examined factors associated with cabazitaxel treatment duration in a real-life setting.

Methods: Patients ≥18 years of age with mCRPC previously treated with docetaxel, received cabazitaxel 25 mg/m^2 intravenously every 3 weeks until disease progression, death, unacceptable toxicity or physician/patient decision. Of note, treatment was capped at 10 cycles in some countries.

Results: The CUP/EAP/CAPRISTANA studies combined included 1,621 patients (CUP/EAP, N = 1,432; CAPRISTANA, N = 189). The median number of cabazitaxel cycles received was 6. Overall, 708 patients (43.7%) received >6 cycles (Table); 211 (13.0%) received >10 cycles. For patients receiving >10 cycles, the median number of cabazitaxel cycles received was 14. Patients receiving more cabazitaxel cycles tended to have better ECOG performance status of 0–1 (Table; P = 0.0017 for ≤6 vs > 6 cycles). In total, 348 patients (21.5%) were ≥75 years of age, of which 40% (n = 139) received >6 cabazitaxel cycles. Further analysis into the patient subgroups and reasons for treatment discontinuation are ongoing.

Conclusions: Cabazitaxel was well tolerated by patients across these global studies, including elderly patients. Many patients derived benefit from cabazitaxel and went on to receive a greater number of cycles. Further analyses may identify prognostic factors that could indicate which patients are likely to receive >6 cabazitaxel cycles and derive greater benefit. Funding: Sanofi.

Clinical trial identification: Compassionate Use Program (CUP): CABAZ_C_05005. Expanded Access Program (EAP): NCT01254279. CAPRISTANA Registry Study: CABAZC 06092.

Editorial acknowledgement: Editorial assistance was provided by Danielle Lindley of Meditech Media Ltd, funded by Sanofi.

Legal entity responsible for the study: Sanofi.

Funding: Sanofi.

Disclosure: Z. Malik: Advisory boards, speaker meetings: Sanofi. U. De Giorgi: Consultancy fees: Sanofi, Astellas, Janssen, Bristol-Myers Squibb, Ipsen, Novartis,

Table: 818P

	CUP/EAP/CAPRISTANA N = 1,621	
	Cabazitaxel cycles received	
	≤6 N = 913	>6 N = 708
Median age, years (range)	68.0 (42–89)	68.0 (43–89)
Age, n (%) <65 years 65–75 years ≥75 years	271 (29.7) 433 (47.4) 209 (22.9)	230 (32.5) 339 (47.9) 139 (19.6)
ECOG PS, n (%) 0–1 2*	N = 912 816 (89.5) 96 (10.5)	N = 708 665 (93.9) 43 (6.1)
Median cabazitaxel cycles, n (range)	4 (1–6)	10 (7–49)
Median duration of cabazitaxel exposure, months (range)	2.8 (1–6)	6.9 (5–35)
Median time from prostate cancer diagnosis, years (range)	4.5 (0–22)	4.7 (0–20)
Median time from mCRPC diagnosis, years (range)	1.7 (0–14)	1.8 (0–12)
Median docetaxel cycles at last administration, n (range)	7 (1–69)	8 (1–58)
Metastatic sites, n (%) Bone Visceral Regional lymph nodes	N = 912 829 (90.8) 47 (5.1) 282 (30.9)	N = 707 630 (89.0) 23 (3.2) 214 (30.2)
G-CSF during Cycle 1, n (%) Prophylactic Therapeutic Both	N = 499 385 (42.2) 69 (7.6) 45 (4.9)	N = 380 314 (44.4) 33 (4.7) 33 (4.7)
Pain at baseline (CAPRISTANA study only), n (%) None Moderate Severe	N = 86 15 (17.4) 63 (73.3) 8 (9.3)	N = 68 18 (26.5) 47 (69.1) 3 (4.4)

*Includes one patient with ECOG PS 3 receiving ≤6 cabazitaxel cycles.

Pfizer. S. Hitier, E. Ecstein-Fraisse, A. Ozatilgan: Employee: Sanofi. J. Carles: Consultancy, advisory role: Johnson & Johnson, Astellas Pharma, Bayer, Amgen, Pfizer, Bristol-Myers Squibb, Sanofi; Speakers' bureau: Bayer, Johnson & Johnson. All other authors have declared no conflicts of interest.

819P Prognostic associations of early prostate-specific antigen (PSA) changes in patients with metastatic castration-resistant prostate cancer treated with with abiraterone acetate or enzalutamide

F. López Campos[1], I. Moreno[2], A. Conde-Moreno[3], A. Gómez-Iturriaga[4], M. Ruiz Vico[5], N. Romero Laorden[6], I. Henríquez López[7], P. Peleteiro Higuero[8], R. Lozano Mejorada[9], T. Piquer[10], M. Couselo[11], J. Gómez Ramos[7], J. Navarro[11], P. Barrionuevo Castillo[1], R. García[12], R. Villatoro[13], A. Montesa[14], M.I. Saez[14], B. Herrera[14], E. Castro Marcos[9]

[1]Radiation Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [2]Medical Oncology, Hospital Universitario Virgen de la Victoria, Malaga, Spain, [3]Radiation Oncology, Hospital Universitario y Politécnico La Fe, Valencia, Spain, [4]Radiation Oncology, Hospital de Cruces, Baracaldo, Spain, [5]Medical Oncology, Hospital Regional Universitario Carlos Haya, Malaga, Spain, [6]Prostate Cancer Unit, CNIO- Spanish National Cancer Center, Madrid, Madrid, Spain, [7]Radiation Oncology, Hospital Universitario San Joan de Reus, Reus, Spain, [8]Radiation Oncology, Hospital Clínico Universitario De Santiago de Compostela, Santiago De Compostela, Spain, [9]Prostate Cancer Unit, CNIO- Spanish National Cancer Center, Madrid, Spain, [10]Radiation Oncology, Hospital Provincial de Castellón, Castellón, Spain, [11]Radiation Oncology, Hospital Central de la Defensa Gómez Ulla, Madrid, Spain, [12]Radiation Oncology, Hospital Clínico Universitario de Valencia, Valencia, Spain, [13]Medical Oncology, Hospital Costa del Sol, Malaga, Spain, [14]Unidad de Investigación CNIO-IBIMA, Hospitales Universitarios Virgen de la Victoria y Regional de Málaga, Malaga, Spain

Background: The availability of multiple treatments for metastatic castration-resistant prostate cancer (mCRPC) mandates the need to identify prognostic factors applicable to clinical practice. Variations in (PSA) levels are widely used in the monitoring of response to treatment with abiraterone acetate (AA) or enzalutamide, but are not validated as an early biomarker for overall survival (OS). Objective: To evaluate the association between early PSA changes and OS following enzalutamide or AA treatments in mCRPC.

Methods: We retrospectively evaluated mCRPC patients treated with AA or enzalutamide, before or after docetaxel, in 11 reference hospitals between 2011 and 2017. A descriptive and multivariate analysis of the data was carried out in order to establish the association of PSA variations at 4 and 12 weeks (expressed as 30% and 50% percentage modifications, respectively, relative to baseline value at the start of AA or enzalutamide) with OS. Association with OS was analyzed using multivariate Cox regression and log-rank analyses. Spearman's rho correlation coefficient (r) was calculated to evaluate the association between PSA changes at 4 and 12 weeks.

Results: We analyzed 450 mCRPC patients with a median follow-up of 16 months (1-65). A 30% PSA decline at 4 weeks was associated with longer OS (30 vs 20 months; hazard ratio [HR] 0.55 (0.42-0.73), $p < 0.001$), as well as a 50% PSA decrease at 12 weeks (39 vs 19 months; HR 0.42 (0.31-0.56), $p < 0.001$). We found a detriment in survival in patients with a 30% PSA rise at 4 weeks, with shorter OS (22 vs 26 months; HR 1.5 (1.07-2.21), $p = 0.025$) and a 50% PSA increase at 12 weeks after starting treatment (14 vs 29 months; 2.66 (1.93-3.67) $p < 0.001$), in both univariate and multivariable models. The percentage PSA decline at 4 weeks was significantly correlated with the percentage PSA change at 12 weeks ($r = 0.635$; $p < 0.001$). Limitations include the retrospective design of this analysis.

Conclusions: PSA changes as early as 4 weeks after enzalutamide or AA initiation are highly associated with OS in mCPRC. Prospective multicentre validation studies are needed to confirm these findings.

Legal entity responsible for the study: Fernando López Campos.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

820P Cabazitaxel under routine conditions for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC): Interim results of the non-interventional SCOPE study

J. Gschwend[1], C. Lange[2], C. Bokemeyer[3]

[1]Department of Urology, Klinikum rechts der Isar, Technical University of Munich, Germany, Munich, Germany, [2]Urology, Medical Office Bernburg, Bernburg, Germany, [3]Department of Oncology, Hematology and Bone Marrow Transplant, Hematology and Bone Marrow Transplant, University Medical Center Hamburg-Eppendorf, Germany, Hamburg, Germany

Background: Several treatment options are currently available for patients with mCRPC who were treated with a docetaxel-containing regimen. As one therapeutic option, cabazitaxel (CABA) in combination with prednis(ol)one can be administered. SCOPE is the first multinational, non-interventional study to address this question prospectively.

Methods: Within the ongoing SCOPE study, data on medical history, therapeutic management and outcome of mCRPC patients starting treatment with CABA under routine conditions are assessed with a target recruitment of 900 patients. For the current interim analysis (cut-off: MAR 16, 2018) descriptive statistics were used to analyze preliminary data on treatment outcomes.

Results: Of 551 enrolled patients, 137 patients (median age: 73 (47 to 88) years, ECOG of ≤ 1: 81.8%, median duration of CRPC at study inclusion: 20.4 (0.8 to 109.1) months) have completed CABA therapy. For 27 patients, first line therapy with an androgen-receptor targeted agent (ARTA) was documented (ARTA 1st line), of which 10 patients received an ARTA in 2nd line (ARTA post ARTA). None (0.0%) of the 10 ARTA post-ARTA patients had reductions in PSA levels $\geq 50\%$ (PSA_{50} response) compared to baseline. Median progression-free survival (PFS) after the start of the respective therapy was longer for 1st line ARTA than for ARTA post-ARTA therapy (10.8 vs. 3.5 months, $p = 0.0106$). Fifty patients received docetaxel as 1st line therapy directly followed by CABA (CABA 2nd line) and for 24 patients ARTA therapy was documented after docetaxel and prior to CABA (CABA 3rd line). PSA_{50} response to CABA was 38.0% (CABA 2nd line) and 37.5% (CABA 3rd line), respectively. Median PFS after start of CABA therapy showed no significant differences between the CABA 2nd line and CABA 3rd line group (4.2 vs. 5.1 months, $p = 0.5663$).

Conclusions: The current results indicate that the outcome of ARTA post-ARTA is unfavourable compared to 1st line ARTA therapy and that CABA is effective in both ARTA and docetaxel refractory patients. However, interpretation of results is challenging due to the highly diverse treatment sequences administered in patients with mCRPC under routine conditions.

Clinical trial identification: BfArM data base No: 6658.

Legal entity responsible for the study: Sanofi Aventis Deutschland GmbH.

Funding: Sanofi Aventis Deutschand GmbH.

Disclosure: J. Gschwend: Lectures: Amgen, Astellas, Bayer, Janssen, MSD, Novartis, Roche, Sanofi; Advisor role: Bayer, BMS, Janssen, MSD, Novartis, Pfizer, Roche. C. Bokemeyer: Honoraria: Merck KGaA, Sanofi, Roche, Bayer, Brystol-Meyer Squibb, Servier/Pfizer, AstraZeneca; Consulting: Lilly/ImClone, Merck Serono, Sanofi, Mundipharma, Bayer Schering Pharma, Hexal. All other authors have declared no conflicts of interest.

821P Kinetics of prostate-specific antigen (PSA) as a marker of abiraterone acetate (AA) efficacy in patients (p) with metastatic castrate-resistant prostate cancer (mCRPC)

S. España Fernandez[1], J.M. Piulats[2], N. Sala[3], J.M. Velarde[1], U. Ferrandiz[1], O. Etxaniz Ulazia[1], L. Heras Lopez[4], M.P. Barretina Ginesta[5], X. Garcia del Muro[6], A. Font[1]

[1]Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain, [2]Medical Oncology, Catalan Institute of Oncology, Barcelona, Spain, [3]Medical Oncology, ICO Girona, Hospital Josep Trueta, Girona, Spain, [4]Medical Oncologist, ICO, Barcelona, Spain, [5]Medical Oncology, Catalan Institute of Oncology (ICO)-Hospital Universitari Josep Trueta, Girona, Spain, [6]Medical Oncology, Institut Català d'Oncologia L'Hospitalet, Barcelona, Spain

Background: Studies have suggested an association between PSA kinetics and outcome to AA. In order to identify p with resistance to AA, we assessed potential factors associated with overall survival (OS) in p with mCRPC treated with AA after progression to docetaxel.

Methods: We included 104 p with mCRPC treated with AA plus prednisone after progression to docetaxel at three centers of the Catalan Institute of Oncology from August 2011 to October 2014. All p were assessed monthly to check PSA levels and hematological parameters. We used a multivariable Cox proportional hazards model to explore the association of baseline characteristics and PSA parameters with OS.

Results: Median OS was 16.4 months (m) and the median of duration of treatment was 7.54 m. In the univariate analysis, 14 factors were significantly associated with OS: ECOG PS, metastatic site, hemoglobin, alkaline phosphatase, lactate dehydrogenase (LDH), baseline PSA levels (classified by terciles), neutrophil-lymphocyte ratio (NLR), interval between end of docetaxel and start of AA, early PSA response (decrease >30% at week 4), PSA nadir, time to PSA nadir, PSA decrease >50%, end-of-treatment (EOT) PSA levels, and EOT PSA doubling time (PSADT). The multivariate analysis identified lymph node metastases ($P = 0.016$), NLR <4 ($P = 0.038$), baseline PSA levels <43 ng/ml ($P = 0.026$), normal LDH ($P = 0.035$), early PSA response ($P = 0.001$), and EOT PSADT >1.5 m ($P < 0.001$) as independent markers of longer OS.

Conclusions: Our results suggest an association between PSA kinetics, primarily early PSA response, with outcome to AA after progression to docetaxel. Taken together with other factors, lack of an early PSA response could identify patients that will probably not obtain a benefit from AA and who might be considered for alternative therapies.

Legal entity responsible for the study: Catalan Institute of Oncology, Hospital Universitary Germans Trias i Pujol.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

822P Preliminary safety results of the randomized phase II ABIDO-SOGUG trial: Toxicity profile of concomitant abiraterone acetate + docetaxel treatment in comparison to docetaxel

J. Puente[1], M.J. Mendez Vidal[2], M.I. Saez[3], A. Font Pous[4], I. Duran[5], D. Castellano[6], M.J. Juan Fita[7], C. Santander[8], J.A. Arranz Arija[9], A. Sanchez-Hernandez[10], B. Mellado[11], T. Alonso[12], M.A. Gonzalez del Alba Baamonde[13], P. Maroto[14], M. Lazaro[15], E. Esteban[16], J.G. Cassinello[17], M.A. Climent Duran[18]

[1]Medical Oncology, Hospital Clinico Universitario San Carlos, Madrid, Spain, [2]Medical Oncology, University Hospital Reina Sofia, Cordoba, Spain, [3]Medical Oncology, H Universitarios Virgen de la Victoria y Regional de Málaga, Malaga, Spain, [4]Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain, [5]Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain, [6]Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain, [7]Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [8]Medical Oncology, Hospital Miguel Servet, Zaragoza, Spain, [9]Medical Oncology, Hospital General Universitario Gregorio Marañon, Madrid, Spain, [10]Medical Oncology, Hospital Provincial de Castellón, Castellon De La Plana, Spain, [11]Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [12]Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain, [13]Medical Oncology, Hospital Universitario Son Espases, Palma de Mallorca, Spain, [14]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [15]Medical Oncology, Complejo Hospitalario Universitario de Vigo, Vigo, Spain, [16]Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain, [17]Medical Oncology, University General Hospital, Guadalajara, Spain, [18]Medical oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain

Background: Abiraterone acetate (AA) improves OS and rPFS in asymptomatic/minimally symptomatic mCRPC patients (pts) who are chemotherapy (CT) naïve. Upon progression to this strategy, Docetaxel (D) is currently one of standard treatments. However, the value of maintaining AA along with D despite progression to the former has not been tested yet. ABIDO is a randomized-phase II trial that evaluates efficacy and safety of D + AA vs. D after disease progression to first line AA in mCRPC.

Methods: mCRPC CT naïve pts with no visceral metastases, ECOG PS 0-1, testosterone < 50 ng/dL and adequate, hematologic, hepatic, and renal function were included. The study has two stages. In stage I pts receive AA at the approved regime (AA 1000mg/day-prednisone (P) 5 mgbid) until progressive disease determined by PSCWG2 criteria. Upon progression, in stage II, pts are randomized to receive either three-weekly D + daily AA+P (Arm A) or three-weekly D alone (Arm B).

Results: So far 148 pts have been included and 88 were randomized already. Of those 77 have completed D and have been analyzed (39 in arm A and 38 in Arm B). Median age was 72 y/o, 43% had ECOG 0 and 88% had bone metastases and 16% visceral metastases. Patients received 255 and 274 cycles of D in Arm A and B respectively with a median number of cycles of 7 and 8. Docetaxel median dose intensity was 90% and 92% for each arm and 94% for AA. Nine pts discontinued treatment due to toxicity, 5 in arm A and 4 in arm B. Most frequent G3-4 toxicities per arm (A/B) were: neutropenia (56%; 29%), febrile neutropenia (21%; 8%), diarrhea (10%; 8%), and asthenia (13%; 11%). Most common toxicities all grades per arm were: asthenia (74%; 66%), neutropenia (59%; 34%), alopecia (44%; 45%), nail toxicity (49%; 34%), diarrhea (46%; 42%), neurotoxicity (39%; 42%), nauseas (28%; 26%), mucositis (26%; 29%) and anemia (23%;11%).

Conclusions: In the AA maintenance cohort, more frequent and severe hematological treatment related adverse events (neutropenia, febrile neutropenia and anemia) were observed. No other differences were relevant. Prophylactic G-CSF use is encouraged in all patients. These preliminary data require confirmation once the study is completed.

Clinical trial identification: NCT02036060; EudraCT: 2013-003811-23.

Editorial acknowledgement: Juan Luis Sanz, APICES.

Legal entity responsible for the study: SOGUG: Spanish Oncology Genitourinary Group.

Funding: Janssen-Cilag, S.A.

Disclosure: J. Puente: Honoraria: Astellas, Bayer, Janssen, Roche, Ipsen; Consulting or advisory role: Astellas, Roche, Ipsen, Pfizer, Bristol-Myers Squibb, Merck sharp & Dohme; Research funding: Astellas. M.J. Mendez Vidal: Consulting: Janssen, Pfizer, Astellas, Sanofi, Bayer, Bristol-Myers Squibb, Novartis, Roche. I. Duran: Honoraria: Bristol-Myers Squibb, Ipsen, Roche; Advisory role: Roche, MSD, Bayer, Bristol-Myers Squibb. A. Sanchez-Hernandez: Honoraria: Sanofi, Astellas, Janssen, Bayer, Roche, Boehringer Ingelheim, Pierre-Fabre, Bristol-Myers Squibb, MSD; Consulting: Sanofi, Astellas, Janssen, Bayer, Roche, Boehringer Ingelheim, Pierre-Fabre, Bristol-Myers Squibb, MSD; Spikers bureau: Sanofi, Astellas, Janssen, Bayer, Roche, Boehringer Ingelheim, Pierre-Fabre, Bristol-Myers Squibb, MSD. T. Alonso: Consulting: Sanofi. M.A. Gonzalez del Alba Baamonde: Consulting: Astellas, Sanofi, Bayer, Janssen, Pfizer, Bristol-Myers Squibb, Eisai, Pierre Fabre. M. Lazaro: Expert testimony: Janssen, Pfizer, Roche. M.A. Climent Duran: Honoraria: Janssen, Astellas, Sanofi, Bayer; Consulting: Janssen, Sanofi, Bayer. All other authors have declared no conflicts of interest.

823P Efficacy of therapies after progression to up-front docetaxel (D) with androgen deprivation therapy (ADT) for metastatic hormone-sensitive prostate cancer (mHSPC)

P. Gajate Borau[1], A. Martin Marino[2], I. Gallegos Sancho[3], J.C. Villa Guzman[4], A. Velastegui[5], T. Alonso Gordoa[1], D. Castellano[6], G. Rubio Romero[7], A. Pinto Marin[8], L. Villalobos Leon[9], C. Maximiano Alonso[10], M.J. Sotelo-Lezama[11], M. Sereno Moyano[12], J.F. Rodríguez[13], C. Perezagua Marin[14], J. Ballesteros[15], D. Marrupe Gonzalez[16], L. Rodriguez Lajusticia[17], J.J. Tafalla García[18], C. Aguado[19]

[1]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [2]Medical Oncology, Hospital Universitario Infanta Leonor, Madrid, Spain, [3]Medical Oncology, Complejo Asistencial de Segovia, Segovia, Spain, [4]Medical Oncology, Hospital General Ciudad Real, Ciudad Real, Ciudad Real, Spain, [5]Medical Oncology, Hospital Universitario Rey Juan Carlos, Móstoles (Madrid), Spain, [6]Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain, [7]Medical Oncology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [8]Medical Oncology, Hospital Universitario La Paz, Madrid, Spain, [9]Medical Oncology, Hospital Principe de Asturias, Madrid, Spain, [10]Medical Oncology, Hospital Universitario Puerta de Hierro - Majadahonda, Majadahonda, Spain, [11]Medical Oncology, Hospital Infanta Cristina, Parla (Madrid), Spain, [12]Medical Oncology, Hospital Infanta Sofia, Madrid, Spain, [13]Oncology Unit, HM San Chinarro, Madrid, Spain, [14]Medical Oncology, University Hospital del Henares, Coslada, Spain, [15]Medical Oncology, Hospital Universitario del Sureste, Madrid, Spain, [16]Oncología, Hospital General de Mostoles, Mostoles, Madrid, Spain, [17]Medical Oncology, Hospital Universitario de Fuenlabrada, Madrid, Spain, [18]Medical Oncology, Hospital Central de la Defensa, Madrid, Spain, [19]Medical Oncology, Hospital Clinico Universitario San Carlos, Madrid, Spain

Background: Addition of D to ADT increased overall survival in high volume disease mHSPC. Nevertheless, there is a lack of information about the management after disease progression and predictive factors of efficacy for subsequent therapies are unknown.

Methods: Retrospective analysis of 163 mHSPC patients (pt) treated with D in 23 Spanish Centers from July 2014 to April 2018. Objectives of the study are: describe baseline and progression characteristics, treatment choices and efficacy outcomes of subsequent therapies based on pretreatment features.

Results: After a median follow up of 18.04 months (m), 93 pt (57.1%) developed CRPC. Median time to CRPC was 15.97 m (CI 95%: 10.97 m – 28.16 m). 80 pt received subsequent treatment after progression: 23 (28.8%) received chemotherapy (CT) (3 D, 17 cabazitaxel, 3 carboplatin-etoposide), 52 (65%) androgen receptor axis-targeted agents (31 enzalutamide, 21 abiraterone) and 5 radium-223. Baseline characteristics of pt at CRPC disease were: median age: 67.1 year; median PSA doubling time (PSADT): 2 m, and median PSA, Hemoglobin (Hb), LDH and alkaline phosphatase (alk-P) was 20.3 ng/mL, 12.95 g/dL, 326 UI/mL and 144 UI/mL, respectively. 26.4% of pt had visceral progression. Median progression free survival (PFS) of pt in first-line treatment for mCRPC was 6.93 m (CI95%: 3.58-10.02). In univariate analysis, hormonal therapy showed a significant longer PFS compared to CT (7.49 m vs 6.27 m; HR 0.55; p 0.048), but no association was found after adjustment by other prognostic characteristics (HR 0.77; p 0.79). Although no significant association was observed in multivariate analysis, pt with more aggressive clinical characteristics achieved a longer PFS with CT (Table).

Table: 823P PFS at first-line treatment of mCRPC

	HT (m)	CT (m)	p
PSADT < 3 m PSADT > = 3 m	4.46 9.39	6.27 3.59	0.6 0.07
Visceral PD Non Visceral PD	4.33 5.95	5.59 3.54	0.59 0.12
LDH H LDH L	4.34 12.0	5.59 8.21	0.29 0.3
Hb H Hb L	NR 4.0	5.58 6.27	0.03 0.63
alk-P H alk-P L	3.81 11.99	6.93 5.52	0.94 0.03
PSA H PSA L	3.81 8.54	5.52 5.58	0.35 0.14

Conclusions: Baseline characteristics at CRPC disease could help us to identify the best therapy option for pt pretreated with D + ADT in mHSPC. Our analyses suggest that CT could benefit pt with more aggressive clinical features.

Legal entity responsible for the study: Pablo Gajate Borau.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

824P Radium-223 (Ra-223) therapy after abiraterone (Abi): Analysis of symptomatic skeletal events (SSEs) in an international early access program (iEAP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)

K. Miller[1], D. Heinrich[2], J.M. O'Sullivan[3], J. Carles[4], M. Wirth[5], S. Nilsson[6], L. Huang[7], J. Kalinovsky[8], A. Heidenreich[9], F. Saad[10]

[1]Urology, Charité Berlin, Berlin, Germany, [2]Oncology, Akershus University Hospital, Oslo, Norway, [3]Centre for Cancer Research & Cell Biology, Queen's University Belfast, Belfast, UK, [4]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Urology, University Hospital Carl Gustav Carus, Dresden, Germany, [6]Oncology-Pathology, Karolinska University Hospital, Stockholm, Sweden, [7]Statistics, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, [8]Medical Oncology, Bayer Consumer Care AG, Basel, Switzerland, [9]Urology, University Hospital Cologne, Cologne, Germany, [10]Urology, University of Montreal Hospital Center, Montreal, QC, Canada

Background: Ra-223 phase 3 study (ALSYMPCA) was conducted before Abi became available. The Ra-223 iEAP study included Abi-treated pts. Here, we assessed SSEs, OS and bone health agent (BHA) use in Ra-223-treated pts who received Abi as a prior treatment.

Methods: This open-label, single-arm trial enrolled pts with bone-predominant mCRPC (≥2 bone metastases [BM]). Pts who received prior anti-cancer therapies were included; use of BHAs (bisphosphonates and denosumab) was permitted before/during the study. Median follow-up was 7.5 mo. Baseline characteristics, SSEs, (EBRT, symptomatic pathological fractures, spinal cord compression or surgical intervention) and OS were analysed descriptively for pts who completed prior Abi therapy and Abi-naïve pts.

Results: Of 708 mCRPC pts, 85% of prior Abi and 36% of Abi-naïve pts had previously received docetaxel (Table). During Ra-223 therapy, 14% and 17% of pts received concomitant bisphosphonates and 20% and 17% concomitant denosumab in the prior Abi and Abi-naïve groups, respectively. Median time since BM diagnosis and start of Ra-223 was 37 and 21 mo in the prior Abi and Abi-naïve pts, respectively. Median OS was 15.9 mo overall (11.2 mo for prior Abi and 17.1 mo for Abi-naïve pts). More pts had SSEs in the prior Abi (26%) than the Abi-naïve group (14%); proportions of treatment-emergent fractures were similar in both groups (4% and 3%, respectively), as was incidence of pathological bone fractures (5% for both).

Conclusions: Pts in the prior Abi group had a longer time from diagnosis of BM to Ra-223 initiation. These pts seem more advanced, as reflected by higher median baseline PSA and more pts with prior docetaxel therapy. BHAs appear to be under-utilised in clinical practice in this pt population. A similar rate of pathological and non-pathological fractures was reported in Ra-223-treated pts regardless of prior use of Abi.

Clinical trial identification: NCT01618370.

Editorial acknowledgement: Medical writing support was provided by Rebecca Hopkins, BSc, of Scion, London UK, funded by Bayer.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: K. Miller: Honoraria, consultation fees: Amgen, Bayer, BMS, Ferring, Janssen, MSD, Novartis, Pfizer, Roche, Sotio, Takeda, Tolmar. D. Heinrich: Speaker, consultancy honoraries: Bayer, Janssen-Cilaq (Johnson & Johnson) J.M. O'Sullivan: Advisory boards, speaker's bureau: Bayer, Janssen, Sanofi. J. Carles: Consultant, scientific advisory board attendee: Johnson & Johnson, Astellas, Bayer, Amgen, Pfizer, BMS; Speaker's bureau: Bayer, Johnson & Johnson. M. Wirth: Advisory board:Vital GmbH. S. Nilsson: Advisory boards, remuneration: Bayer. L. Huang, J. Kalinovsky: Employee: Bayer Healthcare. A. Heidenreich: Honoraria, advisory board: Amgen, Astellas, Bayer, Ferring, Ipsen, Janssen, Pfizer, Takeda, Sanofi. F. Saad: Consultant, Research grants: Bayer, Amgen, Astellas, Jansssen, Sanofi, AstraZeneca.

825P Randomized phase II trial of radium-223 (RA) plus enzalutamide (EZ) vs. EZ alone in metastatic castration refractory prostate cancer (mCRPC)

B.L. Maughan[1], A. Hahn[2], J. Hoffman[3], K. Morton[3], S. Gupta[4], J. Batten[3], J. Thorley[3], J. Hawks[3], G. Nachaegari[3], R. Nussenzveig[3], K. Boucher[3], N. Agarwal[5]

[1]Medical Oncology, Huntsman Cancer Institute, Salt Lake City, UT, USA, [2]Internal Medicine, University of Utah, Salt Lake City, UT, USA, [3]Medical Oncology, Huntsman Cancer Institute, Salt Lake City, UT, USA, [4]Oncology, Huntsman Cancer Institute, Salt Lake City, UT, USA, [5]Oncology/ Internal Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA

Background: RA, a bone targeting alpha radiopharmaceutical, and EZ, are approved for mCRPC. Per phase 3 SWOG0421 trial, subset of men with mCRPC with the high serum bone metabolism markers (BMM) had improved survival with concomitant decrease in these markers on treatment (Rx) with atrasentan, a bone targeting agent (Lara P et al, JNCI, 2014). Our hypothesize was that Rx with RA+ EZ will be safe, and decrease bone metabolism markers compared to EZ alone.

Methods: In this phase 2 trial (NCT02199197), men with progressive mCRPC were treated with EZ (160 mg daily) ± RA (standard dose of 55 kBq/kg IV Q4 weeks x 6), until disease progression or unacceptable toxicities. Primary objectives: 1) changes in N-telopeptide compared from baseline to end of treatment or disease progression (whichever occurred first) between the two arms, and 2) safety of combining RA+EZ. Secondary objectives: changes in 4 other markers of bone resorption or formation, and clinical outcomes. The bone markers were compared between treatment arms on the log scale using Analysis of Covariance (ANCOVA) with baseline bone marker values as a covariate.

Results: Combining RA+EZ was safe (2018 ASCO annual meeting abstract: 5057). Efficacy data are presented here. After a safety lead in phase (n = 8), 39 men were randomized (2:1) to RA+EZ vs EZ. The study met the primary endpoint with a significant decline in the N-telopeptide levels in RA+EZ vs EZ. There was a significant decline in all but one BMMs in RA+ EZ vs EZ alone. (Table). The clinical outcomes favored RA+EZ (data will be presented in the meeting).

Table: 825P

Marker	Ratio of RA+EZ to EZ	95% CI	P-value
Bone Specific Alk Phos	0.38	0.27,0.54	<0.001
C Telopeptide	0.66	0.44,1.00	0.060
N Telopeptide	0.61	0.48,0.79	<0.001
Procollagen 1 Intact N-Terminus	0.52	0.35,0.78	<0.001
Pyridinoline	1.02	0.80,1.30	0.87

Table: 824P

	Prior Abi (n = 223)	Abi naïve (n = 321)	Overall population (n = 708)
ECOG: 0 and 1, n (%)	195 (87)	273 (85)	618 (87)
PSA, median (μg/l)	290	100	143
ALP median (U/l)	169	148	150
Time since diagnosis of prostate cancer, median (months)	81	53	64
Time between diagnosis of prostate cancer and bone metastases, median (months)	26	11	19
Time from diagnosis of bone metastases to Ra-223 treatment, median (months)	37	21	26
Prior docetaxel, n (%)	189 (85)	117 (36)	423 (60)
Prior bisphosphonate, n (%)	19 (9)	13 (4)	48 (7)
Prior denosumab, n (%)	6 (3)	6 (2)	14 (2)
Concomitant bisphosphonates, n (%)	30 (14)	56 (17)	122 (17)
Concomitant denosumab, n (%)	44 (20)	53 (17)	129 (18)
Total Ra-223 injections, median (range)	5.0 (1–6)	6.0 (1–6)	6.0 (1–6)
OS, median (95% CI) (months)	11.2 (9.7,13.5)	17.1 (12.7, Not available)	15.9 (13.4, Not available)
Any SSE, n (%)	58 (26)	45 (14)	145 (21)
Treatment-emergent fracture, n (%)	8 (4)	11 (3)	31 (4)
Experienced pathological bone fracture, n (%)	12 (5)	15 (5)	39 (6)

Conclusions: Per SWOG0421 trial, high BMMs in men with mCRPC portends poor prognosis and have improved outcomes with bone targeting agent atrasentan with concomitant decline in BMMs. In the current study, BMMs significantly declined with RA+EZ vs EZ, thus providing the rationale for combining RA with EZ.

Clinical trial identification: NCT02199197.

Legal entity responsible for the study: Neeraj Agarwal.

Funding: Bayer.

Disclosure: All authors have declared no conflicts of interest.

826P Use of bone health agents (BHAs) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 (Ra-223) after abiraterone (Abi): An interim review of REASSURE

C.N. Sternberg[1], B. Tombal[2], K. Miller[3], F. Saad[4], O. Sartor[5], J.P. Sade[6], C. Logothetis[7], J. Bellmunt[8], S. Dizdarevic[9], L.C. Harshman[8], J. Logue[10], S. Baldari[11], T. Richardson[12], D. Bottomley[13], M. Schostak[14], I. Bayh[15], J. Kalinovsky[16], C. Higano[17]

[1]Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy, [2]Dept. of Urology, Cliniques Universitaires St. Luc, Brussels, Belgium, [3]Medical Oncology, Charité Berlin, Berlin, Germany, [4]Urology, Hospital St. Luc du CHUM, Montreal, QC, Canada, [5]Tulane Cancer Center, Tulane Medical School, New Orleans, LA, USA, [6]Dept. of Genitourinary Tumors, Instututo Alexander Fleming, Buenos Aires, Argentina, [7]Medical Oncology, 7MD Anderson Cancer Center, Houston, TX, USA, [8]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [9]Dept. of Imaging and Nuclear Medicine, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK, [10]Medical Oncology, 10The Christie NHS Foundation Trust, Manchester, UK, [11]Nuclear Medicine Unit, University of Messina, Messina, Italy, [12]Medical Oncology, Wichita Urology, Wichita, KS, USA, [13]Dept. of Clinical Oncology, St. James's Institute of Oncology, Leeds, UK, [14]Clinic of Urology, DKG-certified Prostate Cancer Center, University Hospital Magdeburg, Magdeburg, Germany, [15]Bayer AG, SBU Oncology, Pharmaceuticals, Wuppertal, Germany, [16]Medical Oncology, Bayer Consumer Care AG, Basel, Switzerland, [17]Medical Oncology, University of Washington, Seattle, WA, USA

Background: When the Ra-223 phase 3 clinical trial (ALSYMPCA) was conducted, Abi was not available; REASSURE is a prospective, observational clinical study of Ra-223 in pts with mCRPC with a 7-year follow-up (NCT02141438). Pts could have had antihormonal agents, such as Abi, prior to receiving Ra-223. The objective of this interim review was to evaluate the fractures and skeletal-related events (SREs) based on prior Abi and the use of BHAs, denosumab and bisphosphonates.

Methods: Descriptive statistics were generated for baseline characteristics, fractures, SREs and overall survival (OS) by BHA use in pts who had completed Abi treatment prior to receiving Ra-223 (prior Abi) or who had no prior Abi (Abi-naïve). An SRE was defined as any skeletal-related adverse event or any radiotherapy to bone.

Results: As of Nov 2017, 1439 pts were enrolled, with a median follow-up time of 9.1 months. 708 (49%) pts had received BHAs at baseline, and BHAs were given concomitantly with Ra-223 in 553 (38%) pts. 430 (30%) pts received prior Abi, and Ra-223 was given as second line in 37% (157/430) of those pts; 705 (49%) pts were considered Abi-naïve. For the prior Abi group, median time of exposure to Abi was 11 months. In the prior Abi group SREs occurred in 17% and 22% of pts, with and without BHAs, respectively. In the Abi-naïve group, 16% of pts had SREs regardless of BHA use. Fractures were reported in 7/430 pts (1.6%) in the prior Abi group. In the Abi-naïve group fractures were reported in 2/311 (1%) and 8/394 (2%) pts with and without BHAs, respectively (Table).

Conclusions: BHAs were under-utilised in this study despite several guidelines and recommendations. The rate of fracture was the same in those who were Abi-naïve compared with those who received Abi prior to Ra-223. Pts with prior Abi had a shorter OS; these pts received Ra-223 at a later time during their disease course, as reflected by a longer time from CRPC to Ra-223 initiation.

Clinical trial identification: NCT02141438.

Editorial acknowledgement: Medical writing support was provided by Michael Sheldon of Scion, London UK, funded by Bayer.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: C.N. Sternberg: Honoraria or consulting fees: Bayer, Sanofi, Pfizer, Janssen, Astellas, Clovis, Novartis. B. Tombal: Investigator, paid advisor: Bayer, Astellas, Janssen, Sanofi. K. Miller: Honoraria, consultation fees: Amgen, Bayer, BMS, Ferring, Janssen, MSD, Novartis, Pfizer, Roche, Sotio, Takeda, Tolmar. F. Saad: Consultant, research grants: Bayer, Amgen, Astellas, Jansssen, Sanofi, AstraZeneca. O. Sartor: Consultant, investigator: Bayer. J. Bellmunt: Advisory role: Genentech, MSD, Pfizer, GSK, BMS, Pierre-Fabre, Sanofi Aventis, Astellas, OncoGenx, Janssen; Lecture fees: Pfizer, MSD, GSK, Novartis, Pierre-Fabre, Astellas; Research funding: Takeda, Pfizer, Novartis, Sanofi Aventis. S. Dizdarevic: Support, travel expenses, registration costs for occasional conference, advisory role: Bayer. L.C. Harshman: Advisory: Bayer, Genentech, Dendreon, Pfizer, Medivation/Astellas, Kew Group, Theragene, Corvus, Merck, Exelixis, Novartis; Research to institution: Bayer, Sotio, Bristol-Myers Squib, Merck, Takeda, Dendreon/Valient and Janssen. J. Logue: Honoraria: Bayer. T. Richardson: Speaker, peer advisor: Bayer (Xofigo); Speaker: Janssen (Erleada), Astellas (Myrbetriq). D. Bottomley: Honoraria, travel/subsistence grants: Bayer, Janssen, AccelyonBT. M. Schostak: Advisor: Bayer. I. Bayh: Employee, consultant: Fresenius Medical Care; Stocks: Fresenius Medical Care Deutschland GmBH. J. Kalinovsky: Employee: Bayer. C. Higano: Advisory boards: Astellas, Bayer, Blue Earth Diagnostics, Ferring, Janssen, Myriad, Tolmar; Sponsored research: Aragon, Astellas, AstraZeneca, Dendreon, Genentech, Medivation, Emergent, Bayer, Pfizer, Hoffman La Roche: Employment: Spouse employed in leadership position: CTI Biopharma. All other authors have declared no conflicts of interest.

827P Clinical outcome with radium-223 (Ra-223) in patients (pts) previously treated with abiraterone (Abi) or enzalutamide (Enza): A retrospective study of real-world (RW) data from pts with metastatic castration-resistant prostate cancer (mCRPC)

C.S. Higano[1], B. Tombal[2], K. Miller[3], F. Saad[4], O. Sartor[5], K. Tangirala[6], X. Jiao[7], J. Kalinovsky[8], C.N. Sternberg[9]

[1]Division of Oncology, University of Washington, Seattle, WA, USA, [2]Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [3]Urology, Charité Berlin, Berlin, Germany, [4]Urology, University of Montreal Hospital Center, Montreal, QC, Canada, [5]Tulane Cancer Center, Tulane Medical School, New Orleans, LA, USA, [6]Medical Affairs, Bayer US LLC, Pharmaceuticals, Whippany, NJ, USA, [7]RWE Strategy & Outcomes Data Generation, Bayer US LLC, Pharmaceuticals, Whippany, NJ, USA, [8]Medical Oncology, Bayer Consumer Care AG, Basel, Switzerland, [9]Medical Oncology, San Camillo-Forlanini Hospital, Rome, Italy

Background: Ra-223 pivotal phase 3 trial was conducted prior to Abi and Enza becoming available. Here, we analysed registry data to determine clinical outcomes with Ra-223 therapy in pts previously treated with Abi or Enza in a RW setting.

Table: 826P

	Abi-naïve pts (n = 705)		Prior Abi pts (n = 430)		Overall cohort (n = 1439)	
	With BHAs (n = 311)	Without BHAs (n = 394)	With BHAs (n = 216)	Without BHAs (n = 214)	With BHAs (n = 708)	Without BHAs (n = 731)
Time from CRPC to Ra-223 initiation, median months (range)	6 (0–134) 8	10 (0–109)	23 (0–80) 23	23 (0–117)	12 (0–147) 13	13 (0–117)
PSA, median ng/mL (Q1, Q3)	49 (11, 160)	46 (15, 161)	114 (31, 331)	121 (30, 311)	60 (14, 212)	59 (19, 201)
Prior docetaxel,n (%)	95 (31)	106 (27)	122 (57)	120 (56)	273 (39)	269 (37)
Patient outcomes						
≥1 SRE, n (%)	49 (16)	62 (16)	36 (17)	46 (22)	116 (16)	129 (18)
≥1 fracture, n (%)	2 (1)	8 (2)	2 (1)	5 (2)	7 (1)	17 (2)
5–6 Ra-223 injections, n (%)	199 (64)	252 (64)	128 (59)	128 (60)	480 (68)	465 (64)
OS from initiation of Ra-223, median months (95% CI)	15.5 (13.1, 16.6)		11.1 (10.2, 11.8)		14.8 (13.5, 16.0)	

Table: 827P

	Ra-223 pts with prior Abi (n = 187)	Ra-223 pts with prior Enza (n = 164)	All Ra-223 pts (n = 625)
Baseline characteristics			
Age, median (years)	75	75	73
ECOG 0–1, n (%)	84 (45.0)	73 (44.5)	260 (41.6)
ALP (U/L), median	111	113	108
PSA (μg/L), median	67	53	38
LDH (U/L), median	204	207	196
Time from castration resistance to baseline, median (months)	18	16	11
Pts with prior SREs, n (%)	89 (47.6)	87 (53.0)	314 (50.2)
Duration of prior therapy (months)			
Abi, median (range)	5.8 (0.0–46.9)	Not applicable	Not calculated
Enza, median (range)	Not applicable	4.8 (0.0–49.0)	Not calculated
Clinical outcomes with Ra-223 therapy			
Follow-up time, median (months)	7	7	9
Ra-223 doses, median (range)	4 (1–6)	4 (1–6)	4 (1–6)
Pts with SREs, n (%)	39 (21)	33 (20)	168 (27)
Pts with pathological fractures, n (%)	13 (7)	10 (6)	61 (10)
Median time from castration resistance to death (months)	29	26	26
OS, median (95% CI) (months)	10.5 (8.6, 12.3)	9.8 (7.8, 13.2)	15.2 (13.2, 16.3)

Methods: This was a retrospective study of data from the Flatiron prostate cancer registry, providing electronic health records from >245 US cancer clinics. Data were collected from 01/01/2013–30/06/2017. Ra-223-treated mCRPC pts were included; prior to receiving Ra-223, pts completed Abi/Enza/both. Prior Abi and prior Enza groups excluded pts with concomitant/concurrent Abi or Enza. Baseline was defined as the index date at start of Ra-223 therapy. Pts were followed until death or study end. Descriptive analysis was performed for baseline characteristics, prior Abi or Enza therapy, skeletal-related events (SREs) and OS (Kaplan–Meier method).

Results: Among 625 Ra-223-treated pts, 29.9% (n = 187) and 26.2% (n = 164) completed prior Abi or Enza treatment, respectively (Table). At baseline, SREs were documented in 50% (314/625) of pts (48% [89/187] in prior Abi and 53% [87/164] in prior Enza pts). During/following Ra-223 therapy, SREs were reported at a similar rate in prior Abi (21% [39/185]) and prior Enza pts (20% [33/163]). Pathological fractures were reported in 10% (61/623) of pts (7% [13/185] and 6% [10/163] in prior Abi and prior Enza pts, respectively). Median (95% CI) OS was 15.2 (13.2–16.3) months in all pts (10.5 [8.6–12.3] for prior Abi and 9.8 [7.8–13.2] for prior Enza pts).

Conclusions: In this retrospective RW study of 4 yr clinical practice, a high proportion of pts had SREs prior to start of Ra-223. Sequential use of Ra-223 after Abi or Enza does not negatively affect bone-related safety outcomes when compared with the overall cohort. Ra-223 is a feasible treatment option after Abi or Enza.

Editorial acknowledgement: Medical writing support was provided by Samantha Kew, BSc, of Scion, London UK, funded by Bayer.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: C.S. Higano: Advisory boards: Astellas, Bayer, Blue Earth Diagnostics, Ferring, Janssen, Myriad, Tolmar; Sponsored research: Aragon, Astellas, AstraZeneca, Dendreon, Genentech, Medivation, Emergent, Bayer, Pfizer, Hofman Laroche; Employment: Spouse employed in leadership position: CTI Biopharma. B. Tombal: Investigator, paid advisor: Bayer, Astellas, Janssen, Sanofi. K. Miller: Honoraria, consultation fees: Amgen, Bayer, BMS, Ferring, Janssen, MSD, Novartis, Pfizer, Roche, Sotio, Takeda, Tolmar. F. Saad: Consultant, research grants: Bayer, Amgen, Astellas, Jansssen, Sanofi and AstraZeneca. O. Sartor: Consultant, investigator: Bayer. K. TangiralaX. Jiao, J. Kalinovsky: Employee: Bayer Healthcare. C.N. Sternberg: Bayer, Sanofi, Pfizer, Janssen, Astellas, Clovis, AstraZeneca.

828P Symptomatic skeletal event (SSE) dynamics in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 (Ra-223): An interim review of a prospective, non-interventional study (PARABO)

T. Poeppel[1], S. Eschmann[2], A. Werner[3], I. Selkinski[4], M-O. Möllers[5], T. Neußer[6], A. Benson[7], J. Kalinovsky[8], H. Palmedo[9]

[1]Nuclear Medicine, University Hospital Essen, Essen, Germany, [2]Nuclear Medicine, Marienhospital, Stuttgart, Germany, [3]Nuclear Medicine, Radiology Schwetzingen, Schwetzingen, Germany, [4]Nuclear Medicine, Helios Dr. Horst Schmidt Kliniken Wiesbaden, Wiesbaden, Germany, [5]Nuclear Medicine, Prof. Dr. Uhlenbrock & Partner, Dortmund, Germany, [6]Non-Interventional Studies, Bayer Vital GmbH, Leverkusen, Germany, [7]Medical Affairs Statistics and Integrated Analysis, Bayer HealthCare, Whippany, NJ, USA, [8]Medical Oncology, Bayer Consumer Care AG, Basel, Switzerland, [9]Nuclear Medicine, Nuclear Medicine Center for Radiology, Bonn, Germany

Background: Phase III Ra-223 study (ALSYMPCA) was conducted before the availability of abiraterone (Abi). The ongoing PARABO study will investigate the outcome of Ra-223-treated mCRPC pts in real-life clinical practice in Germany (NCT02398526). This analysis aimed to describe the SSE profile in Ra-223-treated pts based on extent of disease (EOD) or prior Abi use.

Methods: PARABO is a prospective, single-arm observational study of 348 pts with mCRPC and bone metastases who initiated Ra-223 treatment. A descriptive analysis was carried out for overall survival (OS) and SSEs (EBRT, symptomatic pathologic fractures, spinal cord compression or surgical intervention) in Ra-223-treated pts who received Abi as part of previous treatment. SSEs were summarised by EOD (0–2: ≤20 metastases; 3–4: >20 metastases/Superscan).

Results: Of 333 Ra-223-treated pts, 165 (50%) had EOD 3–4; 67 (20%) had completed prior Abi (median duration of Abi: 10.8 mo). Median time from castration resistance to Ra-223 treatment: 9.5 mo for all pts, 18.9 mo for prior Abi pts. At baseline, 45/66 (68%) prior Abi pts had EOD 3–4 and 45/67 (67%) had received prior chemotherapy. Bone health agent use at baseline was reported in 22 (33%) prior Abi pts. Median follow-up was 6.4 mo for the overall cohort. Median OS (95% CI): 16.9 (12.6–18.9) mo for all pts, 11.2 (8.1–15.2) mo for prior Abi pts. SSEs occurred in 10% of the overall cohort and 20% of prior Abi pts. Pts with more advanced disease (EOD 3–4) received more EBRT, while pathological fracture rate was ∼3% in all groups.

Table: 828P

SSE, n (%)[a]	All patients N = 333	Prior Abi n = 67	EOD 0–2 (≤20 metastatic lesions) n = 149	EOD 3–4 (>20 metastatic lesions) n = 165
During Ra-223 treatment	8/312 (2.6)	3/57 (5.3)	0/144 (0)	8/151 (5.3)
Follow-up after end of Ra-223 treatment	6/162 (3.7)	2/28 (7.1)	1/84 (1.2)	5/74 (6.8)
During long-term follow-up[b]	21/144 (14.6)	7/30 (23.3)	9/71 (12.7)	12/70 (17.1)
Over the course of the study EBRT Pathological fractures Spinal cord compression Surgical intervention	33/315 (10.5) 24/315 (7.6) 10/315 (3.2) 8/315 (2.5) 6/315 (1.9)	12/59 (20.3) 9/59 (15.3) 2/59 (3.4) 2/59 (3.4) 1/59 (1.7)	10/145 (6.9) 5/145 (3.4) 5/145 (3.4) 3/145 (2.1) 4/145 (2.8)	23/153 (15.0) 19/153 (12.4) 5/153 (3.3) 5/153 (3.3) 2/153 (1.3)

[a]Percentages calculated based on number of pts for whom documentation was available within the specified time period.
[b]>30 days after treatment completion.

Conclusions: Pts previously treated with Abi received Ra-223 18.9 mo after CRPC diagnosis, had generally received prior chemotherapy and had higher tumour burden, resulting in 11.2 mo median OS. Pts with higher tumour burden or prior Abi had more SSEs, mainly related to EBRT use; frequency of fractures was low and similar across groups.

Clinical trial identification: NCT02398526.

Editorial acknowledgement: Medical writing support was provided by Risha Bulusu, MSc, of Scion, London UK.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: T. Neußer: Employee: Bayer Healthcare; Holds stocks: Bayer. J. Kalinovsky: Employee: Bayer Healthcare. All other authors have declared no conflicts of interest.

829P Pain and quality of life in metastasized Castration Resistant Prostate Cancer patients treated with Radium-223 (ROTOR registry): A prospective observational registry in a non-study population

R. Louhanepessy[1], S. Badrising[2], V. Vd Noort[3], J.L. Coenen[4], A. Oostdijk[5], P. Hamberg[6], J.M. Zuetenhorst[6], A. Beeker[7], N. Wagenaar[8], M. Lam[9], F. Celik[10], E. Vegt[11], W. Zwart[12], A. Bergman[12]

[1]Medical Oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, [2]Pulmonary Diseases, Radboud University Medical Center, Nijmegen, Netherlands, [3]Biometrics, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, Netherlands, [4]Medical Oncology, Isala Klinieken, Zwolle, Netherlands, [5]Nuclear Medicine, Isala Klinieken, Zwolle, Netherlands, [6]Medical Oncology, St Franciscus Gasthuis, Rotterdam, Netherlands, [7]Internal Medicine, Spaarne Ziekenhuis, Hoofddorp, Netherlands, [8]Nuclear Medicine, Ziekenhuisgroep Twente, Hengelo, Netherlands, [9]Nuclear Medicine, University Medical Center Utrecht, Utrecht, Netherlands, [10]Nuclear Medicine, Deventer Ziekenhuis, Deventer, Netherlands, [11]Nuclear Medicine, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, Netherlands, [12]Division of Internal Medicine (MOD) and Oncogenomics, Division of Internal Medicine (MOD) and Oncogenomics, Amsterdam, Netherlands

Background: In the ALSYMPCA study a survival benefit of Radium-223 (Ra-223) treated metastasized Castration Resistant Prostate Cancer (mCRPC) patients with bone disease was established. However, the effect of Ra-223 treatment on pain and Quality of Life (QoL) was not explored. 200 mCRPC patients treated with Ra-223 in 20 Dutch hospitals were included in the prospective ROTOR registry.

Methods: QoL (FACT-P) and pain (BPI-S) were recorded at Base-Line (BL) and at every Ra-223 cycle. Patients with complete questionnaires at BL and at least one on treatment were included in the analysis. Patients with a BPI-S Pain At Its Worst (PAIW) of ≥ 4 were considered symptomatic. A decrease of FACT-P and BPI-S PAIW of ≥ 6 points and ≥2 points, respectively, were considered clinically meaningfull.

Results: Currently, data is collected from 244 patients. In 101 (41%) patients QoL and pain could be evaluated. Mean age was 72.9 (range 47.8-89.8) years, 85 (83%) had ≥6 bone metastases, an average of 4.8 (CI 4.6-5.1) cycles were administered and 51 (50%) were treated with 6 cycles. The mean total FACT-P in was 70.6 (CI 68.4-72.8). The lowest FACT-P score was at cycle 3 (67.6; CI65.0-70.1) and was 67.0 (CI 66.3-73.6) at cycle 6, which were 3.0 and 3.6 points lower than BL, respectively. The mean total BPI-S score was 43.5 (CI 38.9-48.0) at baseline. Asymptomatic patients (57; 56%) had a PAIW score of 2.1 (CI 1.8-2.5) and a mean total score of 31.0 (CI 25.9-36.0) at base line. The lowest PAIW score was at cycle 5 (1.7; CI 1.1-2.2) and mean total score of 23.4 (CI 16.2-30.6). Symptomatic patients (54; 53%) had a PAIW of 6.9 (CI 6.5-7.2) and a mean total score of 56.0 (CI 51.0-60.9). The lowest PAIW score was at cycle 2 (6.1; CI 5.6-6.6) and mean total score of 53.2 (CI 44.9-59.4) which were 0.8 and 2.8 points lower than base line, respectively. Patients treated with 6 cycles of Ra-223 had a PAIW of 7.1 (CI 6.1-8.2) and a mean score of 56.1 (CI 35.5-67.7).

Conclusions: QoL and pain remained stable during Ra-223 treatment. The lack of pain response might be related to opiate use, which will be analyzed.

Clinical trial identification: NCT03223727.

Legal entity responsible for the study: Netherlands Cancer Institute-Antoni van Leeuwenhoek hospital.

Funding: Bayer.

Disclosure: A. Bergman: Grants: Bayer BV. All other authors have declared no conflicts of interest.

830P Synthetic DNA immunotherapy in biochemically relapsed prostate cancer

N. Shore[1], E.I. Heath[2], L.T. Nordquist[3], H. Cheng[4], K. Bhatt[5], M. Morrow[6], T. McMullan[7], K. Kraynyak[6], J. Lee[8], B. Sacchetta[8], L. Liu[6], S. Rosencranz[8], S.T. Tagawa[9], L.J. Appleman[10], R. Tutrone[11], J. Garcia[12], Y. Whang[13], W. Kelly[14], I. Csiki[8], M.L. Bagarazzi[8]

[1]Urology, Carolina Urologic Research Center, Myrtle Beach, SC, USA, [2]Oncology, Karmanos Cancer Center, Detroit, MI, USA, [3]Medical Oncology, Urology Cancer Center and GU Research Network, Omaha, NE, USA, [4]Medical Oncology, University of Washington School of Medicine, Seattle, WA, USA, [5]Clinical, Inovio Pharmaceuticals Inc, Plymouth Meeting, PA, USA, [6]Immunology, Inovio Pharmaceuticals, Inc., Plymouth Meeting, PA, USA, [7]Biostatistics, Inovio Pharmaceuticals, Inc., Plymouth Meeting, PA, USA, [8]Clinical, Inovio Pharmaceuticals, Inc., Plymouth Meeting, PA, USA, [9]Medical Oncology, Weill Cornell Medical College, New York, NY, USA, [10]Medical Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA, [11]Medical Oncology, Chesapeake Urology Associates, Towson, MD, USA, [12]Medical Oncology, Cleveland Clinic, Cleveland, OH, USA, [13]Medical Oncology, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA, [14]Medicine, Thomas Jefferson University, Philadelphia, PA, USA

Background: INO-5150 (PSA and PSMA) +/- INO-9012 (IL-12), a synthetic DNA immunotherapy, was assessed for safety, immunogenicity and efficacy in biochemically recurrent prostate cancer patients (pts).

Methods: Phase I, open-label, multi-center study in the US included pts with rising PSA after surgery and/or RT, PSA doubling time (PSADT) >3 months (mos), testosterone >150 ng/dL and no concurrent ADT. Safety, immunogenicity and efficacy (PSA kinetics, PFS) were evaluated in 4 treatment arms of 15 pts each. Arms A: 2mg INO-5150, B: 8.5 mg INO-5150, C: 2mg INO-5150 + 1mg INO-9012 and D: 8.5mg INO-5150 + 1mg INO-9012. Pts received 4 IM doses of vaccine followed by electroporation on day 0, wks 3, 12 and 24 and were followed for 72 wks.

Results: 50/61 (82%) pts completed all visits and treatments were well tolerated with no safety concerns. Median PFS for overall population [N = 61, baseline (D0) PSADT range (mos) 1.5-217.1, median 9.8] and for a subset of pts with D0 PSADT ≤12mos (N = 36) has not yet been reached (FU 3-19 mos). 86% of pts with D0 PSADT ≤12 mos were progression free through 19mos FU. 27 out of 36 (75%) pts with D0 PSADT≤ 12 mos had disease stabilization at wks 27 evidenced by significant improvement in log_2PSA change over time (slope) and PSADT from D0 (Slope=0.19 declined to 0.1, PSADT=5.3 improved to 10.1 mos, p = <0.0001). This effect was maintained at wk 72 (Slope=0.09, PSADT=10.6, p = <0.0001). Immunogenicity was observed in 77% (47/61) of pts by multiple immunologic assessments. Patient immunogenicity to INO-5150 as determined by CD38 and Perforin + CD8 T cell immune reactivity correlated with attenuated % PSA rise compared to pts without reactivity (p = 0.05, n = 50).

Conclusions: INO-5150 +/- INO-9012 was safe, well tolerated and immunogenic. Clinical efficacy was observed in the patients with D0 PSADT≤ 12 mos as evidenced by a significant dampening of log_2PSA change over time and increased PSADT up to 72 weeks FU. Additional genomic analyses are ongoing to further elucidate the correlation of immunologic efficacy and clinical benefit. (NCT02514213).

Clinical trial identification: FDA IND number 15870.

Legal entity responsible for the study: Inovio Pharmaceuticals, Inc.

Funding: Inovio Pharmaceuticals, Inc.

Disclosure: N. Shore: Consulting or advisory role for multiple pharmaceutical companies. E.I. Heath: Consulting or advisory role and honoraria or funding received for multiple pharmaceutical companies. H. Cheng, Y. Whang: Funding received from multiple pharmaceutical companies. K. Bhatt, M. Morrow, T. McMullan, K. Kraynyak, J. Lee, B. Sacchetta, L. Liu, S. Rosencranz, I. Csiki, M.L. Bagarazzi: Employee of the pharmaceutical company sponsoring this research trial. S.T. Tagawa, R. Tutrone, J. Garcia, W. Kelly: Consulting or advisory role and funding received from multiple pharmaceutical companies. All other authors have declared no conflicts of interest.

831P Clinical experience with 100 consecutive patients treated with Lu-177-labeled PSMA-I&T radioligand therapy for metastatic castration-resistant prostate cancer: Final analysis

R.L. Tauber[1], K. Knorr[2], S. Schwaiger[1], M. Retz[1], T. Maurer[1], C. D'Alessandria[2], H-J. Wester[3], J. Gschwend[1], W. Weber[2], M. Schwaiger[2], M.M. Heck[1], M. Eiber[2]

[1]Urology, Klinikum rechts der Isar TUM, Muenchen, Germany, [2]Nuclear Medicine, Klinikum rechts der Isar TUM, Muenchen, Germany, [3]Institute of Pharmaceutical Radiochemistry, Technical University Munich, Munich, Germany

Background: Final analysis of our experience with ^{177}Lutetium-labeled prostate-specific membrane antigen-ligand (^{177}Lu-PSMA-I&T) for systemic radioligand therapy in 100 consecutive patients with metastatic castration-resistant prostate cancer (mCRPC).

Methods: Patients were treated under a review board-approved compassionate use protocol. Eligibility criteria for ^{177}Lu-PSMA-I&T therapy included previous treatment with abiraterone or enzalutamide, taxane-based chemotherapy or unsuitability for taxanes as well as positive ^{68}Ga-PSMA tracer uptake of metastases in a prior PET-scan. Intravenous treatment with ^{177}Lu-PSMA-I&T was given 6- to 8-weekly with an activity of 7.4GBq up to 6 cycles in patients without clinical or radiographic progression. We report prostate-specific antigen (PSA) decline, clinical progression-free survival (cPFS), overall survival (OS), subgroupanalysis and toxicity.

Results: Median age was 72 years (range 46-85) and median PSA level was 165 ng/ml (range 0-6178). Bone, lymph node and visceral metastases were present in 96%, 87% and 35% of patients. The median number of previous treatment regimens for mCRPC was 3 (range 1-6) and 82% of patients were pretreated with chemotherapy. At the time of evaluation, 319 cycles with ^{177}Lu-PSMA-I&T were applied (median 2 cycles per patient, range 1-6). No treatment was ongoing. 4 and 6 cycles were applied in 44 and 20 patients. PSA decline $\geq$30%, $\geq$50% and $\geq$90% was achieved in 47%, 38% and 11% of patients. Median cPFS was 4.1 months (95%CI 2.5-5.7) and median OS was 12.9 months (95%CI 9.9-15.9). In the subgroupanalysis visceral metastases were associated with a worse prognosis concerning PSA decline >50% (26 vs. 44%, p = 0.06), median cPFS (3.1 vs. 5.9 months, p < 0.01) and median OS (8.0 vs. 14.0%, p = <0,05). Treatment-emergent hematologic grade 3/4 toxicities were anemia (9%), thrombocytopenia (4%) and neutropenia (6%). Grade 3/4-non-hematologic toxicities were not observed. The main non-hematologic grade 1/2 toxicities were dry mouth (24%), fatigue (20%) and loss of appetite (10%).

Conclusions: Radioligand therapy with ^{177}Lu-PSMA I&T appears to be safe and active in late-stage mCRPC.

Legal entity responsible for the study: Klinikum rechts der Isar, Technical University Munich.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

832P Association between patient reported quality of life (QOL) and survival: Analysis of E3805 chemohormonal androgen ablation randomized trial in prostate cancer

A.K. Morgans[1], Y-H. Chen[2], D. Jerrard[3], M.A. Carducci[4], R. Dipaola[5], L. Wagner[6], D. Cella[7], C. Sweeney[8]

[1]Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [2]Biostatistics, ECOG, Boston, MA, USA, [3]Urology, University of Wisconsin, Madison, WI, USA, [4]Oncology, Johns Hopkins University, Baltimore, MD, USA, [5]Medicine, University of Kentucky, Lexington, KY, USA, [6]Social Sciences & Health Policy, Wake Forest University School of Medicine, Winston-Salem, NC, USA, [7]Medical Social Sciences, Northwestern University, Chicago, IL, USA, [8]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Chemohormonal therapy (docetaxel and androgen deprivation (ADT+D)) for metastatic hormone sensitive prostate cancer (mHSPC) prolongs overall survival (OS) versus ADT alone. We assessed the association between QOL and OS in men with mHSPC treated with ADT+D vs ADT.

Methods: Men were randomized to ADT+D (6 cycles) or ADT. QOL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P), FACIT-Fatigue, and Brief Pain Inventory (BPI). Logrank test and Cox proportional hazards models were used to evaluate the association between QOL and OS.

Results: 790 men were randomized (ADT+D, N = 397, and ADT, N = 393). OS was significantly poorer for ADT patients with baseline FACT-P $\leq$ median than > median (p = 0.03), but not for ADT+D patients (p = 0.34). FACT-P at 3 months was associated with OS for ADT patients (median OS lowest vs highest quartile 26.5 vs 44.1 mo, p = 0.003), but not ADT+D (median OS lowest vs highest quartile 46.1 vs 48.4 mo, p = 0.98 and Table). Change in QOL from baseline to 12 months in the patients with most improvement and most decline was associated with OS (median OS in best vs worst 25% in ADT 36.1 vs 23.7 mo, p = 0.048; median OS in best vs worst 25% in ADT+D NR vs 37.1 mo, p = 0.006). Baseline fatigue, but not baseline pain, was associated with OS after adjusting for multiple prognostic factors (BPI (p = 0.86); FACIT-Fatigue 3-unit increase HR = 0.95, p = 0.006).

Table: 832P Association between 3-month FACT-P and OS (worst 25% and best 25% of patients)

Treatment	HR (worst 25% vs best 25%)[1]	95% CI
ADT+D	0.70	0.37-1.34
ADT	2.51	1.37-4.58

1. Adjusted for treatment arm, disease volume, ECOG PS, Gleason, prior local therapy and BMI, and stratification factors at randomization.

Conclusions: In men with mHSPC, baseline and 3 month poor QOL are associated with OS in ADT patients but not ADT+D. The latter may be due to positive treatment effect from docetaxel in pts with poor baseline QOL. There was no association between chemotherapy induced poor QOL and OS.

Clinical trial identification: NCT00309985.

Legal entity responsible for the study: ECOG- ACRIN.

Funding: Has not received any funding.

Disclosure: A.K. Morgans: Honoaria: Sanofi, Janssen, AstraZeneca, Genentech. C. Sweeney: Consultant: Genentech/Roche, Sanofi, Janssen, Pfizer, Astellas, Bayer, Tomar, Leuchemix. Research: Sanofi, Janssen, Pfizer, Astellas, Bayer. All other authors have declared no conflicts of interest.

833P AZD8186, a potent and selective inhibitor of PI3Kβ/δ, as monotherapy and in combination with abiraterone acetate plus prednisone (AAP), in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC)

J.S. de Bono[1], A. Hansen[2], A.D. Choudhury[3], N. Cook[4], E.I. Heath[5], C. Higano[6], M. Linch[7], J. Martin-Liberal[8], D.E. Rathkopf[9], K.B. Wisinski[10], S. Barry[11], E. de Bruin[11], W. Brugger[11], S. Colebrook[11], T. Klinowska[11], M. Moschetta[11], P.G.S. Mortimer[11], L.L. Siu[2], G. Shapiro[3]

[1]The Institute of Cancer Research and Royal Marsden, London, UK, [2]Division of Medical Oncology & Hematology, Princess Margaret Cancer Centre, University Health Network and Department of Medicine, University of Toronto, Toronto, ON, Canada, [3]Early Drug Development Center, Dana-Farber Cancer Institute, Boston, MA, USA, [4]The Christie NHS Foundation Trust, Manchester, Cambridgeshire, UK, [5]Karmanos Cancer Institute, Department of Oncology, Wayne State University School of Medicine, Detroit, MI, USA, [6]Department of Medical Oncology, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [7]University College London (UCL) Cancer Institute and UCL Hospital, London, UK, [8]Medical Oncology Department, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain, [9]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA, [10]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI, USA, [11]Oncology IMED Biotech Unit, AstraZeneca, Cambridge, UK

Background: The PI3K pathway plays an important role in cell growth and survival of *PTEN*-null tumours. An ongoing phase 1/2 study (NCT01884285) previously reported that AZD8186, a potent and selective inhibitor of PI3Kβ (minimal PI3Kδ activity), can be well tolerated in pts with solid tumours; here we present preliminary data in heavily pretreated mCRPC.

Methods: Pts with mCRPC received escalating doses of AZD8186 (5 days on, 2 days off; 2 days on, 5 days off; or continuous schedules) as monotherapy (study Part A) or in combination with AAP (1000 mg qd + prednisone 10 mg qd, study Part C1) until progressive disease (PD) or dose-limiting toxicities. Analyses included tolerability, RECIST tumour response, prostate-specific antigen response, circulating tumour cell counts and cell-free DNA.

Results: Fifty-two pts with mCRPC were treated with AZD8186 as monotherapy (n = 39) or in combination with AAP (n = 13). Prior treatment status: AAP (n = 14), enzalutamide (enza, n = 10), both (n = 21) or AAP/enza-naive (n = 7). Diarrhoea (39%) and nausea (27%) were the most frequently reported adverse events (AEs, all grades) related to AZD8186. Grade 3 AEs of interest included diarrhoea/colitis (10%), which was fully reversible with dose interruption/SoC treatment, and rash (7%). Two (4%) pts had grade 4 AEs (thrombocytopenia, hypokalaemia); no grade 5 AEs. AZD8186 did not appear to alter tolerability of AAP. Among pts with RECIST measurable disease, one had a confirmed partial response (Part C1), 10 had stable disease, nine had PD. Nine (17%) pts had reduction in PSA >30%. Twelve pts completed >16 weeks of treatment, five pts >24 weeks (PTEN-proficient [n = 0], PTEN-deficient [n = 3], PTEN-unknown [n = 2]). Recruitment of pts with PTEN-deficient mCRPC into an expansion phase in combination with AAP is ongoing.

Conclusions: Data from this phase 1/2 study indicates that the tolerability of AZD8186 supports combination treatment with AAP in pts with metastatic prostate cancer. Preliminary evidence of antitumour activity has been observed. Updated results will be presented.

Clinical trial identification: NCT01884285.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Tyrone Daniel from Bioscript Medical (Macclesfield, UK) and funded by AstraZeneca.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: J.S. de Bono: Advisory board member: AZ, GSK, Merck Serono, MSD, Sanofi Aventis, Taiho, Genentech-Roche, Seattle Genetics, Bayer, Endocyte, Shattuck, Harpoon, Pfizer Oncology, Janssen, Menarini, Daiichi; Research support: GSK, Sanofi, Genentech, Daiichi, Taiho, Merck Serono, MSD, Bayer, AZ. A. Hansen: Research support: Genentech/Roche, Merck, GlaxoSmithKline, Bristol Myers Squibb, Novartis, Boston Biomedical, Boehringer-Ingelheim, Karyopharm. A.D. Choudhury: Honoraria: Bayer, Astellas, Janssen. C. Higano: Advisory boards and/or steering committees: Astellas, Bayer, Blue Earth Diagnostics, Clovis Oncology, Ferring, Janssen, Myriad, and Tolmar; Institutional research funding: Aptevo, Aragon, Astellas, AstraZeneca, Bayer, Hoffman LaRoche, Janssen, Medivation, Pfizer; Spouse is a co-founder of, and has a leadership role at, CTI Biopharma. D.E. Rathkopf: Advisory/consulting fees: Janssen; Research funding for institution: AstraZeneca, Astellas Pharma, Celgene, Genentech, Janssen, Medivation, Millenium, Novartis, Pfizer, Roche, Taiho, Tracon. K.B. Wisinski: Advisory board: AstraZeneca. S. Barry, E. de Bruin, W. Brugger, S. Colebrook, T. Klinowska, P.G.S. Mortimer: Employment and stock ownership: AstraZeneca. M. Moschetta: Employee: AstraZeneca. L.L. Siu: Honoraria: AstraZeneca/MedImmune. G. Shapiro: Consulting/advisory relationship: Eli Lilly, Pfizer, G1 Therapeutics, Merck/EMD Serono, Roche, Almac; Research funding: Lilly, Pfizer, Merck/EMD Serono. All other authors have declared no conflicts of interest.

834P Interim results of a phase Ib study of niraparib plus androgen receptor-targeted therapy in men with metastatic castration-resistant prostate cancer

F. Saad[1], K.N. Chi[2], N. Shore[3], J.N. Graff[4], E.M. Posadas[5], S. Freeman[6], J. Tryon[7], G.C. Trudel[6], J. de Jong[8], J. Meltzer[9], X. Zhao[10], N. Tran[6], A. Rezazadeh[11]

[1]Urology, Centre Hospitalier de l'Universite de Montréal, Montreal, QC, Canada, [2]Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, [3]Urology, Carolina Urologic Research Center, Myrtle Beach, SC, USA, [4]Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA, [5]Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [6]Clinical Oncology, Janssen R&D, Los Angeles, CA, USA, [7]Clinical Oncology, Janssen R&D, Raritan, NJ, USA, [8]Clinical Pharmacology, Janssen R&D, San Diego, CA, USA, [9]Clinical Biostatistics, Janssen R&D, Raritan, NJ, USA, [10]Clinical Biostatistics, Janssen R&D, San Francisco, CA, USA, [11]Norton Cancer Institute, Norton Healthcare, Louisville, KY, USA

Background: Niraparib is a potent inhibitor of poly (ADP-ribose) polymerase (PARP)-1 and PARP-2, enzymes involved in DNA repair. PARP-1 is involved in modulating androgen receptor (AR) signaling and function. A phase 1b study (Bedivere) of niraparib + AR-targeted therapy (ART), which combines 1000 mg abiraterone acetate and 10 mg prednisone (AA-P), in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) who failed $\geq$1 line of chemotherapy and ART is ongoing.

Methods: The objectives of this multicenter, open-label study were to establish the recommended phase 2 dose (RP2D) of niraparib and to evaluate the safety and pharmacokinetics (PK) of niraparib + ART. A standard 3 + 3 design was used in part 1, followed by niraparib dose expansion in part 2 with the RP2D of niraparib + AA-P. Pts received niraparib 200 or 300 mg once daily + AA-P. Dose-limiting toxicities (DLTs) were evaluated during the first cycle (28 days).

Results: At data cutoff, 16 pts were treated; 12 at 200 mg and 4 at 300 mg niraparib + AA-P. Median age was 62 years (49–81), median PSA was 70.0 ng/mL (2.7–766.9) and median treatment duration was 3.0 months (0.4–6.6). Most pts (11/16) are still on treatment. No DLT was observed with niraparib 200 mg + AA-P. Two pts had grade 4 neutropenia with niraparib 300 mg + AA-P. Niraparib 200 mg + AA-P is selected as the RP2D to be evaluated in part 2. Preliminary PK data (n = 6) suggest the absence of significant interaction between niraparib and AA-P; systemic exposure of the 2 drugs was comparable to that observed with respective monotherapies. At the RP2D (200 mg + AA-P), most common adverse events (AEs) were nausea (5/12, 41.7%), constipation, vomiting, fatigue and back pain (4/12, 33.3% each); serious AEs (SAEs) included nausea and vomiting (1/12, 8.3% each). In the 200 mg cohort, 10 pts (83.3%) had AEs; 1 pt (8.3%) had an SAE. AEs leading to dose interruption/reduction occurred in 3 pts (25%); 2 pts (16.7%) discontinued treatment due to AEs.

Conclusions: Data to date from the Bedivere study support safety and tolerability of a combination of niraparib 200 mg + AA-P in pts with mCRPC. A future phase 3 clinical study will be needed to assess the clinical benefit of the combination in mCRPC pts with DNA repair gene defects.

Clinical trial identification: NCT02924766 First posted: October 5, 2016.

Editorial acknowledgement: Medical writing assistance was provided by Tracy T. Cao, PhD of Janssen Global Services, LLC and was funded by Janssen Global Services, LLC.

Legal entity responsible for the study: Janssen Research & Development.

Funding: Janssen Research & Development.

Disclosure: F. Saad: Honoraria: Astellas, AstraZeneca, Bayer, Janssen, Sanofi; Consulting or advisory role: Astellas, AstraZeneca, Bayer, Janssen, Sanofi; Research funding: Janssen, Astellas, Sanofi, Bayer, AstraZeneca, Bristol-Myers Squibb. K.N. Chi: Honoraria, consulting, advisory role, research funding: Janssen. N. Shore: Research funding: AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Clovis, Dendreon, Ferring, GHI, Innocrin, Inovio, Invitae, Merck, Myriad, Janssen, Pfizer, Sanofi-Genzyme; Consulting, advisory role: AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Clovis, Dendreon, Ferring, GHI, Innocrin, Inovio, Invitae, Merck, Myriad, Janssen, Pfizer, Sanofi-Genzyme. J.N. Graff: Honoraria, travel, accommodations, expenses: Janssen, Astellas, Sanofi, Bayer; Research funding: Janssen, Astellas, Merck, Sanofi. E.M. Posadas: Consulting, advisory role: Genentech; Speakers' bureau: Bayer; Research funding: Pfizer; Travel, accommodations, expenses: Tracon. S. Freeman: Consulting: Janssen. J. Tryon, J. de Jong, X. Zhao, N. Tran: Employee: Janssen; Stock: Johnson & Johnson. G.C. Trudel: Employee: Janssen; Stock: Johnson & Johnson. J. Meltzer: Employee, contractor: Janssen; Stock: Johnson & Johnson. A. Rezazadeh: Consulting, advisory role: AstraZeneca, Exelixis, Novartis, Pfizer; Speakers' bureau: Janssen, Astellas, Exelixis, Genentech, AstraZeneca, Bristol-Myers Squibb, Novartis, Amgen, Pfizer, Sanofi; Research funding: Janssen, Medivation, Exelixis, Genentech, AstraZeneca, Bristol-Myers Squibb, Bayer, Macrogenics, Eisai, Bioclin, Clovis; Travel, accommodations, expenses: Janssen, Astellas, Exelixis, Genentech, AstraZeneca, Bristol-Myers Squibb, Novarits, Amgen, Pfizer, Sanofi.

835P CYP11A1 inhibition as a therapeutic approach for the treatment of castration resistant prostate cancer

R. Oksala, K. Räsänen, M. Karimaa, R. Riikonen, M. Ramela, P. Vehmaan-Kreula, O. Simola, P. Rummakko, G. Wohlfahrt, M. Mustonen

Orion Corporation, Orion Pharma, Espoo, Finland

Background: Prostate cancer is a major global challenge due to the increasing number of aging population and frequency of diagnosis. During the past decade new treatments have been targeted to the androgen signaling axis either by inhibiting the binding of androgens to androgen receptor (AR) and AR nuclear translocation, or by inhibiting androgen production via CYP17A1 enzyme. Despite the significant progress on the research and new therapies, CRPC is still incurable and there is urgent need for better, more effective treatments. ODM-208 is an oral, non-steroidal and selective inhibitor of CYP11A1 enzyme, suppressing the synthesis of all steroid hormones that could be potential AR ligands.

Methods: The inhibition of CYP11A1 was measured in vitro by the formation of radiolabelled isocapronic acid in a human adrenal cortex cell line (H295R). The tumor growth inhibition of ODM-208 was studied in VCaP CRPC xenograft model. Full length AR (AR-FL) and AR-V7 were analysed from the tumors by western blot and also key enzymes of androgen biosynthesis, CYP17A1, AKR1C3, SRD5A1 were quantified by qPCR. At the end of the xenograft study, plasma ACTH and LH, and key steroid hormone concentrations were analysed from plasma and target tissues.

Results: ODM-208 potently inhibits CYP11A1 enzyme in vitro. In addition, in vivo in the VCaP CRPC xenograft model ODM-208 significantly inhibited tumor growth. Importantly, the amount of AR-FL and AR-V7 levels remained unchanged in the tumors after ODM-208 treatment. Slight increase of CYP17A1 and SRD5A1 enzyme levels was observed, indicating the activation of steroidogenesis in VCaP tumors in vivo. Treatment had no effect on plasma LH, whereas ACTH was significantly increased demonstrating reduction in glucocorticoid levels by negative feedback. In line with ACTH, all measured steroid hormones were significantly reduced both in plasma and target tissues.

Conclusions: ODM-208 shows promising antitumor activity in preclinical CRPC models and has favorable toxicological profile. Thus, ODM-208 might have potential for treating patients with CRPC. Based on the nonclinical results, a phase 1/2 clinical trial (NTC03436485) has been initiated.

Legal entity responsible for the study: Orion Corporation, Orion Pharma.

Funding: Orion Corporation, Orion Pharma.

Disclosure: R. Oksala, K. Räsänen, M. Karimaa, R. Riikonen, M. Ramela, P. Vehmaan-Kreula, O. Simola, P. Rummakko, G. Wohlfahrt, M. Mustonen: Employee: Orion Corporation.

836P Use of nuclear-localized androgen receptor splice variant 7 protein in CTCs after 1st androgen receptor signaling inhibitor (ARSi) as a predictive biomarker for overall survival on a second ARSi or taxane chemotherapy in metastatic castration-resistant prostate cancer (mCRPC)

H.I. Scher[1], R.P. Graf[2], M. Hulling[1], E. Carbone[1], R. Dittamore[2]

[1]Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]Translational Research, Epic Sciences, Inc., San Diego, CA, USA

Background: In the U.S., most mCRPC patients will receive an ARSi (abiraterone, enzalutamide) in 1st line. More than 60% will receive a second, sequential ARSi (A-A) as opposed to ARSi then Taxane (A-T). No randomized studies exist comparing A-A and A-T. Recent real-world cohort risk-adjusted analyses were not able to discern differences in overall survival (OS) between A-A and A-T, despite a wide range of observed outcomes within groups. Using a cross-sectional cohort of standard of care in a tertiary center, we sought to determine if observations were consistent with community, and evaluate if nuclear AR-V7 could have additive effect on OS, specifically post-ARSi failure.

Methods: We previously reported utility of nuclear AR-V7 in two cross-sectional cohorts (Scher et al 2016 and Scher et al 2018). Blood was drawn from mCRPC patients prior to new line of therapy, AR-V7 testing by Epic Sciences, and therapy choice by physician without knowledge of AR-V7 status. OS data was updated, and a subset of

these combined cohorts were analyzed (n = 148): those who had failed an ARSi, and were about to go onto a second ARSi (n = 73) or taxane (n = 75). A risk score was used to adjust for underlying patient imbalances and therapy choice propensity.

Results: 75 of 148 (51%) received A-T and 73 of 148 (49%) received A-A. Adjusting for patient risk, a discernable difference in OS was not detected (HR: 1.16, CI: 0.73 – 1.85, p = 0.52). Incorporating AR-V7, there was a significant interaction between positivity for AR-V7 and OS on taxanes (HR: 0.16, CI: 0.052 – 0.52, p = 0.0020). In risk-matched analysis, there was a significant difference in OS between AR-V7(+) patients on taxanes vs. ARSi (11.6mo vs. 5.5mo, p = 0.0029).

Conclusions: Sequential ARSi use in the U.S. is common. Adjusting for patient risk and physician therapy choice, AR-V7 use after ARSi failure identifies patients who would live longer on taxanes vs. ARSi. Physician intuition alone was not sufficient to achieve predictive effect of AR-V7.

Legal entity responsible for the study: MSKCC.

Funding: NIH/NCI P50-CA92629 SPORE in Prostate Cancer, NIH/NCI Cancer Center Support Grant P30-CA008748, NIH grant R01-CA207220, Department of Defense Prostate Cancer Research Program (PC121111 and PC131984), Prostate Cancer Foundation Challenge Award, and David H. Koch Fund for Prostate Cancer Research.

Disclosure: H.I. Scher: Consultant: Sanofi, Clovis, Janssen, Pfizer; Grant/research support to MSK: Innocrin, Janssen; Board of directors: Asterias Biotheraputics; Advisory board: WCG Oncology. R.P. Graf: Employee of Epic Sciences, Inc. R. Dittamore: Employee: Epic Sciences. All other authors have declared no conflicts of interest.

837P Prediction of prostate cancer gleason score upgrading from biopsy to radical prostatectomy (RP) using a validated 17-gene panel assay

J. Cullen[1], H.J. Lawrence[2], Y. Chen[1], R. Lu[2], S. Srivastava[1], I. Rosner[1], T. Brand[1], I. Sesterhenn[1]

[1]Surgery, Center for Prostate Disease Research, USUHS, Rockville, NY, USA, [2]Urology, Genomic Health, Redwood City, CA, USA

Background: We have previously shown that a 17-gene, biopsy-based RT-PCR assay (Oncotype Dx® Genomic Prostate Score™, GPS™) is a strong independent predictor of 1) adverse pathology (defined as surgical GS > 4 + 3 and/or non-organ confined disease) at radical prostatectomy (RP), and 2) biochemical recurrence after RP in men with biopsy GS 6 and 7 prostate cancer. We performed a more refined analysis of the association between GPS and upgrading from biopsy to surgery.

Methods: Patients in a prior clinical validation study of the GPS assay were assigned a biopsy Gleason sum (BxG) and pathologic ISUP 2014 surgical Gleason grade (pGS) by a single uropathologist (IS) in a blinded fashion. We performed logistic regression analyses to model the association of GPS with Gleason upgrading (GU) defined as (i) Any downgrade, (ii) Any increase in GS, (iii) BxG 6 to pGS 3 + 4, (iv) BxG 6 to pGS 4 + 3, and (v) BxG 7 to pGS 8-10, all versus no change in GS. GPS values, as determined from diagnostic biopsy tissue, are reported on a scale of 0-100, and predictions of GU were modeled in 20-unit GPS increments.

Results: Among 395 patients, median patient age at RP and GPS score was 62 years and 30.3, respectively. There were 249 patients (63%) who had no change in GS from biopsy to surgery, 45 patients (11%) were down-graded (BxG 7 to pGS 6) and 101 patients (31%) were upgraded (85 BxG 6 to pGS3 + 4, 10 BxG 6 to pGS 4 + 3, and 6 BxG 7 to pGS 8-9). GPS was a significant predictor of any GS upgrade, BxG 6 to pGS 3 + 4, and BxG 7 to pGS 8-9 (see Table).

Table: 837P

BxG vs pGS	OR/ per 20 units in GPS	95% CI of OR		P value
Any GS Downgrade	1.00	0.58	1.74	0.978
Any GS upgrade	1.77	1.20	2.60	0.004
bGS6 to pGS3 + 4	1.61	1.06	2.41	0.027
bGS6 to pGS 4 + 3	2.46	0.90	6.73	0.079
bGS 7 to pGS 8-9	4.49	1.32	15.533	0.017

Referent in all models is no change in GS.

Conclusions: GPS is a significant predictor of the likelihood of Gleason score upgrading from biopsy to RP. Incorporation of GPS results into treatment decision making can improve risk assessment for newly diagnosed patients with clinically low-risk prostate cancer.

Legal entity responsible for the study: GHI & CPDR.

Funding: Genomic Health, Inc.

Disclosure: H.J. Lawrence: Consultant, stock owner: GHI. All other authors have declared no conflicts of interest.

838P PI3K/AKT pathway deleterious mutations in lethal prostate cancer

P. Rescigno[1], M. Rediti[1], D. Dolling[2], D.N. Rodrigues[1], D. Bianchini[1], R. Riisnaes[2], C. Messina[1], M. Barrero[1], A. Petremolo[1], A. Sharp[1], S. Sumanasuriya[1], G. Seed[2], I. Figueiredo[2], S. Miranda[2], J. Goodall[2], J. Mateo[2], R. Chandler[1], W. Yuan[2], S. Carreira[2], J.S. de Bono[1]

[1]Prostate Cancer Targeted Therapy Group, The Royal Marsden Hospital and Institute of Cancer Research, London, UK, [2]Prostate Cancer Targeted Therapy Group, The Institute of Cancer Research, London, UK

Background: PI3K/AKT signaling is commonly hijacked in prostate cancer (PC), associating with poorer prognosis and worse response to next generation hormonal treatment (NGHT) including abiraterone and enzalutamide. We studied deleterious pathway mutations in metastatic castration resistant PC (mCRPC) patients correlating these to prognosis and response to NGHT in a case-control study.

Methods: Patients with mCRPC and available treatment-naïve and/or CRPC tumor samples were evaluated. Mutation analyses involved MiSeq™ based targeted next generation sequencing (NGS); PTEN was assessed by immunohistochemistry (IHC) with the control cohort having no PTEN IHC loss. Correlations between pathway mutations and outcomes and response to NGHT utilized Cox and Kaplan-Meier analyses.

Results: Overall 418 samples (from Feb/15 to Dec/17) were sequenced by targeted NGS; 46 (11%) had mutated pathway genes of which 26 (6%) (PIK3CA, n = 18; AKT1, n = 6; PIK3R1, n = 2) were pathogenic pathway activating mutations. Among these 25 were previously described, while an undescribed PIK3R1 mutation (R543*), located in the iSH2 domain, was also identified. We then randomly selected 56 tumour samples with normal PTEN expression by IHC as a control group without detected pathway aberrations. Overall, 43% (10/23) of patients with mutated cancers had NGHT in pre-, and 57% (13/23) in post-chemotherapy settings, while 3 were NGHT naïve. In the control group, 14 patients (25%) were pre-chemotherapy while 42 (75%) post-chemotherapy. Deleterious pathway mutations were associated with a shorter median overall survival (2.8 vs 4.3 years; HR: 2.73; p < 0.001) and median duration of NGHT (5.9 vs 10.0 mo; p < 0.001), despite a higher proportion of post-chemotherapy patients in the control group.

Conclusions: PI3K/AKT pathway deleterious mutations impart a poor prognosis from mCRPC and are associated with shorter responses to NGHT. We envision that these data can impact treatment selection in a targeted treatment approach for mCRPC.

Legal entity responsible for the study: The Institute of Cancer Reserach.

Funding: CRUK, Movember, PCF, PCUK.

Disclosure: All authors have declared no conflicts of interest.

839P Clinico-genomic profiling and outcome prediction of neuroendocrine prostate cancer (NEPC)

V. Conteduca[1], C. Oromendia[2], M. Sigouros[1], A. Sborner[3], D.M. Nanus[1], S.T. Tagawa[1], K. Ballman[2], H. Beltran[1]

[1]Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York, NY, USA, [2]Department of Healthcare Policy & Research, Weill Cornell Medical College, New York, NY, USA, [3]Institute of Precision Medicine, Weill Cornell Medical College, New York, NY, USA

Background: NEPC is a variant of prostate cancer that may present "de novo" or after androgen receptor (AR)-targeted therapies ("treatment related") with a spectrum spanning both small cell prostate cancer (SCPC) and adenocarcinoma with neuroendocrine differentiation (adeno-NE). The comprehensive clinical and molecular landscape of different NEPC subtypes and its potential impact on outcome is poorly understood.

Methods: 274 prostate cancer patients (pts) with metastatic biopsy tumor morphology confirming NEPC (n = 97; 36 with SCPC and 51 with adeno-NE) or castration resistant adenocarcinoma (CRPC) (n = 187) between 2004 and 2017 in a single academic center were evaluated. Baseline, treatment and outcomes data along with tumor whole-exome and RNA-seq data were retrospectively reviewed. Statistical comparisons utilized Cox regression analysis and Kaplan-Meier method for association with NEPC, CRPC and overall/progression-free survival (OS/PFS).

Results: In NEPC, PSA at time of biopsy was lower compared with CRPC (median 1.18 vs 38.0, p = 0.001) and liver metastases were more common (32.2% vs 52.1%, p = 0.027). OS from time of prostate cancer diagnosis differed by subtype, with SCPC having shortest survival (median 2.98 years), followed by adeno-NE (median 5.98 years) then CRPC (median 12.14 years) (log rank p < 0.0001), with similar results seen with time from metastases (log rank p < 0.0001). AR alterations were more frequent in CRPC (p < 0.001), while RB1 (p = 0.001) and TP53 (p = 0.048) alterations and high NEPC mRNA score (p = 0.007) were more common in NEPC. For CRPC pts treated with abiraterone or enzalutamide, shorter PFS was observed when somatic alterations in RB1 (p = 0.067) or TP53 (p < 0.0001) were present. Elevated NEPC score (p = 0.006), serum CGA above upper limit of normal (p = 0.033), and presence of liver metastases (p < 0.001) were prognostic for time to death from diagnosis among pts with CRPC.

Conclusions: NEPC is associated with lower PSA, higher frequency of liver metastases, and worse prognosis compared with CRPC, with SCPC having the shortest OS. The presence of NEPC clinical or molecular features in CRPC is also prognostic. Further studies of this aggressive form of prostate cancer are warranted.

Legal entity responsible for the study: Weill Cornell Medicine.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

840P Prognostic value of free testosterone (FT) levels during salvage chemotherapy with carboplatin plus weekly docetaxel in metastatic castration- and docetaxel-resistant prostate cancer (mDRPC)

C.W.M. Reuter[1], S. Brunotte[1], P. Ivanyi[1], M.A. Morgan[2], V. Grünwald[3]
[1]Hematology, Hemostaseology, Oncology and Stell Cell Transplantation, Hannover Medical School, Hannover, Germany, [2]Exp. Hematology, Hannover Medical School, Hannover, Germany, [3]Hematology, Hemostaseology, Oncology and Stem Cell Transplantation, Medical School Hannover, Hannover, Germany

Background: Recent data suggest that carboplatin plus weekly docetaxel (DC) may be effective in mDRPC. Platinum(II)-complexes have been shown to interfere with steroid biosynthesis lowering testosterone levels by inhibiting the cholesterol side chain cleavage enzyme (CYP11A1), 3β-hydroxysteroid dehydrogenase (HSD3B1,2) and 17α hydroxylase/C17,20-lyase (CYP17A1).

Methods: Docetaxel failure/resistance was defined according to the Prostate Cancer Working Group (PCWG2 2007) criteria. Treatment consisted of at least two cycles of carboplatin AUC5 iv for 30 min on day 1 every 4 weeks (q4w), docetaxel at a dose of 35 mg/m2 iv for one hour on days 1, 8, (15) plus prednisone 2x5mg/day orally after receiving informed consent until disease progression or occurrence of intolerable adverse effects. Efficacy measures were done following PCWG2 recommendations. Free testosterone levels were measured before (n = 82) and during carboplatin/docetaxel chemotherapy (n = 76).

Results: Of the 106 pts. treated since February 2005, 96.2% had bone and 63.2 % soft tissue metastases (45% lymph node, 27% liver and 21% lung involvement). At the time of the current analysis, the median follow-up time was 13.5 months, 101 pts. had died and 102 had progressive disease. The objective response rate was 43.2% and the disease control rate 64.2% in the 67 pts. with measureable disease. Response of prostate-specific antigen (≥50%) was observed in 50 patients (47.1%). Median progression-free survival (PFS) for all patients was 6.9 months (CI 95% 5.7, 8.0) and median OS was 14.1 months (CI 95% 10.9, 17.3). The most common reversible grade 3/4 toxicity was leukopenia/ neutropenia (40.5/32.1%). Median free and total testosterone levels were reduced below the detection limit during DC treatment (from 0.55 pg/ml to < 0.18 pg/ml and 0.08 to < 0.05 ng/ml, respectively). Testosterone nadir values <0.18 pg/ml during DC treatment were associated with longer PFS, OS and post-hoc OS ($p < 0.05$).

Conclusions: These data suggest that carboplatin plus weekly docetaxel may be an important second-line treatment option for DRPC patients by inhibition the testosterone biosynthesis.

Legal entity responsible for the study: Christoph Reuter.
Funding: Has not received any funding.
Disclosure: C.W.M. Reuter: Advisory board: Eisai, Bayer, Tesaro, Sanofi, Astellas, Janssen. All other authors have declared no conflicts of interest.

841P Prevalence of clinically actionable germline pathogenic variants (PVs) in advanced prostate cancer (aPC)

A.W. Hahn[1], A.L. Kapron[2], J. Boyle[2], W. Kohlmann[3], A. Poole[1], D.M. Gill[1], S. Greenberg[3], P. Hale[1], C. Teerlink[2], B.L. Maughan[1], L. Cannon-Albright[2], N. Agarwal[4], K.A. Cooney[1]
[1]Medical Oncology, Huntsman Cancer Institute/University of Utah, Salt Lake City, UT, USA, [2]Internal Medicine, University of Utah, Salt Lake City, UT, USA, [3]Clinical Genetics, Huntsman Cancer Institute/University of Utah, Salt Lake City, UT, USA, [4]Oncology/ Internal Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA

Background: Recently, germline PVs in 20 cancer predisposition genes were found in 11.8% of patients with aPC in a multi-center study (Pritchard et al, NEJM 2017).These PVs appeared to be predictive of response to PARP inhibitors (PARPi). We sought to evaluate the prevalence of clinically actionable PVs in a comparable aPC cohort and investigate possible associations of PVs with baseline patient and disease characteristics.

Methods: Clinical data and germline DNA samples from 352 consecutive aPC patients were retrospectively collected. A custom target panel (Qiagen QiaSeq V3) composed of 35 genes deemed clinically actionable and/or included in the Pritchard publication were sequenced on an Illumina HiSeq2500. GATK best practices were followed for alignment and variant calling. Variants were filtered based on ClinVar pathogenicity and reviewed by genetic counselors to confirm clinical significance. Baseline patient characteristics were compared using the Chi-squared, Fisher's, and Mann-Whitney U tests.

Results: Clinically actionable, germline PVs were found in 26/352 (7.4%) of this aPC cohort. 11 of the 26 mutation carriers had a PV in BRCA1, BRCA2, or ATM (overall prevalence 3.1%). 96.6% of men were Caucasian of North European descent. Baseline characteristics were similar in those with or without PVs in clinically actionable genes, including age at diagnosis ($p = 0.77$), Gleason score ($p = 0.22$), or presence of metastatic disease at diagnosis ($p = 0.08$).

Conclusions: Our aPC cohort appears to have a lower prevalence of clinically actionable, germline PVs than previously reported studies. These findings may help inform recommendations for clinical genetic testing in this population, and help estimate the pace of enrollment on multiple ongoing clinical trials with PARPi in this population.

Legal entity responsible for the study: Huntsman Cancer Institute and University of Utah.
Funding: Has not received any funding.
Disclosure: N. Agarwal: Consultancy: Pfizer, Novartis, Merck, Genentech, Eisai, Exelixis, Clovis, EMD Serono. All other authors have declared no conflicts of interest.

842P CTC-based biomarkers & PSMA-targeted imaging in patients with metastatic castrate-resistant prostate cancer (mCRPC)

M.J. Morris[1], N.J. Vogelzang[2], O. Sartor[3], A. Armour[4], R. Messmann[5], M. Groaning[5], A. Robarts[6], A.W. Tolcher[7], M. Gordon[8], H.M. Babiker[9], P. Kuo[9], M. Kearney[10], A. Jendrisak[10], Y. Wang[11], M. Landers[11], D.P. Petrylak[12]
[1]Memorial Sloan-Kettering Cancer Center, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]US Oncology Research c/o Comprehensive Cancer Crts of NV, US Oncology Research c/o Comprehensive Cancer Crts of NV, Las Vegas, NV, USA, [3]Tulane Cancer Center, Tulane Medical School, New Orleans, LA, USA, [4]Endocyte, Indianapolis, IN, USA, [5]Medical Affairs, Endocyte, West Lafayette, IN, USA, [6]GU, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [7]Clinical Research, NEXT OncologyTM, San Antonio, TX, USA, [8]Medical Oncology, HonorHealth Virginia G Piper Cancer Care Network, Scottsdale, AZ, USA, [9]Cancer Center, University of Arizona Cancer Center, Tucson, AZ, USA, [10]Clinical Operations, Epic Sciences, San Diego, CA, USA, [11]Translational Research, Epic Sciences, San Diego, CA, USA, [12]Medical Oncology, Yale University School of Medicine Medical Oncology, New Haven, CT, USA

Background: Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancers, making it an imaging & therapeutic target of interest. The utility of the PSMA-targeted imaging agent ^{99m}Tc-EC0652 is being evaluated, along with biomarker analysis of circulating tumor cells (CTCs), in pts with mCRPC in a completed PSMA-targeted chemotherapeutic study. We now report the PSMA heterogeneity via CTC vs. imaging in the pt population treated to date.

Methods: A total of 51 pts evaluated at the time of the data cut had baseline CT & bone scans performed in addition to a ^{99m}Tc-EC0652 SPECT/CT as a measure of imaging-based PSMA expression. 41 of 51 pts provided pre-treatment blood samples evaluable for CTC biomarker analysis, which included PSMA expression & predicted genomic instability status (pGI). Images collected from pts were analyzed for both their PSMA$^+$ status as well as sensitivity relative to conventional imaging.

Results: 41 of 51 pts (80.4%) had detectable CTCs in their samples prior to therapy while 32 of 38 (84.2%) of the analyzed paired on-therapy samples had CTCs after treatment. At baseline PSMA$^+$ CTCs were found in 19 of 51 (37.2%) pts and overall was expressed on 33% (IQR 11.3% - 40.1%) of CTCs within each pt sample. 15 of 17 (88%) PSMA$^+$ pt samples were also pGI$^+$. 31 of the 51 pts (60.7%) of the pts had bone scan (BS) data available to analyze. 27 of the 51 pts had CT scan data available to analyze for nodal lesions. Concordance between Conventional Imaging & ^{99m}Tc-EC0652.

Table: 842P

	^{99m}Tc-EC0652$^+$	^{99m}Tc-EC0652$^-$	BS$^+$	BS$^-$	CT$^+$	CT$^-$
Bone Lesion (770)	770 (100%)	0	587 (76.2%)	183 (23.8%)	N/A	N/A
Nodes >1.5cm (54)	48 (88.9%)	6 (11.1%)	N/A	N/A	54	N/A
Nodes <1.5cm (69)	69	N/A	N/A	N/A	N/A	N/A

Conclusions: In this cohort, most pts had CTCs for assessment. The majority of pts with CTCs had PSMA$^-$CTCs. The pts CTCs expressing PSMA accounted for a small percentage of the total CTCs observed. These PSMA$^+$ CTCs had high pGI. Pts with CTCs had PSMA imagable disease, especially in bone. The discordance between CTCs & imaging illustrate the disease heterogeneity in regards to PSMA expression. These data should be considered in designing future PSMA-directed regimens.

Clinical trial identification: NCT02202447.
Legal entity responsible for the study: Endocyte Inc.
Funding: Endocyte, Inc.
Disclosure: M.J. Morris, O. Sartor: Consultant: Endocyte. A. Armour, R. Messmann, M. Groaning: Employee: Endocyte. All other authors have declared no conflicts of interest.

843P The neutrophil-to-lymphocyte ratio (NLR) as a predictive marker of response to abiraterone acetate: A retrospective analysis of the COU302 study

T. Loubersac[1], S. Chakak[2], M. Nguile-Makao[2], V. Fradet[2], P. Toren[2]
[1]Urology, CHU de Nantes, Nantes, France, [2]Uro-oncology, CHU Hotel dieu quebec, Quebec City, QC, Canada

Background: The neutrophil–lymphocyte ratio (NLR) is recognized as a prognostic marker in many cancers, including metastatic castration-resistant prostate cancer (mCRPC). In this study, we perform a retrospective analysis of the pivotal COU302 study of abiraterone acetate (AA) as first line therapy for men mCRPC.

Methods: The COU302 study randomized men with minimally symptomatic mCRPC to 1000mg AA once daily plus 5mg prednisone (AA + P) twice daily or placebo plus 5mg prednisone (P) twice daily. We utilized Kaplan–Meier survival and cox proportional hazard analyses to assess the effect of baseline NLR on response to AA + P versus P. Adjustment co-variates were selected from a recently reported analysis of the PREVAIL study of enzalutamide in men with mCRPC. Based on this analysis, we selected a NLR cut-off value of 2.5. Outcomes assessed included the co-primary endpoints from the COU302 study overall survival (OS) , radiographic progression free-survival (RPFS) and PSA progression-free survival (PFS).

Results: Among the 1088 patients in the COU302 study, baseline NLR values showed significant differences according to baseline albumin below median (3.16 vs 2.92, $p = 0.011$), but no other baseline covariates. Mean NLR significantly increased following treatment initiation and at the end of study compared to baseline. Among patients with a baseline NLR $\geq$2.5, there was similar OS in AA + P and P treatment arms ($p = 0.26$), which was confirmed on adjusted cox proportional hazards (AA +P HR 0.95, $p = 0.65$). AA + P showed a significant OS benefit versus P ($p = 0.0011$) in men with baseline NLR <2.5, with an adjusted HR of 0.723($p = 0.012$). For RPFS, benefits for AA + P were seen in men with NLR <2.5 or $\geq$ 2.5, with the magnitude of benefit greater in men with NLR <2.5. In the AA + P arm, men with baseline NLR <2.5 had significantly better PSA PFS compared to baseline NLR $\geq$2.5 ($p = 0.03$); no significant differences were seen in men in the placebo arm.

Conclusions: In the COU302 study, we observed that patients with a screening NLR<2.5 had a significant benefit to AA + P compared to P, whereas for patients with a screening NLR $\geq$2.5, this benefit was less evident. Increases in the NLR value from baseline could not be used to predict response to AA.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: V. Fradet: Speaker: Abbvie, Bayer, Ferring, Janssen, Sanofi; Consultant: Amgen, AstraZeneca, Astellas, Bayer, Ferring, Janssen, Sanofi; Adviser: Amgen, Astellas, Bayer, Ferring, Janssen, Sanofi; Research grant: Amgen, AstraZeneca, Astellas, Janssen, Sanofi; Clinical trial: AstraZeneca, Bayer, Janssen; Meeting sponsor: Bayer, Janssen, Lilly; Educational grant: Janssen. P. Toren: Scientific study or trial: Innocrin Pharma, Roche; Consultant, Advisor: Sanofi Canada, Ferring, Astellas, Abbvie. All other authors have declared no conflicts of interest.

844P The clinical impact of targeted next generation sequencing (tNGS) in the treatment of metastatic prostate cancer

P.M.C. Coelho Barata, P. Mendiratta, M. Sadaps, S. Klek, M. Ornstein, T. Gilligan, P. Grivas, B.I. Rini, D. Sohal, J.A. Garcia

Medical Oncology, Taussig Cancer Institute Cleveland Clinic, Cleveland, OH, USA

Background: Tumor profiling by tNGS is increasingly common in patients (pts) with metastatic solid tumors. It is unclear if this strategy leads to changes in treatment decision for mPCa pts.

Methods: A retrospective analysis of mPCa pts treated at Cleveland Clinic with available comprehensive genomic profiling using tumor tissue (FoundationOne, F1) or cell-free circulating tumor DNA (FoundationAct, Guardant360) was conducted. Targetable genomic alterations (tGA) were defined as a change in the copy number (amplification/duplication) or a mutation (deletion/rearrangement/truncation/fusion) in AR, DNA repair genes, mismatch repair (MMR) genes, cyclin-dependent kinases (CDK), ERBB2, BRAF, TSC and PIK3-mTOR pathway.

Results: Within 2013-2017, 66 pts, median age 68y (49-85), median ECOG PS1 (0-2), with mPCa, Gleason 9 (6-10), 86% castration-resistant (CRPC), received a median of 3 (0-7) systemic treatments for CRPC before tNGS panel. The most common tNGS platform used was F1 (91%) based on archival tumor tissue (45% primary, 55% metastatic). Overall, frequent alterations included TP53 (42%), PTEN (35%), AR (30%), DNA repair (30%), PIK3CA signaling pathway (21%), CDK (15%) and MSI-H/MMR (9%). Median tumor mutational burden was 7 (0.8-32) mutations/Mb. Among 45 with tGA+ pts, tNGS influenced treatment in 13 pts: PARP inhibitor (n = 7; olaparib 6, niraparib 1), mTOR inhibitor (n = 4; everolimus 3, temsirolimus 1), pembrolizumab 2, trastuzumab 1. PSA decline was observed in 54% and median (m) PFS was 4.1 months (95%CI, 2.8-5.4) with 9 pts (69%) progressing on therapy to date. Among tGA+ pts not treated with tGA-based therapy, first subsequent treatment (n = 17) included chemotherapy (71%), abiraterone (18%), cabozantinb (6%) and other (6%). PSA decline was observed in 24% and mPFS was 4.3 months (95%CI, 2.6-6.0); 12 pts (71%) progressed on therapy. There was no difference in mPFS between tGA+/tGA- pts ($p = 0.652$). The median OS was 60.4 months (95%CI, 51.9-68.9) compared with 17 months (95%CI, 10.5-23.5) after tNGS was ordered.

Conclusions: tNGS was ordered somewhat late in the course of the disease. tGA results only impacted therapy selection in 20% of pts but with modest clinic benefit.

Legal entity responsible for the study: Taussig Cancer Institute Cleveland Clinic.

Funding: Has not received any funding.

Disclosure: P. Grivas: Consultant, advisor: Foundation Medicine, Genentech, Dendreon, Bayer, Exelexis, Merck, Bristol-Myers Squibb, AstraZeneca, Biocept, Clovis Oncology, EMD Serono, Seattle Genetics; Research funding: Mirati Therapeutics, Genentech/Roche, Merck, Oncogenex, Bayer, Pfizer, AstraZeneca. B.I. Rini: Consultant, advisor: Corvus Pharmaceuticals, Merck, Pfizer; Research funding: Bristol-Myers Squibb (Inst), Merck (Inst), Pfizer (Inst), Roche/Genentech (Inst); Funding travel, accommodations and expenses: Pfizer. D. Sohal: Consultant, advisor: Perthera, Foundation Medicine; Research funding: Novartis, Celgene, OncoMed, Bayer, Genentech/Roche. J.A. Garcia: Consultant, advisor: Sanofi, Pfizer, Bayer, Eisai, Exelexis, Medivation/Astellas, Genentech/Roche; Research funding: Pfizer, Astellas Pharma, Orion Pharma GmbH, Bayer, Janssen Oncology, Genentech/Roche, Lilly. All other authors have declared no conflicts of interest.

845P Phase III double-blind study evaluating lens opacifications (LO) in patients with nonmetastatic prostate cancer (PCa) receiving denosumab (Dmab) for bone loss due to androgen deprivation therapy (ADT)

S.T. Tagawa[1], T. Dai[2], D. Jandial[3]

[1]Urology, Weill Cornell Medical College, New York, NY, USA, [2]Biostatistics, Amgen Inc., Thousand Oaks, CA, USA, [3]Oncology, Amgen Inc., Thousand Oaks, CA, USA

Background: Men with PCa undergoing ADT experience bone loss that may be associated with fracture risk and reduced survival. Therapy with Dmab (Prolia®, Amgen, Inc) significantly increased bone mass and reduced vertebral fracture risk in men with nonmetastatic PCa receiving ADT. However, in that study (unlike other Dmab randomized trials), cataracts were reported more often in the Dmab group (4.7% vs 1.2% for placebo [PBO]). This trial (NCT00925600) assessed the effect of Dmab on LO (cataract) development or progression in men with nonmetastatic PCa receiving ADT.

Methods: Men aged $\geq$30 years with nonmetastatic PCa with bilateral orchiectomy or initiated ADT were randomized 1:1 to receive Dmab 60 mg or PBO subcutaneously every 6 months, stratified by Lens Opacities Classification System III (LOCS III) score (<3.0 at all sites, $\geq$3.0 at any site), age (<75, $\geq$75 years), and prior cataract history. The primary endpoint was LO development or progression by month 12 based on a change of $\geq$ 1.0 in posterior subcapsular cataract, $\geq$1.0 in cortical cataract, or $\geq$ 0.7 in nuclear opalescence per LOCS III score. Noninferiority was demonstrated if the upper bound of the 95% 2-sided CI was <10%.

Results: 769 men with median age 71 were randomized to receive Dmab (n = 383) or PBO (n = 386). Baseline demographics were balanced. Development or progression of LO by month 12 was similar in the Dmab and PBO groups (33.5% vs 33.2%); the absolute risk difference was 0.4% (95% CI, –6.3 to 7.2; noninferiority P = 0.0026), indicating that Dmab was noninferior to PBO for the primary endpoint. Results for other LO endpoints also showed no increased risk of cataracts with Dmab (Table). Rates of AEs, serious AEs, AEs leading to treatment discontinuation, AEs of interest, and death were similar in the 2 groups.

Table: 845P

Endpoint (Parameters)	Dmab, n/N* (%)	PBO, n/N* (%)	Risk Difference (95% CI)
Development or progression of LO by month 12	127/379 (33.5)	124/374 (33.2)	0.4 (–6.3 to 7.2) Noninferiority P = 0.0026
Incidence of LO development or progression by month 12	32/379 (8.4)	40/374 (10.7)	–2.2 (–6.4 to 2.0)
Incidence of LO development or progression by month 6	72/379 (19.0)	72/374 (19.3)	–0.3 (–5.9 to 5.3)
Incidence of confirmed LO development or progression by month 12†	59/367 (16.1)	66/361 (18.3)	–2.2 (–7.6 to 3.3)

*N is the number of patients with at least one post-baseline LOCS III measurement by month 12. †A confirmed LO development or progression was defined as two directly subsequent events per protocol assessments at the same location; for this endpoint, N is the number of patients with at least two post-baseline LOCS III measurements by month 12.

Conclusions: Dmab did not increase the short-term risk of cataracts in men with PCa.

Clinical trial identification: NCT00925600.

Editorial acknowledgement: This study was funded by Amgen Inc. The authors also wish to acknowledge Rick Davis (Complete Healthcare Communications, LLC, West Chester, PA), whose work was funded by Amgen Inc., and Albert Rhee (Amgen Inc.,Thousand Oaks, CA) for assistance with the writing of this abstract.

Legal entity responsible for the study: Amgen Inc.

Funding: Amgen Inc.

Disclosure: S.T. Tagawa: Consulting fees, research grants (paid to Weill Cornell Medicine): Lilly, Sanofi, Janssen, Astellas, Progenics, Millennium, Amgen, BMS, Dendreon, Rexahn, Bayer, Genentech, Newlink, Inovio, AstraZeneca, Immunomedics,

Novartis, Aveo, Boehringer Ingelheim, Merck, Abbvie, Endocyte, Pfizer, Exelixis, Clovis, and Karyopharm; Consulting fees: Astellas, Janssen, Bayer, Sanofi, Endocyte, Immunomedics, Karyopharm, Abbvie, Tolmar. T. Dai, D. Jandial: Employee, Stockholder: Amgen Inc.

846P Patterns of therapy in pelvic lymph node positive prostate cancer in Europe and Asia: A real-world data analysis

M. Prentice[1], S. Mpima[2], P. Nasuti[2], A. Martinez-Pinillos[2], I. Wong[3], K. Durno[1], R. Davda[1], H. Payne[1]

[1]Oncology, University College London Hospital UCLH NHS Foundation Trust, London, UK, [2]Real World and Analytics Solutions, IQVIA, London, UK, [3]Department of Policy and Practice, UCL School of Pharmacy, London, UK

Background: Treatment for node positive prostate cancer can vary from palliation to radical therapy. Guidance for N1 prostate cancer is unclear but evidence supports a multimodal approach including radical radiotherapy, hormonal manipulation and possible surgery while a survival benefit for neoadjuvant docetaxel has been demonstrated. Recent improvements in diagnostic techniques and technical advances in radiation therapy including intensity modulated radiotherapy (IMRT) which is capable of delivering a radical dose of radiation to pelvic nodes within acceptable toxicity profiles are anticipated to result in an increased use of radiation in this patient population. This study assesses changes in treatment modality for N1 prostate cancer over time to reflect real world practice.

Methods: Patient data from 17,695 prostate cancer cases taken from a cross-sectional survey of physicians in France, Germany, Italy, Spain, UK, China, Japan and S. Korea between Jan 1997 – Dec 2016 was reviewed. Patients with non-metastatic, node positive cancer were included for analysis. Any exposure to any of three therapy types (systemic, radiation, surgery) prior to recurrence.

Results: 2542 patients were included in the analysis. Over the time studied, the use of surgery has decreased (from 36% in pre 2009 to 16% in 2016) and initially, this decline was matched by a rise in the use of systemic therapy alone (37% to 51%). Since 2011 systemic therapy alone has reduced to 40%. In the same time period, there has been an increase in the use of radiation (with or without systemic therapy) to treat node positive prostate cancer (15% to 29%). The average increase in radiotherapy use across European countries was 11% (range Italy 2% - Spain 19%). A group of patients receiving combined surgery, radiation and systemic therapy comprise 11% of all cases, a figure that does not vary over time.

Conclusions: These data have demonstrated an international change in the management of node positive prostate cancer with decreasing use of surgery and increasing use of radiation. Although initially rising, the recent decline in the use of lone systemic therapy is likely to represent an increasing view that N1 prostate cancer is no longer a definitively palliative diagnosis.

Legal entity responsible for the study: IQVIA.

Funding: IQVIA.

Disclosure: I. Wong: Honoraria: Janssen, Sanofi Aventis. H. Payne: Honoraria, advisory boards, travel expenses, consultant: AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Amgen, Ipsen, Ferring, Sandoz and Novartis; Work support: UCLH/UCL Comprehensive Biomedical Research Centre. All other authors have declared no conflicts of interest.

847P The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system in patients with high-risk prostate cancer

J. Liu, J. Zhao

Department of Urology, Institute of Urology, West China Hospital, SiChuan Univer, West China Hospital, Sichuan University, Chengdu, China

Background: Since the new 2014 grading system was recommended by international society of urological pathology (ISUP), it has been validated in patients with localized prostate cancer(PCa) with excellent prognostic value. However, its predictive power in high-risk PCa has not been verified.

Methods: A total of 420 patients with high-risk PCa underwent radical prostatectomy(RP) were included. The predictive accuracy of the 2005 and 2014 grading systems were validated and compared. Biochemical-recurrence free survival (BRFS) was set as the endpoint.

Results: Compared to the 2005 system, the 2014 system could fairly well distinguish BRFS of patients into five groups with higher predictive accuracy(C-index: 0.599 vs 0.646). In multivariate analyses, together with baseline prostate specific antigen, extraprostatic extension and perineural invasion status, the new system was independent predictor for BRFS in these population. The relatively higher proportion of tertiary Gleason pattern 5 (TGP5) among patients with Gleason grade group 3(GGG3) could be considered as an important interfering factor leading to the overlap of survival between GGG4 and GGG3.

Conclusions: This is the first study to validate the new 2014 ISUP grading system in patients with high-risk PCa underwent RP. The new system could better separate patients into five groups with higher predictive accuracy over the old one. It should be paid attention that, the existence of TGP5 need to be routinely reported in clinical practice, which could help retaining the predictive ability of the new grading system. Due to miscellaneous factors among these patients, the prognostic prediction need to be comprehensively evaluated.

Legal entity responsible for the study: Department of Urology, Institute of Urology, West China Hospital, SiChuan University.

Funding: National Natural Science Foundation of China (NSFC 81402110, 81672547, 81572380, and 81272820); Science and Technology Support Program of Sichuan Province (2015SZ0142); 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University.

Disclosure: All authors have declared no conflicts of interest.

848P Overall survival (OS) implications for patients with mCRPC through coverage and adoption of nuclear AR-V7 testing by healthcare systems

J. Hornberger[1], R.P. Graf[2], M. Hulling[3], G. Attard[4], A. Allan[5], R. Dittamore[2], H.I. Scher[3]

[1]Clinical Economics and Outcomes Research, Genomic Health, Redwood City, CA, USA, [2]Translational Research, Epic Sciences, Inc., San Diego, CA, USA, [3]Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [4]Medical Oncology, The Institute of Cancer Research and The Royal Marsden, London, UK, [5]Oncology and Anatomy and Cell Biology, Western University, London, ON, Canada

Background: Nuclear-localized AR-V7 testing of circulating tumor cells (CTCs) has been validated as a predictive biomarker of chemotherapy response and ARSI non-response in 2nd+ line therapy for metastatic castration-resistant prostate cancer (mCRPC). A validation study showed that AR-V7(+) pts have improved OS with taxane chemotherapy, and AR-V7(-) pts have improved OS with ARSi. We assessed the effect of AR-V7 testing on OS when generalized to non-trial clinical settings, as found in third-party US healthcare systems.

Methods: The causal effect of treatment and nuclear AR-V7 status on OS was estimated from risk-adjusted hazard rates of the MSK, ICR, LHS validation study. Therapeutic strategies assessed were (1) taxanes only, (2) ARSi only, (3) current US utilization rate of ARSis, and (4) nuclear AR-V7-guided treatment. Quality of life adjustments were extracted from meta-analysis of large cohort studies. We applied US utilization rate of consecutive ARSi administration (abiraterone after enzalutamide, or enzalutamide after abiraterone) and compared to switching with taxane-based chemotherapy (docetaxel after abiraterone, or docetaxel after enzalutamide).

Results: The following table shows OS, adjusted and unadjusted for quality of life, and treatment by strategy. The net effects on OS were robust to variation on the clinical effects, and on systems covariates, e.g., demographic, patient, and payer case-mix.

Table: 848P

2nd line mCRPC therapy strategy	% ARSi	OS (months) QALY (Unadj / Adj.)	Net OS gain (months) QALY (Unadj / Adj)
Only use taxanes	0%	19.2 / 12.2	-3.7 /-2.0
Only use ARSi's	100%	25.4 / 15.6	2.5 / 1.4
Current use of ARSi (US)	60%	22.9 / 14.2	- REF -
AR-V7 guided treatment	77%	27.3 / 16.7	4.4 / 2.5

Conclusions: Health outcome modeling of the validation data support that current use and access to 2nd ARSi therapy can improve OS of patients over strict use of taxane chemotherapy (+3.7mo OS). 2nd+ line nuclear-localized AR-V7 guided treatment for men with progressive mCRPC provides higher OS than non-guided, almost doubling the gain (+4.4 mo OS) observed with current US utilization rate of ARSi versus taxanes only. Cost effectiveness analyses of the adoption/coverage of nuclear AR-V7 testing in healthcare systems is ongoing.

Legal entity responsible for the study: MSKCC.

Funding: NIH/NCI P50-CA92629 SPORE in Prostate Cancer, NIH/NCI Cancer Center Support Grant P30-CA008748, NIH grant R01-CA207220, Department of Defense Prostate Cancer Research Program (PC121111 and PC131984), Prostate Cancer Foundation Challenge Award, and David H. Koch Fund for Prostate Cancer Research were used to support the design and conduct of the study at Memorial Sloan Kettering Cancer Center. Funds from the London Regional Cancer Program Catalyst Grant and TELUS Ride For Dad/Prostate Cancer Fight Foundation were used to support the study at London Health Sciences Centre. A Medical Council Clinical Research Fellowship (AJ) and NHS funding to the Royal Marsden and Institute of Cancer Research Biomedical Research Centre.

Disclosure: J. Hornberger: Employee: Genomic Health. R.P. Graf: Employee: Epic Sciences. G. Attard: Honoraria: Astellas Pharma; Janssen; Consulting, Advisory role: Abbott Laboratories, Astellas Pharma, Bayer, ESSA, Janssen-Cilag, Medivation, Millennium, Novartis, Ventana Medical Systems; Veridex Speakers' bureau: Astellas Pharma, Janssen, Sanofi, Takeda, Ventana Medical Systems; Research funding: Arno Therapeutics (Inst), Innocrin Pharma (Inst), Janssen (Inst), Patents, Royalties: Other intellectual property: The ICR rewards to inventors list of abiraterone acetate; Travel, accommodations, expenses: Abbott Laboratories, Astellas Pharma, Astellas Pharma (I), Bayer, ESSA, Janssen, Janssen (I), Medivation, Ventana Medical Systems. R. Dittamore:

Employee: Epic Sciences. H.I. Scher: Consultant: Sanofi (C), Clovis (C), Janssen (U), Pfizer (U); Grant/Research support: MSK, Innocrin, Janssen; Board of Directors: Asterias, Biotherapeutics; Advisory board: WCG Oncology (C). All other authors have declared no conflicts of interest.

849P Quality of docetaxel toxicity reporting for castration resistant prostate cancer (CRPC): A systematic review

S. Cheng, M. Qureshi, V. Arciero, K.K-W. Chan, U. Emmenegger
Medical Oncology, Sunnybrook Odette Cancer Center, Toronto, ON, Canada

Background: Prostate cancer trial design is structured following the Prostate Cancer Clinical Trials Working Group (PCWG) guidelines which focus on harmonization of inclusion criteria and outcome data. The PCWG, however, does not provide clear outlines for reporting of safety data. In fact, there is a perceived lack of widely accepted guidelines for safety reporting.

Methods: A PubMed search of phase II and III clinical trials published until 2015 (included) was conducted using keywords "prostate cancer" and "docetaxel." Docetaxel-naïve CRPC patients who received 75 mg/m^2 docetaxel monotherapy every three weeks were included. To assess quality of toxicity reporting, the Consolidated Standards of Reporting Trials (CONSORT) harms checklist was adapted and each trial scored by two independent reviewers. CONSORT scores as well as PSA and radiological response rates over time were examined with Spearman correlation coefficients. Univariable and multivariable linear regression examined associations between scores and phase II versus III trials, publication year, midpoint of accrual, number of patients, sponsor type, journal impact factor, presence of supplementary data, and geographical region.

Results: From 21 clinical trials including 5,460 patients in docetaxel monotherapy arms, the median CONSORT score was 15.3 (IQR 13.7–16.5) out of 22. Correlation coefficients were not significant for all comparisons of CONSORT scores and response rates versus years of accrual or year of publication. In univariable linear regression, phase III clinical trials were associated with a significantly higher CONSORT score ($p = 0.01$) as was a journal impact factor greater than 15 ($p = 0.02$). In exploratory analyses, none of the examined factors were significant in multivariable linear regression.

Conclusions: CONSORT scores and thus toxicity reporting quality in CRPC trials studying docetaxel show need for improvement and should be subject to further discussion. There has been no significant improvement in toxicity reporting quality over time. It remains to be studied if our findings also apply to other agents used for the treatment of CRPC. Legal entity responsible for the study: Sunnybrook Research Institute.

Funding: Joseph and Silvana Melara Cancer Fund.

Disclosure: All authors have declared no conflicts of interest.

850P Intermittent short course enzalutamide in biochemically recurrent prostate cancer: Analysis of PSA recovery, testosterone levels and tolerability

M. Al Harthy[1], H. Singh[2], F. Karzai[3], P. Arlen[4], M. Theoret[5], J. Marte[3], M. Bilusic[6], A. Couvillon[3], H. Owens[3], A. Hankin[3], L. Cordes[6], I. Rosner[7], J. Strauss[6], W.D. Figg[8], J. Schlom[9], W. Dahut[6], J. Gulley[6], R. Madan[3]
[1]Genitourinary Malignancies Branch, National Cancer Institute, Bethesda, MD, USA, [2]Hematology and Oncology, Food and Drug Administration, Silver Spring, MD, USA, [3]Genitourinary Malignancies Branch, National Cancer Institute, Bethesda, MD, USA, [4]Medical Oncology, Precision Biologics, Rockville, NY, USA, [5]Office of Oncology Drug Products, Food and Drug Administration, Silver Spring, MD, USA, [6]Medical Oncology, National Cancer Institute, Bethesda, MD, USA, [7]Medical Oncology, Walter Reed Medical Center, Washington, DC, USA, [8]Genitourinary Malignancies Branch, NCI /NIH, Bethesda, MD, USA, [9]Laboratory of Tumor Immunology and Biology, National Cancer Institute, Bethesda, MD, USA

Background: Androgen deprivation therapy (ADT) and surveillance are standard options for patients (pts) with biochemically recurrent (non-metastatic, castration sensitive) prostate cancer (BCRpc) after localized therapy. Enzalutamide (enz) extends survival in advanced prostate cancer and is being tested in earlier stages of disease.

Methods: Eligible pts had a PSA between 2.0-20.0 ng/ml, no metastatic disease, normal testosterone (T), and a PSA doubling time of less than 12 months. Treatment for all pts included enz 160 mg daily for 84 days (D) with/without PROSTVAC (recombinant poxvirus PSA vaccine), but no ADT. After an amendment, pts were eligible for a 2nd course of enz after PSA returned to baseline and confirmation of non-metastatic disease. This analysis evaluated all pts for the impact of enz on PSA and T regardless of randomization as findings were similar in each group.

Results: Median age for all pts ($n = 36$) was 64 years (range: 54-85) with a median baseline PSA of 5.02 (range: 2.02–19.43). The median PSA decline during the first course of enz was >99% (range: 84 - >99). After enz was discontinued, the median time to first PSA rise was 28 D (range:13–182) and median recovery to baseline PSA was 224 D (range:84–924+). 22 of the 36 evaluable pts received a 2ndcourse of enz. Similarly, these patients had a median PSA decline of 99% (range 87->99). After the 2ndcourse of enz, the median time to first PSA rise was 29 D (range:0–83) with a median time to 2nd PSA recovery of 189 D (range:78–400). Enz was well tolerated with no grade 4 or 5 adverse events (AEs). Grade 3 AEs included increased ALT (5%) and decreased ANC (3%). The most common grade 2 AEs included fatigue (18%), dizziness (8%), decreased WBC (8%), and a decreased ALC (8%). T increased above normal limits in 20/36 pts (median Tmax = 834 ng/dl).

Conclusions: Intermittent, short course (84 d) enz without ADT leads to deep and prolonged PSA suppression below baseline in pts with BCRpc, a median of more than 7.5 months beyond treatment period. Pts who received a 2nd 84 D course of enz had similar depth and duration of PSA suppression below baseline (more than 6.5 months after enz treatment). Intermittent enz was well tolerated and warrants further study in BCRpc.

Clinical trial identification: NCT01875250.

Legal entity responsible for the study: National Institutes of Health/National Cancer Institute.

Funding: National Institutes of Health.

Disclosure: P. Arlen: Stock, Salary: Precision Biologics. All other authors have declared no conflicts of interest.

851P Pharmacokinetic/pharmacodynamic relationship of enzalutamide and its active metabolite N-desmethyl enzalutamide in metastatic castration-resistant prostate cancer patients

M-L. Joulia[1], E. Carton Vienet Legue[1], M. Allard[2], O. Huillard[3], M. Peyromaure[4], M. Zerbib[4], M. Vidal[2], F. Goldwasser[1], J. Alexandre[1], B. Blanchet[2]
[1]Medical Oncology, Hôpital Cochin, Paris, France, [2]Clinical Pharmacology, Hôpital Cochin, Paris, France, [3]Medical Oncology, Hôpital Cochin, Paris, France, [4]Urology, Hôpital Cochin, Paris, France

Background: Enzalutamide (ENZA) is an oral androgen receptor inhibitor approved for the treatment of metastatic Castration-Resistant Prostate Cancer (mCRPC). ENZA is extensively metabolized by CYP 3A4 into N-desmethyl enzalutamide (NDE). Based on in vitro assays, NDE has been identified as pharmacologically active metabolite. We aimed to explore the relationship between ENZA, NDE plasma concentration and progression-free survival (PFS) in mCRPC.

Methods: Trough plasma concentrations of ENZA and NDE were measured at steady-state one month after treatment start, using liquid chromatography. Trough ENZA and NDE plasma concentrations were dichotomized into 2 groups (high and low) according to their median value. Progression was defined as clinical progression, PSA increase or imaging progression according to the prostate working group criteria 3 or death. A survival analysis was used to explore relationship between PFS and plasma drug exposure.

Results: From January 2015 to May 2017, 18 mCRPC patients treated with ENZA (median age 77.5 years, Interquartile range (IQR) 67.2-82.7) were prospectively included. Median follow-up was 10.6 months (ms) (IQR 5.1-21.3 ms). Median trough plasma concentration of ENZA and NDE were 10.5 ± 3.7 µg/mL (Coefficient of variation (CV) = 33.8%; IQR 8.2-13.2) and 8.1 ± 4.2 µg/mL (CV = 52.7%; IQR 5,4-10,1), respectively. Pearson correlation coefficient value was 0,3 ($p = 0.21$). Eleven patients (61%) achieved a PSA response. Median PFS in the whole cohort was 11.2 ms (IQR 3.4-12.4). High trough plasma concentration of ENZA was associated with a shorter PFS (9 ms vs 22.6 ms respectively in the high and the low group) (Hazard Ratio (HR) 0.2; 95% CI 0.04-0.57; $p = 0.005$). Conversely, a high trough plasma concentration of NDE was associated with a longer PFS: 12,8 ms vs 7.2 ms respectively in the high and low group (HR 3.04; 95% CI 1.19-48.45; $p = 0.03$).

Conclusions: Overall, these results suggest that NDE could be more pharmacologically active than ENZA in vivo. Plasma monitoring of ENZA and NDE could lead to early identification of patients who will not benefit from ENZA as well as to optimize their treatment choice.

Legal entity responsible for the study: Department of Medical Oncology, Cochin Hospital, Paris Descartes University, Pr Goldwasser.

Funding: Has not received any funding.

Disclosure: O. Huillard: Consultant/advisor: Astellas Pharma, Sanofi, Janssen Oncology, Bristol-Myers Squibb; Travel, accommodations reimburse: Roche/Genentech, Astellas Pharma, Pfizer; Sanofi. F. Goldwasser: Consultant/advisor: Fresenius Kabi, Baxter. J. Alexandre: Consultant/advisor: Novartis, Roche; Honoraria: Novartis, AstraZeneca, Roche, Ipsen; Research funding: Jansen; Travel, accommodations reimburse: Jansen. All other authors have declared no conflicts of interest.

852P Pharmacokinetic (PK) analysis of concurrent administration of enzalutamide (enza) and crizotinib (crizo) in patients with metastatic castration resistant prostate cancer (CRPC)

A. tripathi[1], J.G. Supko[2], K.P. Gray[3], Z. Melnick[1], M-E. Taplin[1], A.D. Choudhury[1], M. Pomerantz[1], J. Bellmunt[1], C. Yu[1], Z. Sun[4], S. Srinivas[5], P.W. Kantoff[6], C. Sweeney[7], L.C. Harshman[1]

[1]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [2]Clinical Pharmacology Laboratory, Massachusetts general Hospital, Boston, MA, USA, [3]Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA, [4]Department of Urology, Stanford University, Stanford, CA, USA, [5]Department: Medicine - Med/Oncology, Stanford University, Stanford, CA, USA, [6]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [7]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Androgen receptor (AR) inhibition can upregulate c-MET expression which can drive CRPC progression. We have previously described the safety and toxicity profile of concurrent treatment with enza and crizo, a potent c-MET inhibitor in a phase 1 study. Since crizo is a substrate for CYP3A4, which is strongly induced by enza, we performed a PK analysis to evaluate its impact on steady state crizo levels.

Methods: A 3 + 3 dose escalation design was employed to test increasing doses of crizo at 250mg daily (dose level 1; n = 3), 200 mg BID (dose level 2; n = 6) and 250mg BID (dose level 3; n = 15) in combination with a fixed dose of enza 160 mg daily in 28 day cycles. PK samples drawn during cycle 2 were used to estimate steady state PK parameters including peak (Cmaxss) and trough (Cminss) plasma concentration and area under the curve over a dosing interval (AUCτss), reported as the geometric mean ± SD.

Results: The crizo Cminss increased progressively across dose levels from 20.7 ± 1.8 ng/mL (250 mg QD) to 70.2 ± 36.4 ng/mL (250 mg BID). Among the 12 patients enrolled on dose level 3 with available PK data, the crizo Cmaxss and AUCτss were 104 ± 45 ng/mL and 1,000 ± 476 ng-h/mL respectively. This represents a 73.8% decrease in crizo steady state exposure compared to a historical data for NSCLC patients with normal renal function treated with crizo monotherapy at 250 mg BID (Cminss: 285.0 ng/mL; Cmaxss: 315 ng/mL and AUCτss: 3,817 ng-h/mL; Tan et al Inv. New Drugs 2016). Enza Cminss was similar across the crizo dose levels (250mg QD: 10.6 ± 4.6 μg/mL; 250mg BID: 12.5 ± 3.2 μg/mL) and was in excellent agreement with previously reported steady state levels in the phase 3 AFFIRM trial (11.7 ± 2.9μg/mL; Gibbons et al Clin Pharmacokinetics 2015).

Conclusions: Concurrent administration of enza resulted in a clinically significant ~74% increase in the apparent oral clearance of crizo suggestive of a clinically significant PK drug interaction. Further investigation into the optimal combination of c-MET inhibitors with novel AR inhibitors is required. Our results highlight the importance of considering PK interactions when evaluating novel combination strategies in CRPC.

Clinical trial identification: NCT02207504.

Legal entity responsible for the study: Dana-Farber Cancer Institute.

Funding: Astellas Pharma Inc.

Disclosure: K.P. Gray: Stock ownership: DVAX M-E. Taplin: Research funding, Advisory board, Honorarium: Medivation/Pfizer. A.D. Choudhury: Honoraria: Bayer, Astellas Australia, Janssen Latin America; Research funding: Bayer (pending). M. Pomerantz: Advisory Board/committee: NCI/PDQ; Speakers bureau: Astellas, APACE, MD Anderson, PCF. J. Bellmunt: Advisory role: Genentech, MSD, Pfizer, GSK, BMS, Pierre-Fabre, Sanofi Aventis, Astellas, OncoGenex, Janssen; Lectures fee: Pfizer, MSD, GSK, Novartis, Pierre-Fabre, Astellas; Research funding: Takeda, Pfizer, Novartis, Sanofi Aventis. C. Yu: Employee: Daiichi Sankyo, Inc. S. Srinivas: Advisory board; Research funding: Exelexis DSMC: Pfizer P.W. Kantoff: Scientific Advisory board; BIND Biosciences, Inc., BN Immunotherapeutics. Context Therapeutics LLC, DRGT, GE Healthcare, Janssen, Metamark (-no longer in business), New England Research Institutes, Inc., OncoCellMDX, Progenity, Sanofi, Seer Biosciences, Tarveda Therapeutics (previously Blend), Thermo Fisher; Investment interests: Context Therapeutics, DRGT, placon, Seer, Tarveda therapeutics. C. Sweeney: Stock or Other ownership: Leuchemix Consulting; Advisory Role: Sanofi, Janssen Biotech, Astellas Pharma, Bayer, Genentech, AstraZeneca, Pfizer, Tolmar; Research funding: Janssen Biotech (Inst), Astellas Pharma (Inst), Sanofi (Inst), Bayer (Inst), Sotio (Inst) Patents, royalties; Other Intellectual Property: Leuchemix: Parthenolide, dimethylaminoparthenolide; Exelixis: Abiraterone plus cabozantinib combination L.C. Harshman: Advisory role: Bayer, Genentech, Dendreon, Pfizer, Medivation/Astellas, Kew Group, Theragene, Corvus, Merck, Exelixis, Novartis; Research institution: Bayer, Sotio, Bristol-Myers Squib, Merck, Takeda, Dendreon/Valient, Jannsen, Medivation/Astellas, Genentech, Pfizer. All other authors have declared no conflicts of interest.

853P Long-term adverse effects (AEs) after dose-escalation with high-dose rate brachytherapy in combination with external beam radiation therapy (BT/RT). Comparison to external beam radiation therapy alone (RT)

T.B. Wedde, S.D. Fosså, A. Dahl, M-B. Schulz, W. Lilleby

Oncology, Oslo University Hospital, Oslo, Norway

Background: Few studies have compared long-term patient reported AEs of men with Prostate Cancer (PCa) treated with dose-escalation by means of BT/RT to RT (70-78 Gy) alone. In this study, we compare AEs and quality of life (QoL) between these two treatment modalities.

Methods: 259 eligible men from the BT/RT cohort (2004-2011) and 123 patients (2009-2010) from a RT cohort assessed their AEs and QoL by questionnaires a minimum of 5 years after treatment. Hormonal therapy was given for 1-2 years. EPIC-26 covered urinary, sexual and bowel function and bother. The hormone domain was excluded. The SF-12 questionnaire covered QoL. The scores ranged from 0 (worst) to 100 (best). Clinical significance was set to a score difference > 10 points. Statistical significance was evaluated by Student t-test with significance level $p < 0.05$. Chronic fatigue was reported as percentage.

Results: Median age at survey was 74 years for both cohorts. The EPIC-26 and SF12 scores for the above domains were similar in the two cohorts with no clinical or statistical significance (Table). Chronic fatigue was higher after treatment with RT compared BT/RT, although not significantly.

Table: 853P

Measure	BT/RT Mean (SD)	RT Mean (SD)	P value
Sexual function	27.9 (29.5) n = 255	20.8 (24.3) n = 120	0.06
Sexual bother	48.2 (37.5) n = 254	45.9 (34.7) n = 121	0.56
Urinary function	83.6 (18.0) n = 258	80.1 (20.5) n = 123	0.10
Urinary irritation/obstruction	81.3 (19.6) n = 249	81.8 (16.8) n = 113	0.80
Urinary incontinence	88.7 (18.1) n = 258	85.0 (22.5) n = 123	0.11
Urinary bother	79.9 (26.5) n = 257	77.6 (30.0) n = 123	0.47
Bowel function	86.7 (20.6) n = 254	83.1 (21.7) n = 121	0.12
Bowel bother	83.0 (25.1) n = 258	80.4 (26.7) n = 121	0.34
PCS12 (SF12)	46.4 (10.5) n = 224	45.1 (10.1) n = 101	0.30
MCS12 (SF12)	53.6 (8.0) n = 224	52.7 (9.2) n = 101	0.38
Chronic fatigue	22.0% n = 199	27.1% n = 86	0.28

Conclusions: Dose-escalation by means of BT/RT does not increase the AEs reported for the urinary, bowel and sexual domains of EPIC-26 or health-related QoL. Hence, BT/RT is a good treatment option for eligible patients.

Legal entity responsible for the study: Wolfgang Lilleby.

Funding: Raagholt Foundation, Bergersen Foundation, Eckbo Foundation.

Disclosure: All authors have declared no conflicts of interest.

854P Clinical characteristics, treatment outcomes and potential novel therapeutic options for patients with neuroendocrine carcinoma of the prostate (NEPC)

L. Apostolidis[1], C. Nientiedt[1], E.C. Winkler[1], A.K. Berger[1], C. Kratochwil[2], A. Kaiser[3], D. Jäger[1], M. Hohenfellner[4], C. Hüttenbrink[5], S. Pahernik[5], F. Distler[5], C. Grüllich[1]

[1]Department of Medical Oncology, National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany, [2]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany, [3]Institute of Pathology, Klinikum Nürnberg, Paracelsus Medical University, Nürnberg, Germany, [4]Department of Urology, University Hospital Heidelberg, Heidelberg, Germany, [5]Department of Urology, Klinikum Nürnberg, Paracelsus Medical University, Nürnberg, Germany

Background: Neuroendocrine Carcinomas of the prostate (NEPCs) are rare tumors with poor prognosis. While platinum and etoposide based chemotherapy regimens (PE) are commonly applied in first-line for advanced disease, clinical-grade evidence for treatment options in second-line and beyond is very limited. The aim of this study was to analyze the treatment outcomes of NEPC patients.

Methods: Retrospective analysis of all patients NEPCs including mixed differentiation with adenocarcinoma component and well differentiated neuroendocrine tumors (NETs, carcinoids) at two high volume oncological centers between 12/2000 and 11/2017.

Results: Of 43 identified patients 18 (41.9 %) had a prior diagnosis of prostatic adenocarcinoma only, 19 (44.2 %) had a mixed differentiation at NEPC diagnosis, 29 (67.4 %) developed visceral metastases, 5 (15.4 %) showed paraneoplastic syndromes. Overall survival from diagnosis of any prostatic malignancy was 69.2 months, from NEPC diagnosis 15.5 months. 31 patients received palliative first line chemotherapy, mostly PE. Overall response rate (ORR) for PE was 50 %, median progression-free survival (PFS) was 6.6 months. 15 patients received second line therapy, mostly with poor response rates. Regimens with notable activity were topotecan (1 PR, 3 PD), enzalutamide (1 SD), abiraterone (1 SD), FOLFIRI (2 SD), and ipilimumab+nivolumab (1 PR). A single patient with prostatic carcinoid was sequentially treated with octreotide, peptide receptor radionuclide therapy (PRRT) and everolimus and survived for more than 9 years.

Conclusions: Visceral metastases and paraneoplastic syndromes are frequent in NEPC. EP in first-line shows notable ORR, however limited PFS. For patients with progression after first line therapy, topotecan, FOLFIRI, enzalutamide, abiraterone and immune checkpoint blockade are possible treatment options. Prostatic carcinoids can be treated in analogy to well differentiated NETs of the gastrointestinal tract.

Clinical trial identification: The trial was approved by the institutional research ethics committee (approval S-428/2014).

Legal entity responsible for the study: National Center for Tumor Diseases, University Hospital Heidelberg.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

855P Effect of prednisone on docetaxel pharmacokinetics in metastatic prostate cancer: A randomized drug-drug interaction study

B.P.S.I. Belderbos[1], K.G.A.M. Hussaarts[1], L. van Harten[1], E. Oomen-De Hoop[1], P. de Bruijn[1], P. Hamberg[2], R.J. van Alphen[3], B.C.M. Haberkorn[4], R.J. van Soest[1], R. de Wit[1], R.H.J. Mathijssen[1]

[1]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [2]Department of Medical Oncology, St Franciscus Gasthuis, Rotterdam, Netherlands, [3]Department of Medical Oncology, Twee Steden Ziekenhuis, Tilburg, Netherlands, [4]Department of Medical Oncology, Maasstad, Rotterdam, Netherlands

Background: In metastatic hormone-naïve prostate cancer it is currently unclear whether docetaxel chemotherapy should be administered with or without prednisone. Furthermore, the role of corticosteroids in metastatic castration-resistant prostate cancer is controversial, concerning its limited effect on chemotherapy-induced toxicities, small biological anti-tumor effect on PSA-response, and potential toxicity of long-term use. Prednisone is known to induce CYP3A4, which metabolizes taxanes, resulting in a possible drug-drug interaction (DDI). Therefore, we investigated the pharmacological aspects of the addition of prednisone to docetaxel chemotherapy in men with metastatic prostate cancer.

Methods: We conducted a prospective randomized pharmacokinetic (PK) cross-over study in metastatic prostate cancer patients, who received 6 cycles of docetaxel (Q3W, 75mg/m^2), in which prednisone was added to 3 consecutive chemotherapy cycles. These were followed or preceded (determined by randomization) by 3 consecutive cycles of docetaxel monotherapy. Blood sampling for PK purposes occurred during cycle 3 and cycle 6. Primary endpoint was the difference in docetaxel exposure ($AUC_{0\text{-}inf}$) with concomitant prednisone, compared to exposure of docetaxel monotherapy by means of a linear mixed model analysis on log-transformed data.

Results: Eighteen patients were evaluable for the primary endpoint. Docetaxel exposure with concomitant prednisone (geomean $AUC_{0\text{-}inf}$ 2784 ng*h/mL, CV 27%) was slightly higher (1.8%; 95% CI -9.9% till 15.2%, $p = 0.75$) as compared to docetaxel monotherapy (geomean $AUC_{0\text{-}inf}$ 2647 ng*h/mL, CV 22%). Toxicity rates were similar for docetaxel cycles with and without prednisone.

Conclusions: No difference in docetaxel pharmacokinetics in cycles with or without prednisone was observed. Moreover, we found similar toxicity profiles in the docetaxel cycles with concomitant prednisone as in the docetaxel monotherapy cycles. This suggests that docetaxel for metastatic prostate cancer can be administrated safely without prednisone from a pharmacological perspective.

Clinical trial identification: EudraCT: 2016-001269-10; Dutch trial register: NTR6037.

Legal entity responsible for the study: Erasmus MC Cancer Institute.

Funding: Dutch Uro-Oncology Studygroup.

Disclosure: R.J. van Soest: Honoraria: Astellas, Sanofi, Janssen. R. de Wit: Consultancy role, speakers fee: Sanofi. R.H.J. Mathijssen: Research support: Astellas, Bayer, Boehringer Ingelheim, Cristal Therapeutics, Novartis, Pamgene, Pfizer, Roche en Sanofi; Consultation fees: Novartis, Servier; Travel support: Astellas, Pfizer. All other authors have declared no conflicts of interest.

856P Differences in treatment recommendations for advanced prostate cancer according to region and medical specialization: Analysis of the APCCC 2017 voting results

S. Fischer[1], S. Gillessen[2], M.R. Sydes[3], A.G. Omlin[1]

[1]Medical Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, Switzerland, [2]Division of Cancer Sciences, University of Manchester and the Christie, Manchester, UK and Division of Medical Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, University of Bern, Switzerland, [3]MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology-UCL, London, UK

Background: Development of new agents & therapy combinations in prostate cancer has led to uncertainty in best management approaches. The widely-attended Advanced Prostate Cancer Consensus Conference (APCCC) 2017 convened in Mar-2017 to provide expert opinions on open questions.

Methods: The 52 invited APCCC 2017 panelists were 15 urologists, 26 medical oncologists (onc), 11 radiation onc (incl. 4 clinical onc), from the following regions: 19 Europe, 24 N America, 9 other incl. Australia. We assessed the relationship of panelists' specialization & regions with the responses to the consensus questions.

Results: Voting results of 3 APCCC 2017 consensus questions (Table) cover adding docetaxel to androgen deprivation (ADT) in low-volume (LV) castration-naïve metastatic PCa (mCNPC), adding radium-223 in men with progression on treatment with abiraterone/enzalutamide and first-line treatment for castration-resistant prostate cancer (CRPC) after chemo-hormonal therapy. There was a confirmed difference in preference for docetaxel in LV pts by region; there may be differences on other matters by region of practice and specialization. Results of further questions will be presented.

Conclusions: This dataset allows exploration of expert recommendations by region and medical specialization. Our data suggests that there are substantial differences highlighting the importance of international and multidisciplinary representation in consensus conferences.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 856P

	Region			Speciality		
Question	Europe	North America	Other	Urology	Medical Oncology	Radiation Oncology
N	19	24	9	15	26	11
Do you recommend docetaxel plus ADT in de novo low-volume mCNPC?						
In majority	53%	13%	22%	27%	23%	45%
In selected minority	47%	79%	67%	67%	69%	55%
No	0%	8%	11%	7%	8%	0%
In mCRPC pats on abi/enza with progress only in the bone, do you recommend the addition of radium-223?						
In majority	28%	52%	50%	50%	29%	64%
In selected minority	39%	39%	38%	36%	46%	27%
No (inc stop abi/enza)	33%	9%	13%	14%	25%	9%
Preferred first-line mCRPC treatment in symptomatic men with PD within 6 m after chemo-hormonal therapy for CNPC?						
Abi/Enza	37%	70%	71%	62%	56%	55%
Cabazitaxel	42%	13%	29%	38%	28%	9%
Docetaxel	0%	0%	0%	0%	0%	0%
Radium-223	16%	4%	0%	0%	4%	27%
Other or no pref.	5%	13%	0%	0%	12%	9%

857P United in fight against prostate cancer registry (UFO): First results from a large, multi-center, prospective, longitudinal cohort study in Asia

H. Uemura[1], D. Ye[2], R. Kanesvaran[3], H. Zeng[4], Y-S. Pu[5], E. Chiong[6], B. Lojanapiwat[7], S.K. Rawal[8], B.H. Chung[9], A.H.A. Razack[10], Y-S. Tsai[11], Y. Liu[12], M. Asinas-Tan[13], W. Liu[14], G.K.M. Low[13], M.A.G. van Kooten Losio[15]

[1]Faculty of Medicine, Kinki University Hospital, Osaka, Japan, [2]Dept of Urology, Fudan University Shang Hai Cancer Center, Shang Hai, China, [3]3. Division of Medical Oncology, National Cancer Centre Singapore, Singapore, [4]West China Hospital, Sichuan University, Sichuan, China, [5]Department of Urology, National Taiwan University Hospital, Taipei, Taiwan, [6]Department of Urology, National University Health System, Singapore, [7]Division of Urology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, [8]GenitoUro-Oncology, Rajeev Gandhi Cancer Institute, New Delhi, India, [9]Department of Urology and Urological Science Institute, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, [10]Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [11]Department of Urology, National Cheng Kung University Hospital, Tainen, Taiwan, [12]Janssen Research and Development, Epidemiology, Titusville, FL, USA, [13]Janssen Medical Affairs, Singapore, [14] SDS China Department, Janssen (China) Research & Development Center, Shanghai, China, [15]Medical, Janssen Cilag Australia, Macquarie Park, Australia

Background: The way in which prostate cancer (PC) is diagnosed and treated is fragmented across some Asian countries. We have established a PC registry (UFO) with the aim of providing a comprehensive picture of PC diagnosis, prognosis, treatment and outcome. The registry will collect patient-reported treatment outcomes and underlying reasons for clinical decision-making.

Methods: This is a large multi-national, prospective, observational registry of PC patients presenting to tertiary care hospitals in China, India, Japan, Malaysia, Singapore, South Korea, Taiwan and Thailand. Patients with existing or newly diagnosed high-risk localized PC (HRL), non-metastatic biochemically recurrent PC (M0), or metastatic PC (M1), are being consecutively enrolled and followed for up to 5 years. Patient history, demographic and disease characteristics were collected at first PC diagnosis and enrollment. The first interim analysis of baseline characteristics includes all patients enrolled from study start (15 Sept 2015) until 17 May 2017.

Results: 2,063 eligible patients were enrolled in the interim analysis: 357 (17%), 378 (19%), and 1328 (64%) had HRL, M0 or M1 PC. Among M1 patients, 1038 had hormone-sensitive PC (mHSPC) and 290 had castration-resistant PC (mCRPC). Mean age at first diagnosis was similar in each group (Table). At enrollment, 62% of patients had at least one co-morbidity; mainly cardiovascular disease or diabetes and 14.3% of M0 patients were castration-resistant. A total of 84.5% of patients with mHSPC and 75.9% with mCRPC had de novo metastases. Decisions to start therapy were mainly driven by PSA or clinical progression. Decision to discontinue therapy was most often due to disease progression (hormonal therapy) or completion of therapy (chemotherapy).

Conclusions: The UFO registry will provide descriptive data on current disease characteristics and treatment landscape among patients with PC in Asia.

Editorial acknowledgement: Writing assistance was provided by Joanne Wolter (independent) on behalf of of Janssen.

Legal entity responsible for the study: Johnson & Johnson.

Funding: Janssen.

Table: 857P Baseline characteristics of patients with prostate cancer

Characteristic	HRL N = 357	M0 N = 378	mHSPC N = 1038	mCRPC N = 290
Years from diagnosis until enrolment, median (IQR)	2.7 (0.5-4.0)	6.7 (3.7-9.7)	2.5 (0.2-3.5)	4.3 (1.8-5.5)
Age at first diagnosis (years) mean (SD)	68.3 (8.10)	65.7 (6.83)	69.1 (7.91)	67.6 (8.38)
PSA at diagnosis (ng/mL), median (IQR)	29.1 (14.7-59.5)	13.2 (7.7-25.1)	105 (40.8-498)	100 (3.5-9883)
Reasons that triggered suspicion of PC				
Symptom driven	56.9%	42.1%	68.6%	77.5%
During regular health screening	31.4%	46.1%	14.5%	13.0%
Incidental finding	11.7%	11.8%	16.9%	9.5%
Had undergone radiologic imaging at enrollment	29.1%	16.7%	100%	100%
% castrated at enrollment	79.3%	70.4%	85.6%	100%
Prior treatment				
Radiotherapy	37.4%	52.4%	11.8%	26.9%
Hormonal therapy	56.9%	58.7%	55.2%	79.7%
Chemotherapy	0.0%	0.0%	8.8%	21.4%
Orchiectomy	2.3%	2.6%	11.0%	24.1%
Prostatectomy	37.7%	65.3%	7.8%	9.3%
Reason for initiating hormonal therapy				
PSA progression	17%	52%	24.6%	37.5%
Clinical progression	10%	8.3%	11.4%	11.2%
Radiographic progression	2%	0.5%	3.7%	13.3%
Following treatment guidelines (international, national or site)	40.6%	23.2%	36.3%	55.8%
Disease characteristics	7.4%	11.2%	13.6%	11.2%
Reason for initiating chemotherapy				
PSA progression	-	-	30.4%	48.3%
Clinical progression	-	-	12.5%	25.0%
Radiographic progression	-	-	8.3%	15.0%
Following treatment guidelines (international, national or site)	-	-	29.2%	15.0%
Disease characteristics	-	-	7.7%	1.7%
Reason for stopping hormonal therapy				
Treatment-related side-effects	2.3%	2.6%	2.8%	14.0%
Stable disease	5.8%	9.2%	-	-
Disease progression	26.7%	39.5%	42.0%	62.3%
Reason for stopping chemotherapy				
Treatment-related side-effects	-	-	8.0%	9.1%
Completed therapy	-	-	54.5%	50.0%
Disease progression	-	-	20.5%	34.1%
New or deterioration of existing comorbidities	-	-	-	4.5%
Patient's decision	-	-	1.1%	2.3%

SD = standard deviation, IQR = interquartile range

Disclosure: H. Uemura: Grants: Janssen, Astellas, Takeda, AstraZeneca; Personal fees: AstraZeneca, Astellas, Sanofi; Other: Sanofi, outside the submitted work. R. Kanesvaran: Grants, Personal fees: Johnson & Johnson, outside the submitted work. E. Chiong: Institutional grants: Janssen during the conduct of the study; Honoraria, Conference support: Janssen outside the submitted work. Y. Liu: Employee: Janssen Research and Development, LLC; Stock owner: J&J. M. Asinas-Tan: Employee: Johnson & Johnson Pte Ltd. W. Liu: Employee: Johnson & Johnson (China) Investment Ltd. G.K.M. Low: Employee: Janssen Asia Pacific, Medical affairs; Stock owner: J&J. M.A.G. van Kooten Losio: Employee: Johnson & Johnson Pte Ltd; Stock owner: J&J. All other authors have declared no conflicts of interest.

858P Deployment of advanced real-world data (RWD) analytics for the accelerated recruitment of patients into an ongoing metastatic castrate-resistant prostate cancer (mCRPC) trial, together with the development of a sophisticated patient referral network

M.G. Cushion

Analytics Centre of Excellence, IQVIA, London, UK

Background: Proprietary advanced analytics were applied within US RWD, e.g. medical/prescription claims and physician reference data, to identify high potential sites and physicians treating eligible mCRPC patients, with the aim of accelerating recruitment into an ongoing mCRPC clinical trial. Furthermore, a bespoke methodology to identify physician-to-investigator relationships was used to implement an advanced data driven patient referral network.

Methods: Relevant standard diagnosis, drug, and procedure codes were applied to medical and prescription claims datasets and cross-linked with physician reference data, to identify medical oncologists treating the target patient population. Physicians were also referenced to their affiliated sites. Shared patient counts between investigators and local physicians were also quantified, providing valuable insights into physician-to-investigator relationships to prioritise and leverage into a patient referral network.

Results: Selected results summarised below: ~20k eligible patients were identified - 270 sites each with ≥20 eligible patients were identified ~2k oncologists treating eligible patients and with trial experience in the past year were identified ~4k shared patients between targeted physicians and trial investigators were identified.

Conclusions: To facilitate faster patient access to effective medicines, novel methods such as those outlined above are required to optimise clinical trial operations and increase efficiency. Together with the innovative use of RWD to find eligible mCRPC patients and the physicians and sites treating these, we implemented sophisticated techniques to quantify shared patient counts between identified physicians and investigators. This created a foundation for a referral network that has been successfully implemented, as an alternative to the lengthy and costly initiation of a new site(s). This approach would be invaluable in future trials with ever smaller patient populations, for example within rare diseases and precision medicine.

Legal entity responsible for the study: IQVIA.

Funding: IQVIA.

Disclosure: The author has declared no conflicts of interest.

859TiP TALAPRO-1: An open-label, response rate phase II study of talazoparib (TALA) in men with DNA damage repair defects (DDR) and metastatic castration-resistant prostate cancer (mCRPC) who previously received taxane-based chemotherapy (CT) and progressed on ≥ 1 novel hormonal therapy (NHT)

J.S. de Bono[1], C. Higano[2], F. Saad[3], K. Miller[4], M. Casey[5], A. Czibere[6], C. Healy[5], K. Fizazi[7]

[1]Drug Development Unit, The Royal Marsden NHS Foundation Trust, London, UK, [2]Medical Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Urology, Centre Hospitalier de l'Universite de Montréal (CHUM), Montreal, QC, Canada, [4]Medical Oncology, Charité–Universitätsmedizin Berlin, Berlin, Germany, [5]Medical Oncology, Pfizer, Inc., Collegeville, PA, USA, [6]Medical Oncology, Pfizer, Inc., Cambridge, MA, USA, [7]Cancer Medicine, Institut Gustave Roussy, Villejuif, France

Background: No therapies are currently approved for men with mCRPC who have progressed on taxane and NHT. Preclinical evidence has shown that DDR+ prostate tumours may be sensitized to PARP inhibition. TALA inhibits PARP activity and traps PARP on DNA, preventing DNA damage repair and causing cell death in BRCA1/2-mutated cells.

Trial design: Approximately 100 patients (pts) will be enrolled. Eligible pts are ≥18 yrs with measurable soft tissue disease per RECIST v1.1 and have progressive mCRPC, DDR likely to sensitize to PARP inhibition, ECOG PS ≤ 2, no brain metastases, and received 1-2 CT regimens (including ≥1 taxane-based regimen) and progressed on ≥ 1 NHT (enzalutamide or abiraterone acetate). Pts who received a prior PARP inhibitor, cyclophosphamide, mitoxantrone, or a platinum-based CT within 6 mos of study entry or progressed on a platinum-based CT at any time are excluded. Pts will receive TALA 1 mg/d orally (or 0.75 mg/d for those with moderate renal impairment) until radiographic progression, unacceptable toxicity, or withdrawal of consent. Study drug should not be discontinued based on increased PSA or circulating tumour cell (CTC) count alone. Primary endpoint is best objective response (OR) rate (exact 2-sided 95% CI), defined as a complete or partial soft tissue response per RECIST v1.1. Responses must be confirmed ≥4 wks later by CT/MRI with no evidence of confirmed bone progression per PCWG3 criteria on repeat bone scan ≥6 wks later. Secondary endpoints include time to OR, duration of response, PSA decrease ≥50%, CTC count conversion (to CTC=0 and CTC <5 per 7.5 mL of blood), time to PSA progression, radiographic progression-free survival, overall survival, safety, patient-reported outcomes, and pharmacokinetics of TALA. Efficacy will be assessed every 8 wks during the first 24 wks, then every 12 wks thereafter. An initial safety and efficacy analysis will be performed on 20 pts after receiving study drug ≥8 wks. An interim efficacy analysis is planned when 60 pts have completed ≥6 mos of treatment.

Clinical trial identification: NCT03148795.

Editorial acknowledgement: Editorial and medical writing support funded by Pfizer Inc. were provided by Edwin Thrower, PhD, Mary Kacillas and Paula Stuckart of Ashfield Healthcare Communications, Middletown, Connecticut.

Legal entity responsible for the study: Pfizer, Inc.

Funding: This study was sponsored by Pfizer Inc.

Disclosure: J.S. de Bono: Consulting fees: AstraZeneca, Sanofi, Genentech, Astellas, Bayer, Pfizer, Merck Sharp & Dohme, Merck Serono, Boehringer Ingelheim; Honoraria: AstraZeneca, Sanofi, Astellas, Pfizer, Genentech; Contracted research: AstraZeneca, Genentech, Sanofi. C. Higano: Consulting fees: Dendreon, Bayer, Ferring, Orion Corp, Astellas, Clovis, Asana Biosciences, Endocyte, Blue Earth Diagnostics, Myriad Genetics, Tolmar; Honoraria: Genentech; Contracted research Aragon, AstraZeneca, Dendreon, Genentech, Medivation, Emergent BioSolutions, Bayer, Pfizer, Roche, Astellas. F. Saad: Consulting fees: Astellas, Janssen, Amgen, Sanofi, AstraZeneca; Honoraria: Astellas, Abbvie, Amgen, Janssen, Sanofi, Bayer; Contracted research: Astellas, Bayer, Amgen, Janssen, BMS, Oncogenex, Sanofi. K. Miller: Consulting fees, Honoraria: Advanced Accelerator Applications, Amgen, Bayer, BMS, Ferring, Janssen, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sotio, Tolmar. M. Casey, A. Czibere, C. Healy: Employee: Pfizer, Inc. K. Fizazi: Consulting fees, honoraria: Astellas.

860TiP Phase II trial evaluating olaparib maintenance in patients with MCRPC after docetaxel treatment reaching partial or stable response

M.J. Juan Fita[1], L. Heras Lopez[2], B. Mellado[3], M.J. Mendez Vidal[4], U. Anido[5], D. Lorente[6], J.M. Sepulveda[7], C. Alvarez[8]

[1]Medical Oncologist, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [2]Medical Oncologist, ICO, Barcelona, Spain, [3]Medical Oncologist, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [4]Medical Oncologist, University Hospital Reina Sofia, Cordoba, Spain, [5]Medical Oncologist, CHU Santiago, Santiago, Spain, [6]Medical Oncologist, HULa Fe, Valencia, Spain, [7]Medical Oncologist, Juan Manuel Sepúlveda, Valencia, Spain, [8]Medical Oncologist, HCU Asturias, Asturias, Spain

Background: Durable and complete responses following docetaxel chemotherapy in patients with advanced prostate cancer (PC) are uncommon. Most patients will ultimately experience disease progression within 6-months after initial response. Optimal second line therapy in metastatic castration resistant PC (MCRPC) is not well established and several options are possible. Maintenance treatment in tumpurs as non-small cell lung cancer or ovarian cancer has become a standard improving overall survival (OS), and a phase II study in bladder cancer has demonstrated longer progression-free-survival (PFS) after first-line platinum with vinflunine maintenance.Recently PARP-inhibitors have demonstrated improvement in response and PFS in MCRPC with somatic or germline DNA-repair defects (1-4).

Trial design: IMANOL (NCT03434158) is a phase II trial of olaparib (300 mg tablet bid) maintenance in patients with MCRPC and a complete or partial response to docetaxel treatment and germline or somatic mutation studied by a next-generation sequencing panel of homologous recombination repair genes. Primary endopint is to assess the effect of olaparib maintenance on radiologic PFS in these patients (RECIST v1.1). Secondary endpoints are: effect of maintenance treatment on PSA-PFS and clinical PFS, PSA response rate, safety and tolerability. Exploratory objectives are: to determine the frequency of BRCA and other genes mutations and to stablish a correlation between tumour and germline mutation presence. Previous studies showed that one year rPFS was about 10%. To accept treatment efficacy we will assume that the 12 months rPFS with olaparib maintenance will be at least 30%. An overall simple size of 27 patients achieves 80% power at a 0,05 significance level (alpha) to accept the efficacy of this treatment after completion 6-8 cycles of docetaxel. An accrual time of 12 months in 8 SOGUG centres in Spain is planned.

Clinical trial identification: NCT03434158.

Legal entity responsible for the study: SOGUG.

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.

861TiP Multimodality treatment for pN1 prostate cancer: Adding elective para-aortic radiation in the PART trial

C. Berghen[1], S. Joniau[2], C. Draulans[1], G. De Meerleer[1]

[1]Radiation Oncology, University Hospitals Leuven, Leuven, Belgium, [2]Urology, University Hospitals Leuven, Leuven, Belgium

Background: Multimodality treatment offers promising results in patients with histopathological proven pelvic lymph node metastatic (pN1) prostate cancer. Improved cause-specific survival rates are reported when treating the primary tumor combined with whole pelvic radiotherapy and androgen deprivation therapy (ADT) compared to ADT alone. However, in case of tumoral invasion of > 1 pelvic lymph node, approximately 40% of the patients relapse biochemically and clinically. This clinical relapse is located in the para-aortic lymph nodes (M1a disease) in up to 77% of relapsed cases. We hypothesize that adding elective para-aortic radiation will reduce the development of both retroperitoneal nodal (M1a) and distant metastasis (M1b/M1c), postpone the need for palliative ADT and prolong the time to castration-refractory disease.

Trial design: This is a multicenter, non-randomized phase 2 trial (NCT03079323) conducted in 5 sites in Belgium. Men are eligible for the study when (1) age >18 years, (2) histological proven adenocarcinoma of the prostate at biopsy (cT1-4) and referred for primary high-dose radiotherapy or after radical prostatectomy (pT2-4), and (3) presence of pN1 disease after extended pelvic lymph node dissection. If pN1 disease is present, patients are eligible if one of the following criteria is fulfilled: $\geq$ 2 positive lymph nodes, a ratio positive / removed lymph nodes > 7% or presence of extracapsular metastatic extension at the level of any lymph node. Patients will receive radiotherapy on the prostate (bed), pelvic lymph nodes and the para-aortic lymph nodes combined with 24 months of ADT. We aim to include 137 patients to detect an improvement in clinical relapse free survival (cRFS) by 15% at 5 years (power of 80%).

The primary endpoint is 5 year-clinical relapse-free survival (cRFS) defined as the absence of any clinical relapse that would be visible at top of the line imaging. Secondary endpoints are Quality of life (QoL), treatment-related acute and late toxicity, time to palliative ADT, time to castration refractory prostate cancer (CRPC), cause-specific survival (CSS) and in field pelvic and para-aortic disease control. Recruitment is ongoing, with the first patient included in the trial on 06/02/2017.

Clinical trial identification: NCT03079323.

Legal entity responsible for the study: University Hospitals Leuven, Belgium.

Funding: "Kom op tegen kanker (Stand up to Cancer), the Flemish Cancer Society". (ref. 0010048).

Disclosure: All authors have declared no conflicts of interest.

862TiP ReCab II: A phase II trial of Cabazitaxel +/- Rhenium -188-HEDP in patients with metastatic castration resistant prostate cancer who progressed on or after a docetaxel containing treatment

E. Bouman-Wammes[1], J.M. van Dodewaard-De Jong[2], H. Bloemendal[2], H.M. Verheul[1], J.M.H. de Klerk[3], A.J.M. van den Eertwegh[1]

[1]Medical Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [2]Medical Oncology, Meander Medical Center, Amersfoort, Netherlands, [3]Nuclear medicine, Meander Medical Center, Amersfoort, Netherlands

Background: Bone is the most common site of metastases in patients with castration resistant prostate cancer (CRPC) leading to serious morbidity and mortality. Nowadays, cabazitaxel is the standard second line of chemotherapy. Besides, a survival benefit has been proven for the alfa-emitting radiopharmaceutical Radium-223-chloride and has been suggested for other, beta-emitting, radiopharmaceuticals such as rhenium-188-HEDP as well. Rhenium-188-HEDP has a proven and favorable effect on pain caused by bone metastases. In this trial, we will investigate the effect of the addition of rhenium-188-HEDP to standard treatment with cabazitaxel on the progression free survival, overall survival and quality of life.

Trial design: In total, 86 patients with CRPC metastatic to bone and progressive disease during or after treatment with docetaxel will be included. Patients will be randomized between two arms. Patients in arm A will be treated with the standard schedule of cabazitaxel; cabazitaxel 25mg/m^2 every three weeks. Patients in the intervention arm will receive an injection of rhenium-188-HEDP 40 MBq/kg three weeks after the second and three weeks after the fourth administration of cabazitaxel 25mg/m^2. The interval between the injection of the rhenium-188-HEDP and the next cycle of cabazitaxel will be 4 weeks because of nadir of the expected thrombopenia after 4 weeks. The primary endpoint is progression free survival, with overall survival, clinical benefit, quality of life, PSA and pain response and toxicity as secondary endpoints. PSA, pain and quality of life will be measured every treatment cycle (i.e. every 3 weeks), imaging will be performed pre-cycle 4 and pre-cycle 7, or when progression is suspected based on clinical findings or a rise in PSA. The statistical analysis will be performed by using a stratified logrank test comparing both groups with respect to the time to progression. Time-to-event will be analyzed by the Kaplan-Meier method.

Legal entity responsible for the study: AJM Van den Eertwegh.

Funding: Sanofi Genzyme Teva Pharma.

Disclosure: All authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii303–viii331, 2018
doi:10.1093/annonc/mdy283

GENITOURINARY TUMOURS, NON-PROSTATE

863O Axitinib vs placebo in patients at high risk of recurrent renal cell carcinoma (RCC): ATLAS trial results

M. Gross-Goupil[1], T.G. Kwon[2], M. Eto[3], D. Ye[4], H. Miyake[5], S.I. Seo[6], S.S. Byun[7], J.L. Lee[8], V. Master[9], J. Jin[10], R. Debenedetto[11], R. Linke[12], M. Casey[13], B. Rosbrook[14], M.J. Lechuga Frean[15], O. Valota[16], E. Grande[17], D.I. Quinn[18]

[1]Department of Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France, [2]School of Medicine, Kyungpook National University, Daegu, Republic of Korea, [3]Department of Clinical Medicine, Kyushu University, Fukuoka, Japan, [4]Shanghai Cancer Center, Fudan University, Shanghai, China, [5]School of Medicine, Hamamatsu University, Hamamatsu, Japan, [6]Department of Urology, Sungkyunkwan University, Seoul, Republic of Korea, [7]Bundang Hospital, Seoul National University, Seongnam, Republic of Korea, [8]University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, [9]Department of Urology, Emory University School of Medicine, Atlanta, GA, USA, [10]Department of Urology, Peking University First Hospital, Beijing, China, [11]Clinical Development and Medical Affairs, SFJ-Pharmaceuticals, Pleasanton, CA, USA, [12]Clinical Development and Medical Affairs, SFJ-Pharmaceuticals, Inc., Pleasanton, CA, USA, [13]Department of Oncology, Pfizer Inc, Collegeville, PA, USA, [14]Translational Oncology, Pfizer Inc, La Jolla, CA, USA, [15]Department of Oncology, Pfizer Italia srl, Milan, Italy, [16]Department of Oncology, Pfizer - Srl, Milan, Italy, [17]Head of Medical Oncology Department, MD Anderson Cancer Center Center Espana, Madrid, Spain, [18]Translation and Clinical Science Program/Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA

864O Pembrolizumab for high-risk (HR) non–muscle invasive bladder cancer (NMIBC) unresponsive to bacillus Calmette-Guérin (BCG): Phase II KEYNOTE-057 trial

R. de Wit[1], G.S. Kulkarni[2], E. Uchio[3], E.A. Singer[4], L. Krieger[5], P. Grivas[6], D. Bajorin[7], H.K. Seo[8], L. Mourey[9], A. Kamat[10], H. Nishiyama[11], E. Kapadia[12], K. Nam[12], T. Frenkl[12], A. Balar[13]

[1]Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [2]Surgery and Surgical Oncology, UHN Princess Margaret Cancer Centre, Toronto, ON, Canada, [3]Urology, UC Irvine Health, Orange, CA, USA, [4]Urology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA, [5]Medical Oncology, Royal North Shore Hospital, Northern Cancer Institute, St. Leonards, Australia, [6]Medical Oncology, University of Washington, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [7]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [8]Urology, National Cancer Center, Goyang, Republic of Korea, [9]Medical Oncology, Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France, [10]Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [11]Urology, University of Tsukuba, Tsukuba, Japan, [12]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [13]Medicine, NYU Langone Medical Center, New York, NY, USA

865PD RANGE, a phase III, randomized, placebo-controlled, double-blind trial of ramucirumab (RAM) and docetaxel (DOC) in platinum-refractory urothelial carcinoma (UC): Overall survival results

D.P. Petrylak[1], C.N. Sternberg[2], A. Drakaki[3], R. de Wit[4], H. Nishiyama[5], A. Necchi[6], D. Castellano[7], A. Bamias[8], K.N. Chi[9], M.S. van der Heijden[10], N. Matsubara[11], S. Hussain[12], A. Flechon[13], B.Y. Alekseev[14], E.Y. Yu[15], R.A. Walgren[16], F. Russo[17], A.H. Zimmermann[16], K.M. Bell-Mcguinn[16], T.B. Powles[18]

[1]Medical Oncology, Yale University School of Medicine Medical Oncology, New Haven, CT, USA, [2]Medical Oncology, Azienda Ospedaliera S. Camillo Forlanini, Rome, Italy, [3]Medicine, UCLA Medical Center, Los Angeles, CA, USA, [4]Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, [5]Urology, University of Tsukuba, Tsukuba, Japan, [6]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [7]Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain, [8]Clinical Therapeutics, University of Athens, "Sotiria" General Chest Diseases Hospital, Athens, Attiki, Greece, [9]Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, [10]Medical oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, [11]Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [12]Oncology, Plymouth University, Plymouth, UK, [13]Medical Oncology, Centre Léon Bérard, Lyon, France, [14]Oncology, Herzen Cancer Research Institute, Moscow, Russian Federation, [15]Medical Oncology, University of Washington, Seattle, WA, USA, [16]Oncology, Eli Lilly and Company, Indianapolis, IN, USA, [17]Oncology, Eli Lilly and Company, Florence, SC, USA, [18]Oncology, St. Bartholomew's Hospital, London, UK

866PD Comprehensive biomarker analyses and updated results of PURE-01 study: Neoadjuvant pembrolizumab (pembro) in muscle-invasive urothelial bladder carcinoma (MIBC)

A. Necchi[1], A. Briganti[2], D. Raggi[3], R.' Luciano[4], M. Colecchia[5], S. Massa[5], P. Giannatempo[1], R. Colombo[2], A. Gallina[2], R. Salvioni[6], R. Mortarini[7], F. Montorsi[8], R. Madison[9], S.M. Ali[10], J.S. Ross[11], J. Chung[10], A. Anichini[12]

[1]Medical Oncology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [2]Vita Salute San Raffaele University and Urological Research Institute (URI), IRCCS San Raffaele Hospital, Milan, Italy, [3]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [4]Pathology, IRCCS San Raffaele Hospital, Milan, Italy, [5]Pathology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [6]Urology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [7]Immunology Unit, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [8]Urological Research Institute (URI), IRCCS San Raffaele, Milan, Italy, [9]Clinical Bioinformatics Operations, Foundation Medicine, Cambridge, MA, USA, [10]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA, [11]Medicine, SUNY Upstate Medical University, Syracuse, NY, USA, [12]Human Tumors Immunotherapy Unit, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy

867PD Comprehensive genomic profiling (CGP) of chemotherapy-resistant, primary mediastinal nonseminomatous germ cell tumors (PMNSGCT)

A. Necchi[1], G. Bratslavsky[2], R.J. Corona[2], J. Chung[3], S.Z. Millis[3], L.M. Gay[4], J-A. Elvin[3], J-A. Vergilio[3], S. Ramkissoon[3], E. Severson[3], S. Daniel[3], J.K. Killian[3], S.M. Ali[3], A.B. Schrock[3], V.A. Miller[3], J.S. Ross[5]

[1]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Medical Oncology, Upstate Medical University, Syracuse, NY, USA, [3]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA, [4]Pathology, Foundation Medicine, Cambridge, MA, USA, [5]Medicine, SUNY Upstate Medical University, Syracuse, NY, USA

868PD Brain metastases response to nivolumab in patients with renal cell carcinoma (RCC): Prospective analysis from the GETUG-AFU 26 (NIVOREN) trial

R. Flippot[1], C. Dalban[2], B. Laguerre[3], D. Borchiellini[4], G. Gravis[5], S. Negrier[2], C.M. Chevreau[6], F. Joly[7], L. Geoffrois[8], S. Ladoire[9], H. Mahammedi[10], F. Tantot[11], B. Escudier[12], L. Albiges[13]

[1]Medical Oncology, Gustave Roussy, Villejuif, France, [2]Medical Oncology, Centre Léon Bérard, Lyon, France, [3]Medical Oncology, Centre Eugene - Marquis, Rennes, France, [4]Medical Oncology, Centre Antoine Lacassagne, Nice, France, [5]Medical Oncology, Institute Paoli Calmettes, Marseille, France, [6]31, Institut Universitaire du Cancer - Toulouse- Oncopole, Toulouse, Haute-Garonne, France, [7]Medical Oncology, Centre Francois Baclesse Caen, Caen, France, [8]Medical Oncology, Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandoeuvre les Nancy, France, [9]Medical Oncology, Centre Georges-François Leclerc, Dijon, France, [10]Medical Oncology, Centre Jean Perrin, Clermont-Ferrand, France, [11]Clinical Research, UNICANCER, Paris, France, [12]Medical Oncology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [13]Medical Oncology, Institut Gustave Roussy, Villejuif, France

869PD Tumor molecular characteristics in patients (pts) with international metastatic renal cell carcinoma database consortium (IMDC) good (G) and intermediate/poor (I/P) risk

B. Beuselinck[1], A. Verbiest[2], G. Couchy[3], S. Job[4], A. de Reyniès[4], S. Caruso[3], V. Verkarre[5], N. Rioux-Leclercq[6], P. Schöffski[1], Y. Vano[7], R-T. Elaidi[8], E. Lerut[9], M. Albersen[10], S. Oudard[11], J. Zucman-Rossi[12]

[1]General Medical Oncology, University Hospitals Leuven, Leuven, Belgium, [2]Laboratory of Medical Oncology, KU Leuven, Leuven, Belgium, [3]U1162, INSERM, Paris, France, [4]Biostatistique, La Ligue Contre le Cancer, Paris, France, [5]Pathologie, Hôpital Necker Enfants Malades, Paris, France, [6]Pathology, CHU Pontchaillou, Rennes, France, [7]Oncologie Médicale, HEGP, Paris, France, [8]Oncologie Médicale, ARTIC - Association pour la Recherche de Thérapeutiques Innovantes en Cancérologie, Paris, France, [9]Pathology, University Hospitals Leuven, Leuven, Belgium, [10]Urology, University Hospitals Leuven, Leuven, Belgium, [11]Immunothérapie et Traitement Antiangiogénique en Pathologie Cancérologique, Hopital European George Pompidou, Paris, France, [12]Oncologie Médicale, Université Paris Descartes, Paris, France

870PD Efficacy and safety of axitinib in metastatic papillary renal carcinoma (mPRC): Results of a GETUG multicenter phase II trial (Axipap)

S. Negrier[1], N. Rioux-Leclercq[2], A. Ravaud[3], G. Gravis[4], L. Geoffrois[5], C.M. Chevreau[6], F. Rolland[7], E. Blanc[8], C. Segura-Ferlay[9], D. Perol[10], M. Gross Goupil[3], S. Dermeche[11], A. Flechon[1], L. Albiges[12], B. Escudier[12]

[1]Medical Oncology, Centre Léon Bérard, Lyon, France, [2]Pathology, CHU Pontchaillou, Rennes, France, [3]Medical Oncology, CHU Bordeaux Hôpital St. André, Bordeaux, France, [4]Medical Oncology, Institute Paoli Calmettes, Marseille, France, [5]Medical Oncology, Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandoeuvre les Nancy, France, [6]Medical Oncology, Institut Universitaire du Cancer -Toulouse Oncopole, Toulouse, France, [7]Medical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [8]Clinical Research Department, Centre Léon Bérard, Lyon, France, [9]Biostatistics, Centre Leon Bérard, Lyon, France, [10]Clinical Research, Centre Léon Bérard, Lyon, France, [11]Medical Oncology, Institute Paoli Calmettes, Marseille, France, [12]Medical Oncology, Institut Gustave Roussy, Villejuif, France

871P KEYNOTE-427 cohort A: Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (ccRCC)

F. Donskov[1], D.F. McDermott[2], J.L. Lee[3], C. Szczylik[4], J. Malik[5], B.Y. Alekseev[6], J.M.G. Larkin[7], V.B. Matveev[8], R. Airatovich Gafanov[9], P. Tomczak[10], S.S. Tykodi[11], P.F. Geertsen[12], P. Wiechno[13], S.J. Shin[14], F. Pouliot[15], T. Alonso Gordoa[16], R. Kloss Silverman[17], R.F. Perini[17], C. Schloss[17], M.B. Atkins[18]

[1]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [2]Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]Medical Oncology, Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea, [4]Medical Oncology, Wojskowy Instytut Medyczny, Warsaw, Poland, [5]Medical Oncology, Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK, [6]Onco-Urology, P. A. Herzen Moscow Oncology Research Institute, Ministry of Health of the Russian Federation, Moscow, Russian Federation, [7]Medicine, Institute of Cancer Research, London, UK, [8]Medical Oncology, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [9]Urology, Russian Scientific Center of Roentgenoradiology, Moscow, Russian Federation, [10]Medical Oncology, Clinical Hospital No. 1 of the Poznan University of Medical Sciences, Poznan, Poland, [11]Department of Medicine, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [12]Medical Oncology, Herlev Hospital, University of Copenhagen, Herlev, Denmark, [13]Medical Oncology, Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland, [14]Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [15]Surgery, Université Laval, Quebec, QC, Canada, [16]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [17]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [18]Medical Oncology, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA

Background: KEYNOTE-427 (NCT02853344) is a single-arm, open-label, 2-cohort, phase 2 study to evaluate efficacy and safety of the PD-1 inhibitor pembrolizumab (pembro) as first-line monotherapy in advanced ccRCC and non-ccRCC. Results from the ccRCC cohort (cohort A) are presented.

Methods: Pembro 200 mg was administered intravenously Q3W for 2 y or until confirmed progressive disease, unacceptable toxicity, or patient (pt) decision to withdraw. Pts with histologically confirmed advanced ccRCC who had received no prior systemic therapy were eligible. Additional key eligibility criteria: measurable disease (RECIST v1.1, independent central review [ICR]) and Karnofsky performance status $\geq$70%. Primary end point: ORR per RECIST v1.1, by ICR. Additional end points: DOR, PFS, OS, safety, and biomarkers associated with response.

Results: At data cutoff (Oct 6, 2017), median (range) follow-up was 7.2 (0.9-11.7) mo. 110 pts enrolled; 107 were included in efficacy analysis (opportunity for $\geq$1 postbaseline assessment). Treatment was ongoing for 64 (58.2%) pts. Median age (range) was 64 (29-87) years; 78% were male. 37.3%, 47.3%, and 15.5% had IMDC risk categories of favorable, intermediate, and poor, respectively. Confirmed ORR by ICR was 33.6% (n = 36; 95% CI 24.8-43.4) with 1 complete response (0.9%) and 35 (32.7%) partial responses. 39 (36.4%) had stable disease. ORR for pts with favorable or intermediate/poor risk IMDC was 27.5% and 37.3%, respectively. Median DOR was not reached (range 1.4+ to 8.2+ mo); 86.1% of responders had response $\geq$3 months. Median PFS was 6.9 (95% CI 5.1-NR) mo; PFS rate at 6 mo was 53.6%. OS rates at 3 and 6 mo were 97.2% and 92.4%, respectively. 73.6% of pts had a treatment-related adverse event (AE); most common ($\geq$10%) were fatigue (23.6%), pruritus (21.8%), diarrhea (16.4%), rash (12.7%), and arthralgia (11.8%). 18.2% experienced a grade 3-5 treatment-related AE; 1 pt had grade 5 pneumonitis.

Conclusions: Pembro monotherapy showed encouraging efficacy and acceptable tolerability in pts with advanced ccRCC. Updated analyses will be presented using additional follow-up data and outcomes by PDL-1 status and other relevant subgroups.

Clinical trial identification: NCT02853344. Trial initiated August 2, 2016.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Matthew Grzywacz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: F. Donskov: Research funding: Pfizer, Novartis, Ipsen. B.Y. Alekseev: Research funding: Merck. J.M.G. Larkin: Research funding: BMS, MSD, Novartis, Pfizer; Honoraria: BMS, MSD, GSK, Pfizer, Novartis, EUSA pharma, Roche/Genentech, Secarna, Pierre Fabre, Eisai, Kymab; Travel expenses, including accommodations: BMS, MSD, GSK, Pfizer, Novartis, EUSA Pharma, Roche/Genentech, Secarna, Pierre Fabre, Eisai, Kymab; Consultancy: BMS, MSD, GSK, Pfizer, Novartis, EUSA Pharma, Roche/Genentech, Secarna, Pierre Fabre, Eisai, Kymab. S.S. Tykodi: Advisory board: Calithera Biosciences, Prometheus Laboratories; Research funding (to institution): Merck, Bristol-Myers Squibb, Peloton Therapeutics, Nektar Therapeutics, Calithera Biosciences, Jounce Therapeutics, Pfizer, Genentech, Prometheus Laboratories, Argos Therapeutics. P.F. Geertsen: Research funding: Novartis; Travel expenses: Novartis, BMS, Pfizer. T. Alonso Gordoa: Research funding: Roche; Honoraria: Pfizer, Janssen, Astellas, Novartis, Roche, Sanofi. R. Kloss Silverman, R.F. Perini: Employment: Merck & Co., Inc. C. Schloss: Employment and stock ownership: Merck & Co., Inc. M.B. Atkins: Consulting: BMS, Merck, Novartis, Genentech/Roche, Pfizer, Exelixis, Eisai, AstraZeneca, Array; Research funding: BMS, Novartis, Genentech/Roche; Board of directors or advisory committees: Novartis, Merck, Pfizer. All other authors have declared no conflicts of interest.

872P Phase Ib study (COSMIC-021) of cabozantinib in combination with atezolizumab: Results of the dose escalation stage in patients (pts) with treatment-naïve advanced renal cell carcinoma (RCC)

N. Agarwal[1], U. Vaishampayan[2], M. Green[3], F. di Nucci[3], P-Y. Chang[4], C. Scheffold[4], S. Pal[5]

[1]Internal Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA, [2]Oncology, Karmanos Cancer Center, Detroit, MI, USA, [3]Genentech, South San Francisco, CA, USA, [4]Clinical Science, Exelixis Inc., South San Francisco, CA, USA, [5]Medical Oncology & Therapeutics Research, City of Hope, Duarte, CA, USA

Background: Cabozantinib (C) is an inhibitor of multiple receptor tyrosine kinases involved in tumor cell proliferation, neovascularization, and immune cell regulation, including MET, VEGFRs, and TAM family of kinases (TYRO3, MER, and AXL). Preclinical/clinical studies suggest that C promotes an immune-permissive environment that may facilitate synergistic effects with checkpoint inhibitors. This Phase 1b study evaluates C in combination with the programmed death ligand (PD-L1) targeting antibody atezolizumab (A) in pts with solid tumors (NCT03170960).

Methods: Safety and clinical activity of C (2 dose levels: 40 mg, 60 mg QD) + A (1200 mg Q3W) administered in 3-week cycles were evaluated in a 3 + 3 dose escalation design. Safety data of all pts and criteria for dose limiting toxicity (DLT) determined the recommended dose (RD) for a subsequent expansion stage. Tumor response was assessed by CT/MRI and bone scan (RECIST v 1.1).

Results: 12 pts with treatment-naïve advanced RCC (mostly clear-cell subtype) were treated in the dose escalation stage (6 at each dose level). At data cutoff, all pts were actively receiving study treatment (range, 3–12 cycles). There were no DLTs or serious adverse events (AEs) in either C+A dose cohort. Most AEs were Grade 1/2 including immune-related AEs. Grade 3 AEs included 3 events of hypertension, 2 events each of diarrhea and hypophosphatemia, and 1 pulmonary embolism. There were no Grade 4/5 AEs. Among 10 pts investigator-assessed confirmed ORR was 50% (1 CR, 4 PRs); 2 additional pts had unconfirmed PRs with only 1 tumor assessment at data cut-off.

Conclusions: C+A is well tolerated and shows encouraging anti-tumor activity in advanced RCC. C 40 mg QD + A 1200 mg Q3W was selected as the RD for expansion in multiple solid tumor cohorts including RCC.

Clinical trial identification: NCT03170960.

Legal entity responsible for the study: Exelixis, Inc.

Funding: Exelixis, Inc.

Disclosure: N. Agarwal: Consulting or advisory role: Pfizer, Novartis, Merck, Genentech, Eisai, Exelixis, Clovis, EMD Serono, BMS, AstraZeneca, Astellas. U. Vaishampayan: Honoraria: Astellas Pharma, Bayer, Bristol-Myers Squibb, Exelixis, Genentech, Janssen, Novartis, Pfizer, Sanofi; Consulting or advisory role: Astellas Pharma, Bayer, Bristol-Myers Squibb, Exelixis, Genentech/Roche, Novartis, Pfizer; Speakers' bureau: Astellas Pharma, Bayer, Bristol-Myers Squibb, Exelixis, Genentech/Roche, Novartis, Pfizer, Sanofi; Research funding: Astellas Pharma, Bristol-Myers Squibb, Exelixis, Novartis, Pfizer. M. Green, F. di Nucci: Employee: Genentech. P-Y. Chang: Employee of Exelixis Inc. C. Scheffold: Employee of and owns stock in Exelixis, Inc. S. Pal: Honoraria: Astellas Pharma, Medivation, Novartis; Consulting or advisory role: Aveo, Bristol-Myers Squibb, Exelixis, Genentech, Myriad Pharmaceuticals, Novartis, Pfizer; Research funding: Medivation.

873P Safety and tolerability of atezolizumab (atezo) plus bevacizumab (bev) vs sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC): Pooled analysis of IMmotion150 and IMmotion151

C. Suarez[1], T.K. Choueiri[2], D.F. McDermott[3], B. Escudier[4], M.B. Atkins[5], T.B. Powles[6], B.I. Rini[7], R.J. Motzer[8], S.K. Pal[9], L. Fong[10], U. De Giorgi[11], Y. Wang[12], T. Khaznadar[13], F. Di Nucci[12], C. Kaiser[14], D. Tayama[14], F. Donskov[15]

[1]Vall d'Hebron University Hospital and Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain, [2]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [3]Heme/Onc, Beth Israel Deaconess Medical Center, Boston, MA, USA, [4]Medical Oncology, Gustave Roussy, Villejuif, France, [5]Medical Oncology, Lombardi Cancer Center Georgetown University, Washington, DC, USA, [6]Queen Mary University of London, Barts Cancer Institute and the Royal Free Hospital, London, UK, [7]Medical Oncology, Taussig Cancer Institute Cleveland Clinic, Cleveland, OH, USA, [8]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [9]Comprehensive Cancer Center, City of Hope, Duarte, CA, USA, [10]Oncology, University of California, San Francisco, CA, USA, [11]Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [12]Oncology, Genentech, Inc., South San Francisco, CA, USA, [13]PD Oncology, F. Hoffmann-La Roche, Ltd, Basel, Switzerland, [14]US Medical Affairs, Genentech, Inc., South San Francisco, CA, USA, [15]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Background: Atezo (anti–PD-L1) + bev (anti-VEGF) demonstrated improved PFS and favourable safety vs sun in Ph II and III trials in patients (pts) with untreated mRCC (McDermott 2018; Motzer ASCO GU 2018). To further explore the improved tolerability with this regimen, we performed additional safety analyses using pooled data from the atezo + bev and sun arms of these studies.

Methods: Safety data were assessed from the primary analyses of the Ph II IMmotion150 and Ph III IMmotion151 trials, which enrolled treatment-naive pts with mRCC with clear-cell and/or sarcomatoid histology. Pts were randomised 1:1 to receive atezo 1200 mg IV q3w + bev 15 mg/kg IV q3w or sun 50 mg PO QD 4 wk on/2 wk off until progression (RECIST v1.1) or loss of clinical benefit.

Results: Pooled cohorts included 552 atezo + bev–treated pts and 546 sun-treated pts. Mean duration of treatment for atezo + bev was 11.4 mo for atezo and 10.8 mo for bev vs 10.0 mo for sun. Treatment-related AEs (TRAEs) occurred in 91% of pts with atezo + bev and 96% with sun. Grade 3-4 TRAEs were reported in 40% and 54% of pts with atezo + bev and sun, respectively, with hypertension (14%, 16%), proteinuria (4%, 1%) and fatigue (1%, 6%) as the most common reported events. Grade 5 TRAEs occurred in 1% of pts in each cohort. TRAEs leading to treatment regimen (atezo + bev or sun) discontinuation occurred in 5% of pts with atezo + bev and 8% with sun. AEs of special interest (AESIs), commonly reported with atezo treatment regardless of investigator attribution, were Grade 1-2 in 79% of pts receiving atezo + bev and 78% receiving sun. Corticosteroid use for AESIs (mostly Grade 1-2) occurred in 16% of pts with atezo + bev and 5% with sun. The safety profile in pts with components of sarcomatoid histology or with PD-L1+ tumours was similar to that in pts with clear-cell mRCC. Additional safety data will be reported.

Conclusions: Atezo + bev had a tolerable safety profile in mRCC, with fewer high-grade TRAEs and TRAEs leading to regimen discontinuation than with sun. Corticosteroid use for atezo AESIs was low. Toxicities were consistent with each agent alone, and no new toxicities were identified.

Clinical trial identification: NCT01984242, NCT02420821.

Editorial acknowledgement: Medical writing assistance for this abstract was provided by Paige S. Davies, PhD, of Health Interactions.

Legal entity responsible for the study: F. Hoffmann-La Roche AG.

Funding: F. Hoffmann-La Roche AG.

Disclosure: T.K. Choueiri: Personal fees: Roche; Personal fees: Pfizer; Grants and personal fees: BMS; Personal fees: Merck; Personal fees: Eisai; Personal fees: Novartis, during the conduct of the study. D.F. McDermott: Consulting or advisory role: Bristol-Myers Squibb, Merck, Genentech/Roche, Pfizer, Novartis, Exelixis, X4 Pharma, Array BioPharma; Research funding: Prometheus Laboratories to institution. B. Escudier: Consulting or advisory role: Bristol-Myers Squibb, Bayer, Pfizer, Novartis, Exelixis, Ipsen, EUSA Pharma; Travel, accommodations, expenses funding: Novartis, Pfizer, Bristol-Myers Squibb; Honoraria: Bristol-Myers Squibb, Bayer, Pfizer, Novartis, Ipsen, Exelixis, Roche/Genentech. M.B. Atkins: Consulting or advisory role: Roche/Genentech, Pfizer, Novartis, X4 Pharma, Bristol-Myers Squibb, Nektar, Merck, Exelixis, Acceleron Pharma, Peleton, Eisai, Celldex, Alexion Pharmaceuticals, AstraZeneca/MedImmune, Glactone Pharma, Agenus, Idera, Argos Therapeutics, Array BioPharma, Boehringer Ingelheim, Aduro Biotech; Honoraria: Bristol-Myers Squibb. T.B. Powles: Consulting or advisory role: Roche/Genentech, Bristol-Myers Squibb, Novartis, Merck, AstraZeneca; Honoraria: Bristol-Myers Squibb, Roche/Genentech, Merck; Research funding: AstraZeneca/ MedImmune, Roche/Genentech. B.I. Rini: Consulting or advisory role: Corvus Pharmaceuticals, Pfizer, Merck; Honoraria: Bristol-Myers Squibb, Roche/Genentech, Merck; Travel, accommodations, expenses: Pfizer; Research funding: Pfizer, Bristol-Meyers Squibb, Merck, Roche/Genentech. R.J. Motzer: Consulting or advisory role: Pfizer, Novartis, Eisai, Exelixis, Roche/Genentech, Merck; Travel, accommodations, expenses: Bristol-Meyers Squibb; Research funding: Pfizer, Bristol-Meyers Squibb, GlaxoSmithKline, Novartis, Eisai, Roche/Genentech. S.K. Pal: Consulting role: Pfizer, Novartis, Aveo, Myriad, Genentech, Exelixis, BMS, Astellas, Ipsen, Eisai; Honoraria: Novartis, Medivation, Astellas; Research funding: Medication. L. Fong: Research funding to institution: Roche/Genentech. U. De Giorgi: Personal fees: Astellas, Bristol Myers Squibb, Janssen, Ipsen, Pfizer, Pierre-Fabre, Sanofi; Non-financial support: Astellas, Bristol Myers Squibb. Y. Wang, F. Di Nucci, C. Kaiser, D. Tayama: Employee of Roche/Genentech. T. Khaznadar: Employee of Roche. F. Donskov: Research funding: Novartis, Pfizer, Ipsen. All other authors have declared no conflicts of interest.

874P Treatment-free interval (TFI) following discontinuation of first-line nivolumab plus ipilimumab (N+I) or sunitinib (S) in patients (Pts) with advanced renal cell carcinoma (aRCC): CheckMate 214 analysis

D.F. McDermott[1], B.I. Rini[2], R.J. Motzer[3], N.M. Tannir[4], B. Escudier[5], C.K. Kollmannsberger[6], H.J. Hammers[7], C. Porta[8], S. George[9], F. Donskov[10], H.P. Gurney[11], M-O. Grimm[12], M. Harrison[13], T.E. Hutson[14], J. Doan[15], S. Yang[15], S. Rao[15], S. Mekan[16], A. Ambavane[17], T. Powles[18]

[1]Department of Medicine, Beth Israel Deaconess Medical Center, Dana–Farber/Harvard Cancer Center, Boston, MA, USA, [2]Department of Hematology and Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA, [3]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [4]Department of Genitourinary Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA, [5]Department of Medical Oncology, Gustave Roussy, Villejuif, France, [6]Division of Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, [7]Division of Hematology and Oncology, UT Southwestern – Kidney Cancer Program, Dallas, TX, USA, [8]Department of Medical Oncology, Istituto di Ricovero e Cura a Carattere Scientifico San Matteo University Hospital Foundation, Pavia, Italy, [9]Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA, [10]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [11]Department of Medical Oncology, Westmead Hospital and Macquarie University, Westmead, Australia, [12]Department of Urology, Jena University Hospital, Jena, Germany, [13]Department of Medicine, Duke University Medical Center, Durham, NC, USA, [14]Department of Medicine, Texas A&M HSC College of Medicine, Dallas, TX, USA, [15]Health Economics and Outcomes Research, Bristol-Myers Squibb, Princeton, NJ, USA, [16]Health Economics and Outcomes Research, Bristol-Myers Squibb, Lawrenceville, NJ, USA, [17]Modeling and Simulation, Evidera Inc, London, UK, [18]Department of Medicine, Experimental Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, Royal Free NHS Trust, London, UK

Background: Pts with metastatic melanoma who discontinue N+I may experience sustained clinical benefit and a delayed need for subsequent therapy. In this analysis, TFI was retrospectively analyzed using data from the phase 3 CheckMate 214 trial, in which N+I demonstrated superior efficacy vs S in pts with IMDC intermediate/poor (int/poor)-risk aRCC.

Methods: In CheckMate 214, pts with previously untreated clear cell aRCC were randomized 1:1 to N 3 mg/kg + I 1 mg/kg every 3 weeks for 4 doses followed by N 3 mg/kg every 2 weeks, or S 50 mg daily orally for 4 weeks (6-week cycles). TFI was defined as the time from last dose of N+I or S to the start of subsequent systemic therapy or death. All randomized pts with IMDC int/poor-risk aRCC (N+I, 425; S, 422) were analyzed. Kaplan–Meier curves and log-rank tests were used to compare TFI between N+I and S.

Results: With median overall survival follow-up of 25.2 months, pts in the N+I arm had significantly longer time from randomization to subsequent systemic therapy or death than pts in the S arm (median, 15.4 vs 8.5 months; $P < 0.0001$); 2 years after randomization, 42% vs 19% of pts were alive and not requiring subsequent therapy. Overall, 320 (75%) N+I pts and 359 (85%) S pts discontinued treatment, most commonly due to disease progression (N+I, 42%; S, 58%) or study drug–related adverse events (N+I, 23%; S, 11%). In pts who discontinued, TFI was significantly longer with N+I than with S ($P < 0.0001$); 18 months after discontinuation, 19% of N+I pts vs 4% of S pts remained treatment-free. TFI was also significantly longer with N+I than with S, irrespective of best overall response on study ($P < 0.0001$). 18 months after discontinuation, 48% of N+I pts vs 6% of S pts with complete/partial response were still free of subsequent treatment; at the same time point, 13% of N+I pts vs 4% of S pts with stable disease remained treatment-free.

Conclusions: The use of N+I was associated with a significant longer TFI beyond treatment discontinuation in pts with IMDC int/poor-risk aRCC and irrespective of whether pts achieved response or disease control. TFI should be considered along with traditional efficacy measures when evaluating treatment options for aRCC.

Clinical trial identification: NCT02231749.

Editorial acknowledgement: Professional medical writing and editorial assistance were provided by Richard Daniel, PhD, and Lawrence Hargett of PPSI (a PAREXEL company), funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb and ONO Pharmaceutical Company Limited.

Disclosure: D.F. McDermott: Consulting or advisory role: Array BioPharma, Bristol-Myers Squibb, Eisai, Exelixis, Genentech, Merck, Novartis, Pfizer; Research funding: Prometheus (Inst). B.I. Rini: Consulting or advisory role: Bristol-Myers Squibb. R.J. Motzer: Consulting or advisory role: Eisai, Exelixis, Genentech/Roche, Merck, Novartis, Pfizer; Research funding: Bristol-Myers Squibb, Eisai, Exelixis, Novartis, Pfizer. N.M. Tannir: Research funding: Bristol-Myers Squibb, Epizyme, Exelixis, Mirati, Novartis; Consulting or advisory role: Argos, Bristol-Myers Squibb, Eisai, Exelixis, Nektar, Novartis, Oncorena, Pfizer; Advisory board member: Eisai, Exelixis, Nektar, Novartis, Oncorena. B. Escudier: Honoraria: Bristol-Myers Squibb, Bayer, Novartis, Pfizer, Exelixis, Roche. C.K. Kollmannsberger: Honoraria: Bristol-Myers Squibb, Pfizer; Consulting or advisory role: Bristol-Myers Squibb, Pfizer. H.J. Hammers: Consulting or advisory role: Bristol-Myers Squibb, Pfizer, Exelixis; Research funding: Bristol-Myers Squibb; Travel, accommodations, expenses: Bristol Myers Squibb, Pfizer, Exelixis. C. Porta: Consulting or advisory role: Bristol-Myers Squibb, Pfizer, Novartis, Ipsen, Eisai, EUSA, Janssen. S. George: Consulting or advisory role: Bristol-Myers Squibb, Novartis, Bayer, Pfizer, Exelixis, AstraZeneca, Janssen Oncology, Corvus Pharmaceuticals, Genentech/Roche; Research funding to institution: Pfizer, Acceleron Pharma, Merck, Agensys, Novartis, Bristol-Myers Squibb, Bayer. F. Donskov: Research funding to institution: Ipsen, Novartis, Pfizer. H.P. Gurney: Consulting or Advisory Role: Astellas, Bristol-Myers Squibb, Novartis, Pfizer. M-O. Grimm: Honoraria: Pfizer, MSD, Apogepha; Consulting or advisory role: Roche; Research funding: Novartis, Bristol-Myers Squibb. T.E. Hutson: Speaker, research support and advisor: Bristol-Myers Squibb, Pfizer, Novartis, Aveo, Exelexis, Janssen. J. Doan, S. Yang, S. Rao, S. Mekan: Employment, Stock or other ownership: Bristol-Myers Squibb. A. Ambavane: Employment: Evidera, Inc. which received fees for consulting support from Bristol-Myers Squibb and EMD Serono. T. Powles: Research funding: AstraZeneca, Novartis, Roche Honoraria: AstraZeneca, Merck, Bristol-Myers Squibb, Pfizer, Roche. All other authors have declared no conflicts of interest.

875P Characterization of response to nivolumab plus ipilimumab (N+I) or sunitinib (S) in patients (Pts) with previously untreated advanced renal cell carcinoma (arcc): Checkmate 214

B.I. Rini[1], N.M. Tannir[2], B. Escudier[3], D.F. McDermott[4], M-O. Grimm[5], C. Porta[6], T. Powles[7], C.K. Kollmannsberger[8], H.P. Gurney[9], S.S. Tykodi[10], M. Harrison[11], D.Y.C. Heng[12], V. Grünwald[13], T.K. Choueiri[14], S. Mekan[15], M.B. McHenry[15], H.J. Hammers[16], R.J. Motzer[17], S. George[18]

[1]Department of Hematology and Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA, [2]Genitourinary Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Department of Medical Oncology, Gustave Roussy, Villejuif, France, [4]Department of Medicine, Beth Israel Deaconess Med. Center, Boston, MA, USA, [5]Department of Urology, Jena University Hospital, Jena, Germany, [6]Department of Medical Oncology, Istituto di Ricovero e Cura a Carattere Scientifico San Matteo University Hospital Foundation, Pavia, Italy, [7]Department of Medicine, Barts Cancer Institute, London, UK, [8]Department of Medicine, British Columbia Cancer Agency, Vancouver, BC, Canada, [9]Department of Medical Oncology, Westmead Hospital and Macquarie University, Westmead, Australia, [10]Department of Medicine, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [11]Department of Medicine, Duke University Medical Center, Durham, NC, USA, [12]Department of Oncology, Tom Baker Cancer Center, Calgary, AB, Canada, [13]Department of Hematology and Oncology, Hannover Medical School, Hannover, Germany, [14]Department of Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [15]Clinical Development, Bristol-Myers Squibb Company, Lawrenceville, GA, USA, [16]Department of Hematology and Oncology, University of Texas Southwestern Medical Center at Dallas, Dallas, MD, USA, [17]Department of Genitourinary Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [18]Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA

Background: N+I demonstrated superior objective response rate (ORR) and overall survival (OS) vs sunitinib in pts with IMDC intermediate/poor (int/poor)-risk aRCC in the phase 3 CheckMate 214 trial. Further characterization of response may inform clinical practice.

Table: 875P

Outcome	N+I int/poor-risk pts			S int/poor-risk pts		
	Total n = 425	CR n = 40	PR n = 137	Total n = 422	CR n = 5	PR n = 107
BOR (95% CI), %	42 (37–47)	9	32	27 (22–31)	1	25
Median (range) time to response, months	2.8 (0.9–11.3)	2.8 (0.9–11.0)	2.8 (1.4–11.3)	3.0 (0.6–15.0)	2.9 (2.8–4.2)	3.1 (0.6–15.0)
Median (95% CI) duration of response, months	NR (21.8–NE)	NR	NR (18.8–NE)	18.2 (14.8–NE)	NR	18.2 (13.9–NE)
Pts with ongoing response in responders, n/N (%)	128/177 (72)	34/40 (85)	94/137 (69)	71/112 (63)	5/5 (100)	66/107 (62)
12-month PFS rate (95% CI), %	50 (44–55)	97 (83–100)	81 (73–86)	43 (37–48)	100 (100–100)	79 (69–86)
18-month OS rate (95% CI), %	78 (74–81)	100 (100–100)	94 (89–97)	68 (63–72)	100 (100–100)	92 (85–96)

BOR, best overall response; NE, not estimable; NR, not reached; PR, partial response

Methods: In CheckMate 214, pts with previously untreated aRCC were randomly assigned 1:1 to N 3 mg/kg + I 1 mg/kg Q3W for 4 doses then N 3 mg/kg Q2W or S 50 mg QD for 4 weeks on, 2 weeks off. Efficacy, safety, and quality of life (QoL) were explored in int/poor-risk pts with complete response (CR) or partial response to N+I or S.

Results: At 25.2 months median follow-up, confirmed ORR per independent radiology review committee in int/poor-risk pts was 42% for N+I vs 27% for S ($P < 0.001$; Table) with 36% vs 18% of pts achieving best tumor reduction ≥50% with N+I vs S. Of N+I vs S responders, 72% vs 63% have ongoing response, 47% and 34% remain on treatment, and 53% and 66% discontinued, most often for disease progression (N+I, 22%; S, 40%) or toxicity (N+I, 23%; S, 13%). N+I responders received a median of 21.0 months of treatment (vs 3.8 months for N+I nonresponders). Response lasting ≥18 months was seen in 13% of N+I and 4% of S pts. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 52% of N+I and 68% of S responders. Mean change from baseline at 24 weeks in Functional Assessment of Cancer Therapy–Kidney Symptom Index 19 score was 3.0 in N+I responders (better) vs − 0.7 in S responders (worse). Updated 3-year data on responders, including use of subsequent therapies, will be presented.

Conclusions: ORR and OS were significantly improved with N+I compared with S in pts with int/poor-risk aRCC in CheckMate 214. Responses to N+I were more likely to be CRs and were more durable than responses to S. High-grade TRAEs were less frequent and QoL was better in N+I responders compared with S responders.

Clinical trial identification: NCT02231749.

Editorial acknowledgement: Professional medical writing assistance was provided by Nicolette Belletier, PhD, of PPSI, funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb and Ono Pharmaceutical Company Limited.

Disclosure: B.I. Rini: Consulting or Advisory role: Bristol-Myers Squibb. N.M. Tannir: Research funding: Bristol-Myers Squibb, Epizyme, Exelixis, Mirati, Novartis; Consulting or Advisory role: Argos, Bristol-Myers Squibb, Eisai, Exelixis, Nektar, Novartis, Oncorena, Pfizer; Advisory board member: Eisai, Exelixis, Nektar, Novartis, Oncorena. B. Escudier: Honoraria: Bristol-Myers Squibb, Bayer, Novartis, Pfizer, Exelixis, Roche. D.F. McDermott: Consulting or Advisory role: Array BioPharma, Bristol-Myers Squibb, Eisai, Exelixis, Genentech, Merck, Novartis, Pfizer; Research funding: Prometheus (Inst). M-O. Grimm: Honoraria: Pfizer, MSD, Apogepha; Consulting or Advisory role: Roche; Research funding: Novartis, Bristol-Myers Squibb. C. Porta: Consulting or Advisory role: Bristol-Myers Squibb, Pfizer, Novartis, Ipsen, Eisai, EUSA, Janssen. T. Powles: Research funding: AstraZeneca, Novartis, Roche; Honoraria: AstraZeneca, Merck, Bristol-Myers Squibb, Pfizer, Roche. C.K. Kollmannsberger: Honoraria: Bristol-Myers Squibb, Pfizer; Consulting or Advisory role: Bristol-Myers Squibb, Pfizer. H.P. Gurney: Consulting or Advisory role: Astellas, Bristol-Myers Squibb, Novartis, Pfizer. S.S. Tykodi: Consulting or Advisory role: Bristol-Myers Squibb, Calithera Biosciences, Prometheus Laboratories; Research funding to institution: Bristol-Myers Squibb, Calithera Biosciences, Merck, Nektar Therapeutics, Peloton Therapeutics, Jounce Therapeutics, Pfizer, Genentech, Prometheus Laboratories, Argos Therapeutics. D.Y.C. Heng: Consulting or Advisory role: Bristol-Myers Squibb, Pfizer, Novartis. V. Grünwald: Honoraria: Bristol-Myers Squibb; Consulting or Advisory role: Bristol-Myers Squibb, Novartis, Pfizer, Bayer; Speakers' Bureaus: Bristol-Myers Squibb, Novartis, Pfizer. T.K. Choueiri: Consulting or Advisory role: Merck, Novartis, Peloton, Pfizer, Roche, Eisai, Tracon, Bayer, Cerulean, Foundation Medicine, Inc., GlaxoSmithKline, Prometheus, Corvus; Research Funding to institution: Merck, Novartis, Peloton, Pfizer, Roche, Eisai, Tracon. S. Mekan: Employment or Other ownership: Bristol-Myers Squibb. H.J. Hammers: Consulting or Advisory role: Bristol-Myers Squibb, Pfizer, Exelixis; Research Funding: Bristol-Myers Squibb; Travel, accommodations, Expenses: Bristol- Myers Squibb, Pfizer, Exelixis. R.J. Motzer: Consulting or Advisory role: Eisai, Exelixis, Genentech/Roche, Merck, Novartis, Pfizer; Research funding: Bristol-Myers Squibb, Eisai, Exelixis, Novartis, Pfizer. S. George: Consulting or Advisory role: Bristol-Myers Squibb, Novartis, Bayer, Pfizer, Exelixis, AstraZeneca, Janssen Oncology, Corvus Pharmaceuticals, Genentech/Roche; Research funding (inst): Pfizer, Acceleron Pharma, Merck, Agensys, Novartis, Bristol-Myers Squibb, Bayer. All other authors have declared no conflicts of interest.

876P A new prognostic model for overall survival (OS) in second line (2L) for metastatic renal cell carcinoma (mRCC): Development and external validation

L. Derosa[1], M.A. Bayar[2], L. Albiges[1], G. Le Teuff[2], B. Escudier[1]

[1]Department of Medical Oncology, Gustave Roussy, Villejuif, France, [2]Biostatistics, Institut Gustave Roussy, Villejuif, France

Background: The IMDC classification scheme for OS has been validated in 2L mRCC. Recently, we showed that two new prognostic factors, Time from first to second line (<, ≥ 1 year) and tumor burden (<, ≥100 mm), are independently associated with OS in the same setting. Here, we present a new classification scheme.

Methods: mRCC patients treated in 2L between January 2005 and December 2014 after initial first line clinical trials at Gustave Roussy Cancer Campus (GRCC) formed the discovery set. Patients from 2 phase III clinical trials from Pfizer database (PFIZERDB), AXIS (NCT00678392) and INTORSECT (NCT00474786), formed the external validation set. In addition to the IMDC predictors, the 2 new prognostic factors were tested using a multivariable Cox model with a backward selection procedure. The performance of the new GRCC model and the classification scheme derived from it, measuring by R^2, c-index and calibration, was evaluated on the validation set and compared to MSKCC and IMDC.

Results: Two-hundred and twenty-one patients were included in GRCC cohort and 855 patients in PFIZERDB. Median OS was similar in the two datasets (16.8 [95%CI=12.9-21.7] and 15.3 [13.6-17.2] months, respectively). Time from first to second line and tumor burden confirmed their significant effect on OS with HR = 1.68 [1.23-2.31] and 1.43 [1.03-1.99]. The new classification, derived by counting the number of factors, allows categorizing patients into 4 risk groups: median OS from the start of 2L in the validation cohort was not reached (NE) (95% CI 24.9-NE) in the favorable risk group (n = 20, 4 deaths, 0 risk factor), 21.8 months (11.6–15.8) in the intermediate risk group (n = 367, 135 deaths, 1-2 risk factors), 12.7 months (11.0–15.8) in the low-poor risk group (n = 347, 211 deaths, 3-4 risk factors), and 5.5 months (4.7–6.4) in the high-poor risk group (n = 121, 105 deaths, ≥5 risk factors). Not surprisingly, the incorporation of factors that characterize post first line features and the new stratification allowed a better performance compared to previous models.

Conclusions: The GRCC classification derived from the model is a new reliable prognostic tool that can be applied to better predict OS in previously treated mRCC patients.

Legal entity responsible for the study: Lisa Derosa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

877P First-line (1L) or second-line (2L) avelumab monotherapy in patients (pts) with advanced renal cell carcinoma (aRCC) enrolled in the phase Ib JAVELIN solid tumor trial

U.N. Vaishampayan[1], P. Schöffski[2], A. Ravaud[3], C. Borel[4], T. Song[5], S. Guenther[6], J. Grewal[7], J. Gulley[8]

[1]Oncology, Karmanos Cancer Institute, Detroit, MI, USA, [2]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium, [3]Oncologie, Groupe Hospitalier Saint André - Hôpital St. André, Bordeaux, France, [4]Oncologie Médicale, Centre Paul Strauss, Strasbourg, France, [5]Biostatistics, EMD Serono, Billerica, MA, USA, [6]Medical Affairs, Merck KGaA, Darmstadt, Germany, [7]Immuno-Oncology, EMD Serono, Billerica, MA, USA, [8]Genitournary Malignancies Branch, National Cancer Institute, Bethesda, MD, USA

Background: Avelumab is a human anti–PD-L1 IgG1 monoclonal antibody approved for the treatment of metastatic Merkel cell carcinoma and, in the US/Canada, advanced urothelial carcinoma progressed on platinum therapy. Here, we report phase 1b data from the multicohort JAVELIN Solid Tumor trial (NCT01772004) in pts with aRCC treated with avelumab monotherapy in either the 1L or 2L setting.

Methods: Eligible pts in the 1L subgroup had measurable aRCC with a clear cell component and ECOG ≤1; in the 2L subgroup, pts must have progressed after 1 prior line of therapy. All pts received avelumab 10 mg/kg IV Q2W until disease progression, unacceptable toxicity, or withdrawal. Assessments included objective response rate (ORR; according to RECIST v1.1 per investigator), progression-free survival (PFS), overall survival (OS), and safety.

Results: As of 27 April 2017, 82 pts received avelumab: 62 pts as 1L (median follow-up, 14.2 mo [range, 6-17 mo]; 24 pts remained on treatment) and 20 pts as 2L (median follow-up, 22.1 mo [range, 16-23 mo]; 2 pts remained on treatment). Efficacy data are summarized below. The rates of treatment-related adverse events (TRAEs) were 75.8% (grade ≥3, 12.9%) and 70.0% (grade ≥3, 5.0%) in the 1L and 2L subgroups, respectively. The only grade ≥3 TRAE that occurred in > 1 pt was elevated lipase (n = 4); no TR deaths or unexpected immune-related TRAEs occurred. Updated data will be presented.

Table: 877P

	1L (n = 62)	2L (n = 20)
Response ORR (95% CI), %	16.1 (8.0-27.7)	10.0 (1.2-31.7)
Duration of response, median (95% CI), mo	10.4 (2.8-10.4)	NE (6.9-NE)
PFS Median (95% CI), mo 6-mo rate (95% CI), %	8.3 (5.5-9.7) 55.7 (41.9-67.4)	5.6 (2.3-8.2) 44.9 (21.9-65.6)
OS Median (95% CI), mo 12-mo rate (95% CI), %	NE 85.9 (73.4-92.8)	16.9 (8.3-NE) 65.0 (40.3-81.5)

NE, not estimable.

Conclusions: Avelumab, administered either as 1L or 2L monotherapy, showed durable responses, promising survival outcomes, and an acceptable safety profile in pts with aRCC. These data, as well as those recently reported from a phase 1b trial investigating the 1L combination of avelumab + axitinib (VEGF pathway inhibitor; NCT02493751), provide a rationale for the randomized, phase 3 JAVELIN Renal 101 trial (NCT02684006) comparing avelumab + axitinib with sunitinib as 1L treatment for pts with aRCC.

Clinical trial identification: NCT01772004.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking Inc., Hamilton, NJ, USA.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: This trial was sponsored by Merck KGaA, Darmstadt, Germany and is part of an alliance between Merck KGaA and Pfizer.

Disclosure: U.N. Vaishampayan: Consulting fees: Bayer, Exelixis, Novartis, Pfizer, BMS, Takeda; Research funding: Novartis, Exelixis, Pfizer; Honoraria: Sanofi, Pfizer, BMS, Bayer, Medivation, Takeda. P. Schöffski: Financial interests: Daiichi Sankyo, Eisai, Eli Lilly, Medpace, Novartis, Swedish Orphan Biovitrium, 6th Element Capital, Adaptimmune, Amcure, AstraZeneca, Bayer, Blueprint Medicines, BMS, Boehringer Ingelheim, Cristal Therapeutics, Epizyme, Genzyme, Ipsen, Loxo, Nektar, Novartis, Philogen, Piqur Therapeutics, Plexxikon, GSK, PharmaMar, Cobiores nv, Exelixis. C. Borel: Financial interest: Merck, BMS, AstraZeneca, Amgen. T. Song, J. Grewal: Financial interest: EMD Serono. S. Guenther: Financial interest: Merck KGaA. All other authors have declared no conflicts of interest.

878P TiNivo - tivozanib combined with nivolumab: Safety and efficacy in patients with metastatic renal cell carcinoma (mRCC)

P. Barthelemy[1], B. Escudier[2], A. Ravaud[3], S. Negrier[4], M.N. Needle[5], L. Albiges[6]

[1]Medical Oncology, C.H.U. Strasbourg-Nouvel Hopital Civil, Strasbourg, France, [2]GU Oncology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [3]Medical Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France, [4]Medical Oncology, Centre Léon Bérard, Lyon, France, [5]Aveo Pharmaceuticals Inc, Cambridge, MA, USA, [6]Medical Oncology, Institut Gustave Roussy, Villejuif, France

Background: Recently approved in the EU, tivozanib is a VEGFR-TKI with high specificity and lower incidence of class effect adverse events. We reported earlier that tivozanib can be combined with nivolumab at full dose of each drug. We report herein safety and efficacy data from a phase Ib/II combination of tivozanib and nivolumab.

Methods: In the phase Ib portion of the study, tivozanib was administered orally at 1.0 mg and 1.5 mg, once daily for 21 days every 28 day cycle using a standard 3 + 3 dose escalation design in combination with nivolumab 240 mg every 14 days intravenously. As there were no DLTs in phase I, in the phase II portion of the study tivozanib was administered orally at 1.5 mg in combination with nivolumab.

Results: 28 patients have been enrolled, 6 in phase Ib and 22 in phase II. 25 were treated with full dose tivozanib, 1.5 mg daily for 21 days with nivolumab. The median age was 63; 8 patients were IMDC favorable; 19 IMDC intermediate; 1 IMDC poor. 18 patients were ECOG 0 and 9 ECOG 1; and there were 20 males. 24 had clear cell histology. All patients experienced at least one AE and 52% experienced a grade 3/4 AE. 44% experienced a grade 3/4 AE related to study drug. The most common grade 3/4 adverse events were hypertension, hand foot syndrome, and elevated lipase seen in 4, 2 and 2 patients respectively. The most common AEs (all grades) were hypertension, asthenia, arthralgia, dysphonia, mucocitis, diarrhea, and anorexia. 9 of the first 14 patients (64%) enrolled and treated with full dose tivozanib had a partial response. Final efficacy and safety data on all 28 patients will be available at the meeting.

Conclusions: The combination of tivozanib with nivolumab is safe and manageable at full dose of both drugs. The safety profile and the activity is favorable for a combination of a TKI with a checkpoint inhibitor as would be expected for a highly selective and well tolerated TKI.

Clinical trial identification: NCT03136627.

Legal entity responsible for the study: Aveo Oncology.

Funding: Aveo Oncology; Bristol Myers Squibb.

Disclosure: P. Barthelemy: Consulting relationship: BMS, Novartis, Pfizer, Roche, MSD; Honoraria: Janssen Cilag, Sanofi, Astellas. B. Escudier: Honorarium: Pfizer, Novartis, BMS, Roche, Ipsen, EUSA. A. Ravaud: Member of advisory boards in RCC: Pfizer, Novartis, BMS, Ipsen, Roche; Travel support for meetings or speeches: Pfizer, Novartis, BMS, Ipsen, Roche, AstraZeneca. S. Negrier: Honoraria: Pfizer, Ipsen, BMS, EUSA Pharma, Novartis; Research grant: Pfizer; Travel expenses: BMS, Pfizer, Ipsen. M.N. Needle: Full time employee, officer and shareholder: Aveo Oncology. L. Albiges: Consulting: Bristol-Myers Squibb, Pfizer, Novartis, Ipsen, Roche, Astellas Pharma, Merck, Amgen.

879P Activity of cabozantinib (cabo) after PD-1/PD-L1 immune checkpoint blockade (ICB) in metastatic clear cell renal cell carcinoma (mccRCC)

B.A. McGregor[1], A-K. Lalani[2], W. Xie[3], J.A. Steinharter[1], D.J. Martini[4], P.V. Nuzzo[1], N. Martinez Chanza[1], L.C. Harshman[5], M.A. Bilen[6], T.K. Choueiri[7]

[1]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [2]Medical Oncology, McMaster University, Hamilton, ON, Canada, [3]Biostatistics and Computational Biology, Dana Farber Cancer Institute, Boston, MA, USA, [4]Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA, [5]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [6]Oncology, Emory University Winship Cancer Institute, Atlanta, GA, USA, [7]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Cabo is approved for mccRCC based on trials in which the vast majority of patients were ICB-naive. We analyzed the activity of cabo in mccRCC patients who had progressed on ICB.

Methods: We included 69 patients with mccRCC who received cabo after progression on ICB alone or in combination with VEGF or other therapies. Baseline characteristics, best response (BR, investigator-assessed), time to treatment failure (TTF) and overall survival (OS) were analyzed.

Results: Median age was 62 years (range 37-78). Median number of prior therapies was 2 (range 1-10). Median time on prior ICB was 3.9 months (range 0.5-38). Type of prior therapy was ICB single agent (54%) or in combination with a VEGF inhibitor (35%) or other therapies (12%). At time of cabo initiation, IMDC risk groups were 6% good, 67% intermediate and 27% poor. BR was 33% PR, 46% SD, 17% PD, 3% unevaluable. Median follow up after cabo initiation was 12 months. At time of analysis, 35% (n = 24) remained on cabo and median TTF was 6.6 (95%CI: 5.3-8.5) months. Of those discontinuing cabo, 58% (n = 26) received additional therapy. At time of analysis, 62% (n = 43) were alive with 1-year OS rate of 53% (95%CI: 37%-66%).

Table: 879P

		Best Response to Cabo			
	N	PR	SD	PD	Unevaluable
All patients	69	23(33%)	32(46%)	12(17%)	2(3%)
By prior ICB type					
ICB alone	37	16(43%)	15(41%)	5(14%)	1(3%)
ICB+VEGF	24	6(25%)	12(50%)	5(21%)	1(4%)
ICB+Other	8	1(13%)	5(63%)	2(25%)	
By prior ICB duration					
<6mos	42	12(29%)	22(52%)	8(19%)	
>6mos	27	11(41%)	10(37%)	4(15%)	2(7%)

Conclusions: Cabo is active in patients treated after PD-1/PD-L1 based ICB independent of prior combination therapy with VEGF inhibitors, with 79% achieving disease control at minimum. These results support the continued use of cabo irrespective of ICB timing. Equal contribution: BAM, AAL.

Legal entity responsible for the study: Dana Farber Cancer institute.

Funding: Has not received any funding.

Disclosure: B.A. McGregor: Consulting: Exelixis, Genentech, Astellas, Seattle-Genetics, Bayer, Jannsen, AstraZeneca, Pfizer Institutional research: Bristol-Myers-Squibb. L.C. Harshman: Advisory: Bayer, Genentech, Dendreon, Pfizer, Medivation/Astellas, Kew Group, Theragene, Corvus, Merck, Exelixis; Novartis; Research to the institution: Bayer, Sotio, Bristol-Myers Squib, Merck, Takeda, Dendreon/Valient, Jannsen, Medivation/Astellas, Genentech, Pfizer. M.A. Bilen: Consulting: Exelixis. T.K. Choueiri: Research funding: AstraZeneca, B Bristol-Myers-Squibb MS, Exelixis, Genentech, GSK, Merck, Novartis, Peloton, Pfizer, Roche, Tracon, Eisai; Consulting and Advisory role: AstraZeneca, Bayer, Bristol-Myers-Squibb, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Ipsen. All other authors have declared no conflicts of interest.

880P Subgroups analysis and circulating biomarkers evaluation of RESORT trial: A randomized phase II study in metastatic renal cell carcinoma (mRCC) patients (pts) to evaluate the efficacy of sorafenib after metastasectomy

G. Procopio[1], F. Cognetti[2], R. Miceli[3], M. Milella[4], A. Mosca[5], V.E. Chiuri[6], A. Bearz[7], F. Morelli[8], C. Ortega[9], F. Atzori[10], R. Passalacqua[11], R. Ratta[12], F.G.M. de Braud[13], V. Cappelletti[14], E. Verzoni[1]

[1]Medical Oncology-Genitourinary Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Medical Oncology, Istituto Regina Elena, Rome, Italy, [3]Clinical Epidemiology and Trials Organization Unit, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [4]Medical Oncology 1, Istituto Nazionale Tumori Regina Elena, Rome, Italy, [5]Oncology, Azienda Ospedaliera Universitaria Maggiore della Carità, Novara, Italy, [6]Medical Oncology, Ospedale Vito Fazzi, Lecce, Italy, [7]National Institute for Cancer Research, Aviano, Italy, [8]Oncology Unit, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy, [9]Medical Oncology, IRCCS Istituto di Candiolo, Candiolo, Italy, [10]Medical Oncology, Azienda Ospedaliero Universitaria di Cagliari, Monserrato, Italy, [11]Medical Oncology, Istituti Ospitalieri di Cremona, Cremona, Italy, [12]Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy, [13]Medical Oncology & Haemathology, Istituto Nazionale dei Tumori di Milano – Fondazione IRCCS, Milan, Italy, [14]Dipartimento di Oncologia Sperimentale e Medicina Molecolare, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy

Background: RESORT trial (NCT01444807) was the largest prospective study whose aim was to assess the role of VEGF inhibition in mRCC pts after radical metastasectomy. It showed that sorafenib (SO) was safe and feasible but did not affect Relapse-Free Survival (RFS) compared to observation (OBS) in this population. Early identification of dynamic predictors of outcome, such as Circulating Tumor cells (CTCs) may be helpful to move up clinical tumor relapse.

Methods: Pts were randomized (1:1) within 12 weeks from surgery to receive SO or OBS for a maximum of 52 weeks or until disease recurrence, with stratification according to time from nephrectomy to metastases (more or less than 12 months), site of disease (lung vs others) and number of lesions (single vs multiple). Blood samples for CTCs were performed at baseline, month 6, end of treatment and at disease relapse. Peripheral blood samples (5 mL) were processed with the AdnaTest Prostate Cancer Select kit for CTC enrichment. CTCs identification was based on expression levels of EPCAM, MUC1 and ERBB2 measured by RT-multiplex PCR (Breast Cancer Detect Adna Test kit) using cutoffs defined on purpose based on expression in healthy donors.

Results: From November 2012 to November 2017, 76 pts were enrolled (32 in SO and 36 in Obs arm); 6 were screening failure and 2 pts never started treatment. A total of 55 pts had single metastasis resected, 26 in SO arm and 29 in OBS arm; the remaining 13 pts had multiple lesions, 6 in SO arm and 7 in OBS arm. Pts with single mets showed a longer median RFS in comparison to pts with multiple resected mets (39 vs 29 months), irrespective of the arm. Pts with single mets had an improved RFS when received SO compared to pts in the OBS arm (39 vs 20 months). A positive CTCs status was observed at baseline in 31% of pts in both arms and was not associated with RFS. Similarly, no associations were observed between CTCs status switches during SO or Obs and RFS.

Conclusions: Patients with single metastasectomy had better prognosis compared to pts with multiple lesions; SO improved RFS in this group of pts. CTC status and its changes during treatment were not associated with RFS.

Clinical trial identification: NCT01444807; EudraCT: 2012-000708-14.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori-Milano.

Funding: Bayer.

Disclosure: G. Procopio: Honoraria: Pfizer, Novartis, BMS, Ipsen. E. Verzoni: Honoraria: Pfizer, Novartis, Ipsen. All other authors have declared no conflicts of interest.

881P Correlations between disease-free survival (DFS) and overall survival (OS) in patients (pts) with renal cell carcinoma (RCC) at high risk for recurrence: Results from S-TRAC trial

D.J. George[1], A.J. Pantuck[2], R. Figlin[3], B. Escudier[4], S. Halabi[5], M. Casey[6], X. Lin[7], L. Serfass[8], M.J. Lechuga Frean[9], A. Ravaud[10]

[1]Division of Oncology, Duke University Medical Center, Durham, NC, USA, [2]Department of Urology, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA, [3]Medicine - Hematology Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [4]Department of Medical Oncology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [5]Biostatistics and Bioinformatics, Duke University, Durham, NC, USA, [6]Department of Oncology, Pfizer Inc, Collegeville, PA, USA, [7]Oncology, Pfizer Inc, La Jolla, CA, USA, [8]Medical, Pfizer, Paris, France, [9]Oncology, Pfizer, Milan, Italy, [10]Department of Medical Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France

Background: S-TRAC, a prospective phase 3 randomized trial in pts with resected RCC at high risk for recurrence, demonstrated a statistically significant improvement in DFS with sunitinib (SU) vs placebo; HR 0.76; 95% CI: 0.59, 0.98; P = 0.03. We hypothesized that DFS is a surrogate for OS and evaluated the association of DFS events with OS.

Methods: DFS (by blinded independent review) was defined from randomization to first evidence of recurrence, second primary malignancy, or death, whichever occurred first. Pts were categorized as having DFS or censored $\leq$2 years vs DFS >2 years, and as having OS or censored $\leq$5 years vs OS > 5 years. The odds ratio (OR), positive predictive values (PPV) and negative PV (NPV) were reported. To determine if DFS can be a surrogate for OS, 2 conditions need to be tested: 1) DFS and OS are strongly correlated, and 2) the treatment effect on DFS is sufficiently correlated with the effect on OS. The validity of the surrogate is reflected by the strength of these correlations. The correlation between DFS and OS is tested at the pt level through copula models to estimate the correlation coefficient (Kendall τ). Trial level correlations have been explored considering region as the trial unit.

Results: Median follow-up for OS was approximately 6.5 years with 141 (23%) observed deaths. There were 257 (42%) DFS events. Of 261 pts with DFS or censored $\leq$2 years of enrollment, 97 were alive and in follow-up >5 years (37%). In 354 pts with DFS >2 years, 318 pts were alive >5 years (90%). The OR, PPV and NPV were 14.9, 0.9 and 0.63, respectively. Kendall's τ ranged from 0.51 to 0.88 using the Hougaard, Clayton, and Plackett copula, suggesting a moderate correlation at the individual pt level. Similar results were observed with investigator assessed DFS. Analyses of trial level correlations also suggest a moderate correlation. Further analyses are being explored.

Conclusions: A moderate correlation between DFS and OS was observed in S-TRAC despite immature OS data. Additional analyses across completed trials are warranted to further assess the relationship between DFS and OS.

Clinical trial identification: NCT00375674.

Editorial acknowledgement: Editorial support was provided by Vardit Dror, PhD, of Engage Scientific Solutions, and funded by Pfizer.

Legal entity responsible for the study: Pfizer.

Funding: Pfizer.

Disclosure: D.J. George: Honoraria and consulting: Sanofi, Exelixis, Bayer; Consulting: Merck, Sanofi; Grants: Genentech/Roche, Novartis, Astellas, Celldex, Acerta; Grants & consulting: Exelixis, Janssen, Pfizer, Innocrin Pharma, BMS. A.J. Pantuck: Consulting fees: Pfizer. R. Figlin: Research funding: Peloton, BMS, Argos Therapeutics, Exilexis, and Cerulean; Consulting fees: Novartis, Pfizer, Nektar, Peloton, Calithera, Acceleron. B. Escudier: Consulting fees: Bayer, Pfizer, Novartis; Honoraria: Bayer, Roche, Pfizer, Genentech, Novartis, Aveo. S. Halabi: Data and Safety Monitoring Board member: Eisai. M. Casey, X. Lin, L. Serfass, M.J. Lechuga Frean: Employee of and own stock in Pfizer. A. Ravaud: Advisory boards: Pfizer, Novartis, GSK, Roche, BMS; Institutional support grants: Pfizer, Novartis; Housing and transportation for meetings and speeches: Pfizer, Novartis, BMS.

882P Potent natural killer (NK) and myeloid blood cell remodeling by cabozantinib (Cabo) in pre-treated metastatic renal cell carcinoma (mRCC) patients (pts)

E. Verzoni[1], S. Ferro[2], G. Procopio[1], A. Cova[2], R. Ratta[1], A. Raimondi[1], P. Sepe[1], P. Squarcina[2], L. Lalli[3], V. Huber[2], D. Rinchai[4], D. Bedognetti[4], L. Rivoltini[2]

[1]Medical Oncology Department, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Unit of Immunotherapy of Human Tumors, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [3]Department of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [4]Sidra Medical and Research Center, Research Branch, Doha, Qatar

Background: Cabo is an emerging tyrosine kinase inhibitor in mRCC but its impact on systemic tumor immunity is unknown. We investigated the activity of Cabo in modulating blood innate and adaptive immunity in mRCC pts.

Methods: 15 mRCC pts receiving Cabo (60 mg per os/daily) as per clinical practice were prospectively analyzed at baseline and 3 months for blood immune profiling by 13-color cytofluorimetry on peripheral blood mononuclear cell (PBMC). Pts had clear (n = 12) or non-clear cells (n = 4) histology, with intermediate (n = 7), poor (n = 8) and good (n = 1) risk according to Heng prognostic score, and received at least 2 (n = 9), 1 (n = 2) or none (n = 5) previous therapies, including Nivolumab (n = 4).

Results: A significant reduction of myeloid immunosuppressive cell subsets in favor of protective antitumor adaptive and innate immunity was detected in most post vs pre PBMC. Specifically, granulocytic myeloid-derived suppressor cells (MDSC) ($CD11b^+CD15^+HLA\text{-}DR^{neg}$), monocytic MDSC ($CD11b^+CD14^+HLA\text{-}DR^{neg}$) and TIM3+ myeloid cells ($CD15^+TIM3^+$ and $CD14^+TIM3^+$) were remarkably reduced. Total $CD11b^+CD14^+$ cells were also decreased, while classical protective ($CD14^+CD16^-HLA\text{-}DR^{high}$) and patrolling ($CD14^+CD16^{dim}CX3CR1^+$) monocytes showed a clear boost. Concomitantly, higher frequency of cytolytic and activated NK cells ($CD3^-CD16^+CD56^{dim}$ vs $CD3^-CD56^+CD16^+PD\text{-}1^+$, respectively), paralleled by a decrease of anergic NK cells ($CD3^+CD16^+CD56^+TIM3^+$), was detected in post-Cabo samples. Activated $CD8^+$ and $CD4^+$ T cells ($CD3^+CD8/CD4^+$ $CD69^+$ cells) were also raised by treatment along with a specific increase of ADCC-prone $CD3^+CD16^{dim}CD56^-$ T cells. These latter data indicate that Cabo could intensify direct and Ab-mediated enhancing tumor killing potential in NK and T cells, either as direct effect or through the reduced immunosuppressive pressure exerted by myeloid populations.

Conclusions: Cabo mediates a rapid remodeling of myeloid cells from an immunosuppressive to an antitumor phenotype, with a priming of circulating cytotoxic NK and T cells. Even in advanced disease, Cabo can still contribute to reset systemic immune conditions by creating more favorable conditions for immunotherapy.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori of Milan.

Funding: Has not received any funding.

Disclosure: E. Verzoni: Honoraria: Ipsen, Novartis, Pfizer. G. Procopio: Honoraria: BMS, Ipsen, Novartis, Pfizer. All other authors have declared no conflicts of interest.

883P Metastatic clear cell renal cell carcinoma patients with ECOG performance status 2 treated with pazopanib: The Pazo2 trial of efficacy and safety

E. Porfiri[1], S. Pirrie[2], A-M. Hodgkins[2], D. Farrugia[3], K. Fife[4], C. McDonald-Smith[5], N.S. Vasudev[6], G. Nixon[2], N.D. James[7], C. Stubbs[2]

[1]Cancer Centre, Queen Elizabeth-University Hospital Birmingham NHS Foundation Trust, Birmingham, UK, [2]Cancer Research UK Clinical Trials Unit (CRCTU), School of Cancer and Genomics, Th University of Birmingham - College of Dental and Medical Sciences, Birmingham, UK, [3]Oncology Centre, Cheltenham General Hospital Gloucestershire Oncology Centre, Cheltenham, UK, [4]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust - Addenbrooke's Hospital, Cambridge, UK, [5]Oncology, Ysbyty Gwynedd, Bangor, UK, [6]St James's Institute of Oncology, St. James's University Hospital Leeds, Leeds, UK, [7]Clinical Trials Unit, Queen Elizabeth-University Hospital Birmingham NHS Foundation Trust, Birmingham, UK

Background: Patients with metastatic clear cell renal cell carcinoma (mRCC) and Performance Status 2 have historically been excluded from clinical trials, resulting in a lack of evidence on which to base treatment decisions. Pazo2 was a phase II, multicentre, single arm trial that aimed to determine tolerability and efficacy of pazopanib in

mRCC patients with ECOG PS2. The Bryant and Day design allows for joint evaluation of two primary outcomes. Tolerability was defined as the proportion of patients at 6 months who were free from drug-related grade 3-4 toxicities resulting in SAE reporting or drug discontinuation > =3 weeks. Efficacy was defined as the proportion of patients progression free (RECIST 1.1) and alive at 6 months. Secondary endpoints included response, drug safety, progression free survival (PFS) and overall survival (OS).

Methods: Patients with mRCC and ECOG PS 2 without prior systemic treatment were registered. Undesirable tolerability was set at 40%, with 60% being desirable. Undesirable efficacy was set at 25%, with 44% being desirable (power 85% α 5%). Treatment comprised pazopanib 800mg PO once daily (OD). Dose modifications using 600mg PO, OD and 400mg PO, OD were permitted. Treatment continued until progression or unacceptable toxicity.

Results: A total of 75 patients were registered into the trial from 26 UK sites between 2013-2016. All patients were ECOG PS 2; median age 68 years (IQR 64, 76), 72% were male, HENG poor prognosis 59% and intermediate prognosis 41%. 47 patients met the tolerability criteria (vs 34 required). Further analysis showed that 18 (24%) patients stopped treatment due to toxicity within the same period. 23 patients were required to be progression free and alive at 6 months with 38 being observed. Kaplan Meier 6 month PFS was 66% (95% CI, 54, 76), with a median PFS of 9 months (95% CI 7.6, 13.5). Overall survival data is not yet mature.

Conclusions: Our results suggest that treatment with pazopanib is tolerable and shows similar efficacy in ECOG PS 2 patients as compared to previously reported data with ECOG PS 0/1. This suggests that excluding patients from trials based solely on their performance status may not appropriate.

Clinical trial identification: EudraCT: 2011-001211-31, ISRCTN: 38957238, Cancer Research UK Endorsement: C11225/A12402.

Legal entity responsible for the study: The University of Birmingham.

Funding: Novartis.

Disclosure: E. Porfiri: Grants: Novartis, during the conduct of the study; Personal (speaker and advisory board) fees: Novartis, Pfizer, BMS, Ipsen, outside the submitted work. K. Fife: Non-financial support: BMS; Personal fees: BMS, Ipsen, Pfizer, Roche, Esai, Novartis, outside the submitted work. C. McDonald-Smith: Personal fees: Pfizer, BMS, outside the submitted work. N.S. Vasudev: Non-financial support: Ipsen; Grants and non-financial support: Bristol Myers Squibb, outside the submitted work. All other authors have declared no conflicts of interest.

884P Real-world effectiveness of pazopanib in patients with intermediate prognostic risk advanced renal cell carcinoma (PRINCIPAL study)

G. Procopio[1], A. Bamias[2], M. Schmidinger[3], R. Hawkins[4], A. Rodriguez Sanchez[5], S. Vazquez[6], N. Srihari[7], H. Kalofonos[8], P. Bono[9], C. Pisal[10], Y. Hirschberg[11], L. Dezzani[11], Q. Ahmad[11], C. Suarez Rodriguez[12], E. Jonasch[13]

[1]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Oncology Unit, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece, [3]Oncology, Medical University of Vienna, Vienna, Austria, [4]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [5]Oncology, University Hospital of Leon, Leon, Spain, [6]Medical Oncology, Hospital Lucus Augusti, Lugo, Spain, [7]Medical Oncology, Shrewsbury & Telford Hospitals NHS Trust, Shrewsbury, UK, [8]Medical Oncology, University of Patras, Patras, Greece, [9]Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland, [10]Clinical Research, Novartis Healthcare Private Limited, Hyderabad, India, [11]Clinical Research, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [12]Medical Oncology, Vall d'Hebron University Hospital and Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain, [13]GU Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: Stratification by prognostic risk informs efficacy for various treatments in patients (pts) with advanced renal cell carcinoma (RCC). Whether further stratification beyond prognostic risk aids in predicting treatment outcomes is unknown. We conducted a post-hoc analysis of the real-world PRINCIPAL study (NCT01649778) to assess the effectiveness of pazopanib (PAZ) in pts with intermediate risk advanced RCC.

Methods: In this prospective, observational study, pts with advanced and/or metastatic clear cell RCC were enrolled within 30 days of initiating PAZ. Data on progression, survival, and safety were collected approximately every 3 months (mos) until death, consent withdrawal, or loss to follow-up, for up to 30 mos. Primary efficacy end points included overall survival (OS), progression-free survival (PFS), and overall response rate (ORR). A post-hoc analysis of pts with intermediate risk per Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria was conducted to evaluate effectiveness by number or risk factors (1 vs 2), age (<65 vs ≥ 65 years), and Eastern Cooperative Oncology Group performance status (ECOG PS).

Results: Of the 657 enrolled pts who received ≥1 dose of PAZ, 363 (55.3%) and 343 (52.2%) had intermediate risk per MSKCC and IMDC criteria, respectively. Within the subgroup of pts with intermediate risk MSKCC and IMDC, median PFS (but not OS) was numerically longer in pts with 1 (vs 2) risk factors, and outcomes were poorer in pts with ECOG PS ≥ 2 (vs < 2) (Table). Median OS within each MSKCC and IMDC risk group was longer than anticipated based on previous clinical trial and real-world data.

Table: 884P Median progression-free survival

	MSKCC intermediate risk (n = 363)		IMDC intermediate risk (n = 343)	
	Disease progression or death/N (%)	Median (95% CI) months	Disease progression or death/N (%)	Median (95% CI) months
Number of risk factors*				
1	85/147 (57.8)	13.8 (10.7-18.1)	88/171 (51.5)	13.1 (10.7-18.1)
2	85/141 (60.3)	7.4 (6.2-10.3)	88/133 (66.2)	8.1 (6.4-10.7)
Age				
<65 years	79/142 (55.6)	12.3 (9.0-16.4)	73/136 (53.7)	13.1 (10.3-18.4)
≥65 years	131/219 (59.8)	10.7 (9.0-13.8)	123/205 (60.0)	10.7 (9.0-13.1)
ECOG PS				
<2	189/333 (56.8)	11.2 (9.5-14.1)	177/316 (56.0)	11.8 (9.9-15.4)
≥2	8/8 (100.0)	5.6 (1.3-12.8)	8/8 (100.0)	2.3 (1.2-10.7)

*Patients with 1 missing risk factor were excluded.
CI; confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center.

Conclusions: The results of the PRINCIPAL study suggest pts with advanced RCC of intermediate prognostic risk can be further stratified to predict treatment outcomes.

Clinical trial identification: NCT01649778.

Editorial acknowledgement: Editorial support was provided by Chris Ontiveros, PhD (ApotheCom, New York).

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: G. Procopio: Honoraria: Astellas Pharma, Ipsen Inc., Novartis, Pfizer Inc.; Consulting/advisory roles: Bayer, Bristol-Myers Squibb Company, Ipsen Inc., Novartis Pharma AG, Pfizer Inc. A. Bamias: Personal fees: Novartis Pharma AG, Bristol Meyers Squibb Company, Ipsen Inc. M. Schmidinger: Research funding: Roche Holding AG; Honororia as consulting/advisory role: Pfizer Inc., Roche Holding AG, Bristol-Myers Squibb Company, Ipsen Inc., Novartis Pharma AG, Exelixis; Travel accommodations/expenses: Pfizer Inc., Roche Holding AG, Ipsen Inc. R. Hawkins: Personal fees: BMS, Novartis, Ipsen, EUSA, outside the submitted work; Patent: MRC Phage Antibody with royalties paid. S. Vazquez: Honoraria: Roche Holding AG, Pfizer Inc., Astellas Pharma, AstraZeneca, Bristol-Myers Squibb Company, Sanofi, Eli Lilly and Company; Travel expenses/accommodations: Roche Holding AG, AstraZeneca. N. Srihari: Non-financial support: Janssen. P. Bono: Stockholder: TILT Biotherapeutics; Honoraria: Bristol-Myers Squibb Company, Merck Sharp & Dohme Corp., Orion Corporation, Pfizer Inc., Novartis Pharma AG, Ipsen, Oncorena Holding AB. C. Pisal, Q. Ahmad: Employee of Novartis Pharma AG. Y. Hirschberg: Employee: Novartis Pharma AG; Stockholder: Beckton Dickinson, Novartis Pharma AG. L. Dezzani: Employee and stockholder: Novartis Pharma AG. E. Jonasch: Grants and personal fees: Novartis. All other authors have declared no conflicts of interest.

885P Are adverse events (AEs) predictive of nivolumab activity? Data from the Italian expanded access program in metastatic renal cell carcinoma (mRCC)

E. Verzoni[1], G. Cartenì[2], E. Cortesi[3], F. Roila[4], M.G. Vitale[5], S. Buti[6], S. Pignata[7], F. Cognetti[8], L. Giustini[9], A. Damiani[10], D. Turci[11], C.N. Sternberg[12], C. Porta[13], F. Carrozza[14], G. Tortora[15], D. Tassinari[16], R. Passalacqua[17], A. Pazzola[18], G. Surico[19], G. Procopio[20]

[1]Medical Oncology-Genitourinary Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [2]Oncology Unit, A. Cardarelli Hospital, Naples, Italy, [3]Radiology , Oncology and Pathology, Policlinico Umberto I, Rome, Italy, [4]Medical Oncology, Azienda Ospedaliera Sta Maria, Terni, Italy, [5]Dipartimento di Oncologia ed Ematologia, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [6]Medical Oncology, Azienda Ospedaliera di Parma, Parma, Italy, [7]Urology and Gynecology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [8]Medical Oncology, Istituto Regina Elena, Rome, Italy, [9]Medical Oncology, UOC Oncologia Area Vasta 4, Fermo, Italy, [10]Medical Oncology, San Martino Hospital, Genoa, Italy, [11]Medical Oncology, Ospedale Sta Maria delle Croci, Ravenna, Italy, [12]Medical Oncology, Azienda Ospedaliera S. Camillo Forlanini, Rome, Italy, [13]Medical Oncology, Ospedale San Matteo, Pavia, Italy, [14]Medical Oncology, Ospedale Umberto I (AUSL Romagna), Lugo, Italy, [15]Medical Oncology, AOU Integrata Verona "Borgo Roma", Verona, Italy, [16]Oncology, Ospedale Infermi, Rimini, Italy, [17]Medical Oncology, Istituti Ospitalieri di Cremona, Cremona, (CR), Italy, [18]Medical Oncology, Ospedale Civile SS Annunziata, Sassari, Italy, [19]Medical Oncology, Ospedale Vito Fazzi, Lecce, Italy, [20]Medical Oncology-Genitourinary Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

Background: The Italian Renal Cell Cancer Early Access Program was an expanded access program that allowed access to nivolumab, for patients (pts) with mRCC prior to regulatory approval.

Methods: Pts with mRCC previously treated with agents targeting the vascular endothelial growth factor pathway were eligible to receive nivolumab 3 mg/kg once every 2 weeks. Pts included in the analysis had received $\geq$ 1 dose of nivolumab and were monitored for adverse events (AEs) using CTCAE v.4.0. Association between sex, age, BMI, metastatic sites, number and kind of previous therapies, ECOG PS and related toxicity were evaluated with a logistic regression model that identified only age $\geq$ 65 years (Odds Ratio= 1.54 (1.00-2.38; P = 0.05).

Results: A total of 389 pts were enrolled between July 2015 and April 2016, 79% after 2 or more lines of therapy. The most common any-grade treatment-related AEs were fatigue (13%) and rash (9%). Twenty-two (5.7%) pts discontinued treatment due to AEs. There were no treatment-related deaths. Treatment-related AEs (grade 1-4) were reported in 32% of pts. Median time to appearance of AEs was 1.4 months (range 0-11.4). Grade 3–4 AEs occurred in 27 (7%) pts. Of the 22 serious AEs who induced treatment discontinuation, 11 (50%) were considered irAEs including: grade 4 hyperglicemia (n = 1), grade 3 diarrhea (n = 1), grade 3 pulmonitis (n = 1), grade 3 bronchiolitis obliterans organising pneumonia (BOOP) (n = 1), grade 3 asthenia (n = 1), grade 3 hypertension (n = 1), grade 3 skin toxicity (n = 1), grade 3 tremor (n = 1), grade 2 eyelid ptosis (n = 1), grade 2 liver toxicity (n = 1), grade 2 hypothyroidism (n = 1). AEs were generally manageable with treatment as per protocol-specific guidelines. At a median follow-up of 12 months, the median progression-free survival was 4.5 months (95% CI 3.7 - 6.2), the 12-months overall survival rate was 63%. Pts with toxicity (124 pts) had a significant (P = 0.01) longer survival (1 year OS 69%) in comparison to pts who did not experience AEs (1 year OS 59%).

Conclusions: The appearance of AEs strongly correlates with survival benefit in a real-life population of mRCC pts treated with Nivolumab.

Legal entity responsible for the study: Italian Renal Cell Cancer Early Access Program Group.

Funding: BMS.

Disclosure: E. Verzoni: Honoraria/Consultancy: Novartis, Pfizer, Ipsen, BMS. C.N. Sternberg: Honoraria/Consultancy: Novartis, Pfizer, Ipsen, Eisai, BMS. G. Procopio: Honoraria/Consultancy: Ipsen, BMS, Pfizer, Novartis. All other authors have declared no conflicts of interest.

886P Adiponectin-AdipoR1 axis in renal cell carcinoma plays a pivotal role in tumor progression and drug resistance

G. Sun, X. Zhang, J. Zhao, J. Chen, P. Shen, Z. Liu, H. Zeng

Urology, West China Hospital, Sichuan University, Chengdu, China

Background: It is well established that renal cell carcinoma (RCC) is an obesity-associated cancer. Adiponectin, a major adipocyte-secreted adipokine, plays anti-tumor properties in many malignancies, but exerted paradoxical actions on RCC. Herein, we investigated the effects of adiponectin on RCC progression and resistance to sunitinib, and to exploit this molecular mechanism.

Methods: Tissues were collected from 126 patients with metastatic renal cell carcinoma (mRCC) treated with tyrosine kinase inhibitor (TKI) therapy. Tumor Adiponectine receptor 1 (AdipoR1) and Adiponectine receptor 2 (AdipoR2) were detected by immunohistochemistry. Assays with RCC cell lines were used to examine the signal transduction pathways of adiponectin in RCC.

Results: AdipoR2 was generally lower expressed than AdipoR1 in mRCC tumor (15.6% vs 89.1%, $p < 0.001$). AdipoR1 expression, but not AdipoR2, was a significant independent predictor of favorable responding to TKI and good survival outcomes. In cultured RCC cells adiponectin inhibited migration and invasion of RCC cells and sensitized cells to killing by sunitinib. Mechanistic investigations of ligand–receptor interactions revealed that AdipoR1 could hinder migration and invasion of RCC cells by blocking GSK3β and β-Catenin pathway and increase cells sensitivity to sunitinib through inhibiting AKT and NF-κB pathway. However, AdipoR2 was not associated with the tumor-limiting properties of adiponectin.

Conclusions: These results show that AdipoR1 is a potential prognostic marker for favorable outcomes of mRCC patients. Adiponectin-AdipoR1 axis could be a plausible target to impede tumor progression and sensitize tumors to TKI therapy.

Legal entity responsible for the study: Guangxi Sun.

Funding: National Natural Science Foundation of China (NSFC 81672547, 81402110), the Science and Technology Support Program of Sichuan Province (2015SZ0230-3) and 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University.

Disclosure: All authors have declared no conflicts of interest.

887P Identification of IMDC intermediate-risk subgroups in patients with metastatic clear-cell renal cell carcinoma (ccRCC)

A. Guida[1], G. Le Teuff[2], E. Colomba[3], G. Baciarello[3], L. Derosa[4], Y. Loriot[3], K. Fizazi[3], C. Massard[5], B. Escudier[3], L. Albiges[3]

[1]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, [2]Statistics, Gustave Roussy, Villejuif, France, [3]Department of Medical Oncology, Gustave Roussy, Villejuif, France, [4]INSERM, Gustave Roussy, Villejuif, France, [5]DITEP, Gustave Roussy Institut de Cancérologie, Villejuif, France

Background: Majority of patients (pts) with ccRCC at first line (1L) treatment are classified in the IR subgroup according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model. IR represents a heterogeneous class of pts while frontline strategies will be chosen on prognostic selection. The aim of this study is to better characterize IR pts.

Methods: Retrospective analysis was performed from IGReCC (Institut Gustave Roussy Renal Cell Carcinoma) database. Overall survival (OS) was defined from start of 1L therapy to death or last follow-up. A multivariable Cox model with backward selection procedure (alpha level = 0.01) and a Classification and Regression Tree (CART) analysis were performed to identify which prognostic factors of IMDC score (time from diagnosis to treatment [DDT] < 1 year, Karnofsky Performance Status [KPS] < 80%, Hemoglobin < lower limit of normal [LNL], neutrophils > upper normal level [UNL], platelet > UNL, calcium > UNL) were associated to OS in IR pts.

Results: From 2005 to 2016, 777 pts with ccRCC were treated with an anti-VEGF first line therapy. Among 571 evaluable pts for IMDC score, 199 (35%) pts were classified as good risk, 82 (14%) as poor risk and 290 (51%) as IR. Median OS for IR pts was 24 months (mo). Within the IR population, only platelet (PLT) count was significantly associated to OS with a hazard ratio 1.88 (95%CI 1.27-2.88) p = 0.0017. Median OS for pts with PLT > UNL was 18 months (mo) [95%CI 12-23] versus 29 mo [95%CI 21.4-35.7] for pts with normal PLT count. Therefore, the selection of PLT count was confirmed on bootstrap samples and was also selected for the first split of the CART-tree analysis.

Conclusions: Pts in the IR group have a heterogeneous prognosis. Elevated PLT count seems identifies a subgroup of pts with poor outcome in the IMDC intermediate-risk population with ccRCC.

Legal entity responsible for the study: Laurence Albiges.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

888P Lesion detection by ceCT, 89Zr-girentuximab and FDG PET/CT in newly diagnosed patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC)

S.R. Verhoeff[1], S. Es[2], E. Boon[1], E. van Helden[3], L. Angus[4], S. Elias[5], S. Oosting[2], E. Aarntzen[6], A. Brouwers[2], S. Heskamp[6], O.S. Hoekstra[7], H.M. Verheul[3], A.A.M. Van der Veldt[4], E.G.E. de Vries[2], O. Boerman[6], W.T.A. van der Graaf[8], W.J.G. Oyen[1], C.M.L. van Herpen[1]

[1]Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [2]Medical Oncology, University Hospital Groningen (UMCG), Groningen, Netherlands, [3]Medical Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [4]Medical Oncology, Erasmus University Medical Center, Rotterdam, Netherlands, [5]Epidemiolgy, Julius Center of Health Academy, Utrecht, Netherlands, [6]Radiology and Nuclear Medicine, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [7]Radiology & Nuclear Medicine, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [8]Division of Clinical Studies, Royal Marsden Hospital Institute of Cancer Research, Sutton, Surrey, UK

Background: As slow disease progression is observed in a subset of mccRCC patients, watchful waiting can be considered, thereby postponing toxicity of systemic treatment. To identify those patients, the IMPACT trial evaluated the role of anti-Carbonic

Anhydrase IX antibody ^{89}Zr-girentuximab and ^{18}F-fluorodeoxyglucose (FDG) PET/CT (PET). Here, we report preliminary analyses of a secondary endpoint: comparison of baseline contrast-enhanced(ce)CT, ^{89}Zr-girentuximab and FDG PET to detect metastases.

Methods: mccRCC pts with good or intermediate prognosis (according to IMDC) and eligible for watchful waiting were included. Patients underwent 3 scans, i.e. ceCT, ^{89}Zr-girentuximab and ^{18}F-FDG PET. So far, baseline scans of 29 of the 40 pts to be accrued were independently reviewed by 3 experienced readers. Lesions by ceCT were defined positive according to RECIST1.1. For lesions with prominent uptake of ^{89}Zr-girentuximab or ^{18}F-FDG, maximum Standardized Uptake Values (SUVmax) were calculated. Analyses were performed on a lesion level, taking clustering of data within patients and lesions into account.

Results: In total 325 lesions were detected by at least one modality (mean 11(2-33) per pt); ceCT detected 52% (95%CI:45;58), ^{18}F-FDG PET 61% (95%CI:55;67) and ^{89}Zr-girentuximab PET 69% (95%CI:63;74). Differences in lesion detection varied across organ sites($p < 0.001$). Lesions were visualized by ceCT and ^{18}F-FDG PET in all pts,whereas ^{89}Zr-girentuximab PET detected lesions in 27 of 29 pts. Compared to ceCT, ^{89}Zr-girentuximab PET visualized additional lesions in all organ sites. Location was strongly related with ^{89}Zr-girentuximab uptake; highest uptake in kidney and adrenal gland tumor (mean SUVmax 63.2 and 70.3, resp) and lowest uptake in lung and lymph nodes (mean SUVmax 10.9 and 15.0, resp). After correction for location, no relation was observed between ^{89}Zr-girentuximab SUVmax and tumor size, as measured by ceCT, and ^{18}F-FDG SUVmax.

Conclusions: ^{89}Zr-girentuximab and ^{18}F-FDG PET visualize additional lesions compared to ceCT, however correlation was poor. The addition of ^{89}Zr-girentuximab or ^{18}F-FDG PET might aid in deciding to either delay or start systemic treatment.

Clinical trial identification: NCT02228954.

Legal entity responsible for the study: Radboud University Medical Center (Radboudumc).

Funding: Supported by the Dutch Cancer Society.

Disclosure: All authors have declared no conflicts of interest.

889P Clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin inhibitors (mTORI) after immuno-oncology (IO) checkpoint inhibitors

J. Graham[1], J.C. Wells[1], R. McKay[2], U.N. Vaishampayan[3], A. Hansen[4], F. Donskov[5], G.A. Bjarnason[6], B. Beuselinck[7], G. De Velasco[8], M.S. Duh[9], L. Huynh[9], R. Chang[9], G. Zanotti[10], K. Ramaswamy[10], T.K. Choueiri[11], D.Y.C. Heng[1]

[1]Medical Oncology, University of Calgary, Calgary, AB, Canada, [2]Medical Oncology, University of California San Diego, San Diego, CA, USA, [3]Oncology, Karmanos Cancer Institute, Detroit, MI, USA, [4]Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [5]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [6]Medical Oncology, Sunnybrook Odette Cancer Center, Sunnybrook HSC, Toronto, ON, Canada, [7]General Medical Oncology, University Hospitals Leuven, Leuven, Belgium, [8]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [9]Health Economics and Outcomes Research, Analysis Group, Inc, Boston, MA, USA, [10]Global HEOR, Oncology, Pfizer, Inc., New York, NY, USA, [11]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: In an era of increasing treatment options for mRCC, optimal treatment sequence after IO therapy has not been well established. This study compares the effect of targeted therapy (TT) (VEGFR TKI [axitinib, sunitinib, cabozantinib, pazopanib, bevacizumab, and sorafenib] vs mTORI [everolimus and temsirolimus]) after progression on IO therapy.

Methods: Data from 7 International mRCC Database Consortium (IMDC) centers were used to examine time to treatment discontinuation (TTD: time from TT initiation to discontinuation for any reason) and objective response rate (ORR: complete or partial tumor response) among mRCC patients (pts) treated with TT after IO between 2010-2018. Kaplan Meier analysis and Cox proportional hazards model adjusting for age, sex, IMDC risk score, and line of therapy were conducted. Overall survival will be reported when data is more mature.

Results: Pts treated with VEGFR TKI (N = 156 [85%]) and mTORI (N = 28 [15%]) post IO had similar age and IMDC risk scores (mean age: 61 vs 63 years; IMDC favorable: 5% vs 8%; IMDC intermediate: 62% vs 48%). Most common TT post IO were axitinib (35%), cabozantinib (18%), and sunitinib (15%). Unadjusted median TTD was significantly longer for VEGFR TKI vs mTORI (5.3 vs 2.5 months, p = 0.002). VEGFR TKI vs mTORI post IO was significantly associated with a longer TTD (adjusted hazard ratio [aHR]: 0.44, p = 0.002). A trend toward better TTD with axitinib post IO vs other TT was observed (aHR: 0.66, p = 0.08). ORR was numerically higher in VEGFR TKI vs mTORI. Reported results are across all lines of therapy. The table has descriptive statistics.

Table: 889P Descriptive statistics of clinical outcomes among patients treated with targeted therapy (i.e., VEGFR TKI, mTORI) subsequent to IO treatment

	Total N	Number of treatment discontinuation for any reason (%)	Median TTD, (95% CI) months	Objective response rate[1] N (%)
All	184	118 (64)	4.9 (4.0, 5.6)	20 (17)
By class VEGFR TKI[2]				
All lines	156	93 (60)	5.3 (4.3, 6.9)	19 (20)
2nd line	44	28 (64)	3.8 (3.2, 5.4)	7 (23)
3rd line	72	43 (60)	5.7 (4.3, 9.8)	10 (22)
≥ 4th line	40	22 (55)	6.1 (4.2, 10.9)	2 (10)
mTORI[3]				
All lines	28	25 (89)	2.5 (1.4, 3.4)	1 (5)
2nd line	0	-	-	-
3rd line	20	19 (95)	2.3 (1.0, 4.9)	1 (6)
≥ 4th line	8	6 (75)	3.2 (1.3, 4.9)	0 (0)

IO: immuno-oncology; VEGFR TKI: vascular endothelial growth factor receptor tyrosine kinase inhibitor; mTORI: mammalian target of rapamycin inhibitor; CI: confidence interval; ORR: objective response rate; TTD: time to treatment discontinuation Notes: [1] Objective response rate, defined as the sum of partial responses and complete responses, was assessed during the line of targeted therapy subsequent to IO treatment. The total number of patients assessed was 116. [2] VEGFR TKI included axitinib, sunitinib, cabozantinib, pazopanib, bevacizumab, and sorafenib. [3] mTORI included everolimus and temsirolimus.

Conclusions: Subsequent to IO therapy, VEGFR TKI pts had significantly longer adjusted TTD than mTORI pts. When larger sample sizes are available for TT, further examination of sequences is warranted.

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer, Inc.

Disclosure: R. McKay: Research funding: Pfizer and Bayer; Ad board: Janssen, Novartis. U.N. Vaishampayan: Research funding, Honoraria, and Consulting: Pfizer. A. Hansen: Research funding: Genentech/Roche, Merck, GlaxoSmithKline, Bristol Myers Squibb, Novartis; Advisory board: Pfizer, Roche, Merck, AstraZeneca, Ipsen, Bristol Myers Squibb. F. Donskov: Research funding: Pfizer, Novartis, Ipsen. G.A. Bjarnason: Research funding: Pfizer, Merck; Honoraria: Pfizer, Novartis, Bristol-Myers Squibb, Eisai, Ipsen; Consulting: Pfizer, Novartis, Bristol-Myers Squibb, Eisai, Ipsen; Travel funding: Pfizer, Novartis. B. Beuselinck: Research funding: Pfizer; Speaker's fee: Ipsen, Amgen, Pfizer. G. De Velasco: Research funding: Ipsen; Consulting or advisory role: Janssen, Pfizer, Novartis, Bayer, Astellas Medivation, Bristol-Myers-Squibb, Pierre Fabre. M.S. Duh, L. Huynh: M. Duh R. Chang: Employee of Analysis Group, which received funding from Pfizer for this project. G. Zanotti, K. Ramaswamy: Employee of Pfizer. T.K. Choueiri: Research funding: AstraZeneca, BMS, Exelixis, Genentech, GSK, Merck, Novartis, Peloton, Pfizer, Roche, Tracon, Eisai; Consulting and Advisory Role: AstraZeneca, Bayer, BMS, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Ipsen. D.Y.C. Heng: Consultancies and Honoraria: Pfizer, Novartis, BMS, Ipsen. All other authors have declared no conflicts of interest.

890P Everolimus as first-line or after cytokine therapy in patients with metastatic recurrent and/or unresectable renal cell carcinoma (RCC) (EVERMORE)

A.M. Abdel Hakim[1], Y. Nouira[2], R. Taran[3], D. Amokrane[4], M. Ghosn[5], B. Larbaoui[6], C. Pripatnanont[7], K. Slimane[8], V. Pilipovic[9], H. Boussen[10]

[1]Department of Urology, Cairo University, Cairo, Egypt, [2]Department of Urology, La Rabta Hospital, Tunis, Tunisia, [3]Medical Oncology, CHL-Hospitals and CHL-CBCC Cancer Center, Indore, India, [4]Department of Medical Oncology, Pierre and Marie Curie Center, Algiers, Algeria, [5]Hematology Oncology Department, Saint Joseph University, Beirut, Lebanon, [6]Medical Department of Oncology, Anti Cancer Center "Emir Abdel Kader", Oran, Algeria, [7]Department of Surgery, Prince of Songkla University, Songkla, Thailand, [8]Oncology, Novartis Pharma S.A.S, Rueil-Malmaison, France, [9]Oncology, Novartis Pharma AG, Basel, Switzerland, [10]Department of Medical Oncology, Hopital Abderrahman Mami, Ariana, Tunisia

Background: Novel therapies are needed as an initial or salvage treatment for patients with metastatic or locally advanced RCC. This study aimed to assess the safety and efficacy of everolimus in patients with metastatic recurrent and/or unresectable clear cell RCC.

Methods: EVERMORE is an open-label, multicenter, single-arm, phase 2 study (NCT01206764) that enrolled patients aged ≥ 18 yrs with advanced and histologically confirmed clear or non-clear cell RCC. Everolimus 10 mg/d was administered orally, as a first line or after cytokine therapy, until disease progression (PD), unacceptable toxicity, or study discontinuation for any other reason. The primary endpoint was progression-free survival (PFS) rate over time. The secondary endpoints were disease control rate (DCR; stable disease + partial response [PR] + complete response [CR]), objective response rate (ORR), duration of response (DOR), overall survival (OS), and safety.

Results: From 2009 to 2017, 142 patients with a mean age of 55.5 years from 10 countries were enrolled. Most of the patients (58.2%) have a clear cell adenocarcinoma as histology/cytology and 53.1% had stage IV disease at initial diagnosis. Of 142 patients, everolimus was received in 117 as first-line and in 25 as second-line treatment. The most common reason for early discontinuation of treatment was PD (n = 88, 62.0%). The median PFS for all assessed patients was 7.0 months (95% CI: 22.00, 37.29). The ORR was 12.0% (n = 17; 95% CI: 7.1, 18.5). The median DOR in patients who had either CR or PR was 39.0 months (n = 17). The DCR was 74.6% (n = 106; 95% CI: 66.7, 81.6). The median OS was not evaluable. The most commonly reported adverse events (AEs) of all grades were anemia (45.1%), stomatitis (29.6%), hyperglycemia (26.1%), and decreased appetite (22.5%). The most commonly reported serious AEs were pneumonia (n = 6), dyspnea (n = 4), urinary tract infection, decreased appetite, dehydration and diarrhea (n = 3 each). In the study, 33 deaths were reported, of which, 19 deaths were due to study indication.

Conclusions: The PFS and safety results of everolimus when administered in patients as first-line or after cytokine therapy are consistent with the previously published data (RECORD-3).

Clinical trial identification: NCT01206764.

Legal entity responsible for the study: Novartis Pharma AG.

Funding: Novartis Pharma AG.

Disclosure: D. Amokrane: Advisory board, Speaker or Grants for Clinical research: Novartis, Sanofi, Bayer, Ipsen, Amgen, Roche, Janssen, Pfizer MSD, Pierre Fabre. M. Ghosn: Grants-research support: Pfizer, Novartis. K. Slimane, V. Pilipovic: Employee and shareholder of Novartis. All other authors have declared no conflicts of interest.

891P Correlation between immuno-related adverse events (IRAEs) occurrence and clinical outcome in metastatic renal cell carcinoma (mRCC) patients treated with nivolumab: IRAENE trial, an Italian multi-institutional retrospective study

M.G. Vitale[1], S. Pipitone[1], S. Scagliarini[2], P.A. Zucali[3], L. Galli[4], S. Rossetti[5], C. Caserta[6], R. Iacovelli[7], C. Masini[8], C. Ficorella[9], S. Di Girolamo[10], S. Buti[11], B. Benedetti[12], M. Santoni[13], C. Porta[14], S. Bracarda[15], C. Baldessari[1], S. Giaquinta[1], S. Cascinu[1], R. Sabbatini[1]

[1]Dipartimento di Oncologia ed Ematologia, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [2]Oncology Unit, Antonio Cardarelli Hospital, Naples, Italy, [3]UO Oncologia Medica e Ematologia, Humanitas Cancer Center Istituto Clinico Humanitas - IRCCS, Rozzano, Italy, [4]UO Oncologia Medica 2 Universitaria, Azienda Ospedaliero-Universitaria Pisana Istituto Toscano Tumori, Pisa, Italy, [5]Division of Medical Oncology, Department of Uro-Gynaecological Oncology, Istituto Nazionale Tumori, IRCCS, "Fondazione G. Pascale", Naples, Italy, [6]Oncology, Azienda Ospedaliera Sta Maria, Terni, Italy, [7]Medical Oncology Unit, Azienda Ospedaliera Universitaria Integrata (AOUI), University of Verona, Verona, Italy, [8]Oncologia Medica, Azienda Ospedaliera Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Italy, [9]Medical Oncology Unit, S. Salvatore Hospital, University of L'Aquila, L'Aquila, Italy, [10]Oncologia Medica, AUSL di Imola, Imola, Italy, [11]Oncologia, Azienda Ospedaliera di Parma, Parma, Italy, [12]Oncologia, Ospedale degli Infermi, Faenza, Italy, [13]Oncologia, AOU Ospedali Riuniti Ancona Università Politecnica delle Marche, Ancona, Italy, [14]Oncologia, Ospedale San Matteo, Pavia, Italy, [15]U.O.C. of Medical Oncology, Ospedale San Donato, Arezzo, Italy

Background: Immunotherapy (IO) has brought dramatic clinical benefits to patients with mRCC. Most patients tolerate IO, but serious irAE have been reported. Some studies indicate the correlation of irAEs and clinical response in other cancer types such as lung cancer and melanoma. For mRCC, the impact of irAE on clinical outcome is unknown.

Methods: A retrospective review of patients with mRCC treated with nivolumab as standard of care between March 2017-January 2018 from 13 Italian centers of the IGO group (Innovators in Genitourinary Oncology) was performed. Patients enrolled in clinical trial or expanded access program were excluded. IrAEs were assessed based on the treating physician diagnosis.

Results: A total of 111 patients (pts) met criteria. Median age was 67 yr, 83 pts (75%) were male. Histology was clear cell in 102 pts (92%) and non clear cell in 9 pts (8%). IrAE was noted in 48 pts (43%) with steroid required in 21 pts (44%). The time from the beginning of nivolumab treatment to the irAE occurrence ranged 1-81 weeks (mean 10 weeks). Most patients received nivolumab as a second or third line of treatment (61% and 37% respectively). The most common irAEs were cutaneous (21%), endocrinologic (17%), gastrointestinal and pulmonary (both 15%). In patients who developed irAE, 2% of complete response (CR), 22% of partial response (PR), 41% of stable disease (SD) and 35% of progression disease (PD) (according to RECIST criteria) were observed versus 0% CR, 7% PR, 37% SD and 57% PD in patients who did not develop irAE. Development of irAE had a statistically significant impact on response rates (p = 0.007). There was also no significant association of steroid use with response rates (p = 0.643). Because of the short follow up, survival data were not mature at the time of the analysis.

Conclusions: The development of irAE may be correlated with better response to nivolumab. This data may be limited by sample size and retrospective nature. A long-term follow-up is required to determine the impact of irAE on survival in mRCC patients treated with nivolumab.

Legal entity responsible for the study: Maria Giuseppa Vitale.

Funding: Has not received any funding.

Disclosure: M.G. Vitale: Advisory boards, speaker or investigator: Bristol-Myers Squibb. R. Sabbatini: Advisory boards, honoraria or study participation: Bristol-Myers Squib. All other authors have declared no conflicts of interest.

892P Treatment sequences in metastatic renal cell carcinoma: Efficacy results from the Czech registry (RENIS)

J. Finek[1], R. Demlova[2], K. Kopeckova[3], T. Buchler[4], B. Melichar[5], J. Prausova[3], A. Poprach[6], T. Hrnciarova[7], T. Mlcoch[7], T. Dolezal[7]

[1]Oncology and Radiotherapy, Teaching Hospital Pilsen and Faculty of Medicine in Pilsen, Charles University, Plzen, Czech Republic, [2]Pharmacology Department,, Faculty of Medicine, Masaryk University and Masaryk Memorial Cancer Institute, Brno, Czech Republic, [3]Oncology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic, [4]Oncology, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic, [5]Oncology, University Hospital Olomouc, Olomouc, Czech Republic, [6]Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic, [7]IHETA, Institute of Health Economics and Technology Assessment, Prague, Czech Republic

Background: Efficacy data of treatment sequences in mRCC are rare. In the Czech Republic, data on efficacy and safety of all targeted therapies for mRCC are collected in the RENIS patient registry. Thus, RENIS provides data from the real-world clinical practice. The aim of this study was to compare outcomes of selected treatment

sequences in mRCC while adjusting for differences in patient characteristics using inverse propensity score weighting method (IPWS).

Methods: Data of mRCC patients treated using most common treatment sequences were collected in RENIS between 06/2007 and 02/2018. Overall survival (OS) and progression free survival (PFS) were evaluated. Baseline characteristics were balanced using IPWS. The propensity score was evaluated with nominal logistic model to balance Eastern Cooperative Oncology Group (ECOG) performance status, time from diagnosis to first treatment, nephrectomy, Memorial Sloan-Kettering Cancer Center (MSKCC) score, and age. Median and confidence intervals (CI) were derived from IPWS weighted Kaplan-Meier curves that were compared using log-rank test.

Results: Overall, 745 patients in five treatment sequences were included and analysed. Differences in OS were significant ($p < 0.001$) with sunitinib→axitinib→everolimus and sunitinib→axitinib sequences associated with improved survival over other sequences. These differences could be also linked to time when these drugs were introduced. PFS did not differ between sunitinib and pazopanib used as first line treatments ($p = 0.44$) but the PFS in the second line differed significantly ($p = 0.035$) (Table).

Table: Results of OS and PFS for examined sequences computed using inverse propensity score weighting. Sunitinib → Axitinib → Everolimus sequence should be assessed with caution due to immortal time bias.

Table: 892P

Parameter	Treatment sequence	n	Median	95% CI for median		p
				Lower limit	Upper limit	
OS (months)	Sunitinib → Everolimus	312	26.3	23.8	29.0	<0.001
	Sunitinib → Axitinib	154	47.6	31.3	50.5	
	Sunitinib → Axitinib → Everolimus†	114	46.0	44.7	50.9	
	Pazopanib → Everolimus	74	32.9	30.9	33.8	
	Pazopanib → Sunitinib	91	27.2	26.7	28.8	
PFS 1st line (months)	Sunitinib	580	10.2	9.8	10.8	0.440
	Pazopanib	165	9.2	8.5	10.0	
PFS 2nd line (months)	Sunitinib → Everolimus	312	5.8	5.1	6.3	0.035
	Sunitinib → Axitinib	268	6.4	6.0	7.1	
	Pazopanib → Everolimus	74	5.1	4.1	5.5	
	Pazopanib → Sunitinib	91	5.3	5.1	7.1	

Conclusions: Improved outcomes were associated with sequences using second-line axitinib over those using second-line sunitinib or everolimus in a cohort of patients from a national registry.

Legal entity responsible for the study: Jindrich Finek.

Funding: Value Outcomes.

Disclosure: J. Finek: Honoraria: Amgen, BMS, Roche, Bayer, Teva, MSD, Merck, Sanofi, Pierre Fabre. R. Demlova: Honoraria for lectures: Bayer. K. Kopeckova: Honoraria for lectures: Novartis; Travel grants: Pfizer, Bayer. T. Buchler: Honoraria for advisory boards and/or lectures: Novartis, Pfizer, Bayer, Roche. B. Melichar: Honoraria for advisory boards and/or lectures: Novartis, Pfizer, Glaxo Smith Kline, Roche, Bayer. A. Poprach: Honoraria for lectures: Novartis, Bristol-Myers Squibb, Roche, Bayer. T. Hrnciarova, T. Mlcoch, T. Dolezal: Employee of Value Outcomes. All other authors have declared no conflicts of interest.

893P Cabozantinib in metastatic renal cell carcinoma (mRCC): Data from UK expanded access program (EAP)

A. Gomez de Liano Lista[1], B. Venugopal[2], K. Fife[3], S. Symeonides[4], N.S. Vasudev[5], S.M. Rudman[6], S. Vohra[2], L. Khasati[7], C. Pettinger[4], B. Szabados[1], L. Morrison[8], T. Powles[9], E. Boleti[8]

[1]Medical Oncology, Barts Cancer Institute, London, UK, [2]Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK, [3]Medical Oncology, Cambridge University Hospitals NHS Foundation Trust - Addenbrooke's Hospital, Cambridge, Cambridgeshire, UK, [4]Medical Oncology, Cancer Research UK Edinburgh Centre, Edinburgh, UK, [5]Oncology, St. James's University Hospital Leeds, Leeds, Yorkshire, UK, [6]Medical Oncology, Guy's and St. Thomas' Hospital NHS Trust, London, UK, [7]Medical Oncology, Cambridge University Hospitals NHS Foundation Trust - Addenbrooke's Hospital, Cambridge, UK, [8]Academic Oncology, Royal Free Hospital School of Medicine, London, UK, [9]Barts Cancer Institute, London, UK

Background: Cabozantinib demonstrated increased efficacy over everolimus in patients with mRCC progressing on VEGF targeted therapy in the randomised phase III METEOR trial. We report real world experience with Cabozantinib in 7 centres across the UK.

Methods: In this retrospective study, patients who started Cabozantinib from September 2016 to September 2017 within the UK EAP were included. Patients had mRCC progressing after at least 1 prior systemic treatment, PS 0-2 and adequate organ function. The goal was to analyse toxicities, efficacy and access to other drugs after progression. Adverse events (AEs) were graded using the NCI CTCAE v.4.0.3. Survival times were calculated from the start of Cabozantinib using a Kaplan-Meier model. Radiological response was assessed locally by RECIST 1.1.

Results: 128 patients were included. Median follow-up was 10.5 months. Median age was 62 years, 84% had clear cell histology, and 49% were classified as intermediate risk by IMDC score. 87% had visceral M1 and 52% bone M1. Patients received a median of 2 previous lines (1-6) of therapy. Cabozantinib was used as 2nd line, 3rd line and 4th line or beyond in 56 (44%), 38 (30%) and 34 (26%) patients respectively. Baseline characteristics are summarized in the table. 48 (37%) of the patients developed G3/4 AEs, mainly fatigue (N = 14, 11%), diarrhoea (N = 12, 9%), mucositis (N = 7, 5%) and hand-foot syndrome (N = 6, 5%). No treatment-related deaths were seen. 71 patients (55%) required dose reductions. 12 (15%) discontinued Cabozantinib due to toxicity. Median OS was 9.1 months (95% CI 6.6-11.6), being 14.3 vs 9.3 vs 6.0 months for good, intermediate and poor prognostic patients, respectively (p 0.01). Median PFS was 7.7 months (95% CI 5.3-10.1). Partial response to Cabozantinib was 26%, stable disease 24%, Progressive disease 30% and was not evaluated in 20%. Only 21/81 patients (26%) stopping Cabozantinib started on subsequent treatment.

Conclusions: Cabozantinib was safe and active in pretreated patients with mRCC.

Legal entity responsible for the study: Alfonso Gomez de Liano.

Funding: Has not received any funding.

Disclosure: S. Symeonides: Research funding: Merck Sharp & Dohme. T. Powles: Advisory role and research funding: Roche, AstraZeneca. All other authors have declared no conflicts of interest.

Table: 893P

Baseline characteristic		Number (%)
Gender	Male Female	87 (68) 41 (32)
Age	Median (range)	62 (11-83)
PS ECOG	0 1 2	20 (16) 85 (66) 23 (18)
Histology	Clear Cell Papillary Other	107 (84) 13 (10) 8 (6)
IMDC Risc Category	Good Intermediate Poor Unknown	35 (27) 62 (49) 27 (21) 4 (3)
Nephrectomy	Yes No	93 (73) 35 (27)
Number of metastatic sites	1 2 ≥3	17 (13) 46 (36) 64 (50)
Metastatic sites	Lung Lymph node Bone Liver Brain Pleura/Peritoneal Other	92 (72) 55 (43) 66 (52) 42 (33) 14 (11) 19 (15) 47 (37)
Visceral and bone M1 spread	All patients with visceral M1 Both Visceral + bone M1 Visceral M1 without bone M1	110 (87) 55 (43) 54 (42)
Previous lines of therapy	1 2 ≥3	56 (44) 38 (30) 34 (26)
Duration of 1st VEGFR TKI	≤6 months >6 months	34 (27) 94 (73)
1st subsequent treatment (N = 21)	Nivolumab Axitinib Everolimus Others	15 (71) 3 (14) 1 (5) 2 (10)
PD-1/PDL1 inhibitors prior to Cabo	Nivolumab PD1/PDL1-VEGF combo	27 (21) 10 (8)

894P Comparative effect of body-mass index on outcome with targeted therapy and immunotherapy in patients with metastatic renal cell carcinoma (mRCC)

N. Dizman[1], P. Bergerot[1], C.D. Bergerot[1], E.J. Philip[2], M.M. Salgia[1], J. Hsu[1], J. Adashek[1], S.K. Pal[1]

[1]Medical Oncology, City of Hope, Duarte, CA, USA, [2]The Notre Dame Laboratory for Psycho-Oncology Research, University of Notre Dame, Notre Dame, IN, USA

Background: A previous study identified an association between high body mass index (BMI) and better overall survival (OS) in mRCC patients treated with vascular endothelial growth factor-tyrosine kinase inhibitors (VEGF-TKIs) (Albiges et al JCO 2016). We assessed whether the effect of BMI on OS extended beyond VEGF-TKI to immunotherapy (IO) or VEGF/IO combination regimens.

Methods: A retrospective study was done among patients diagnosed with mRCC treated at a single institution from 2009 to 2017. Demographic and clinical variables were collected. BMI was characterized as high ($\geq$25 kg/m^2) versus low ($<$25 kg/m^2). The Kaplan-Meier method was used to estimate the difference in OS, segregated by BMI and further by treatment type (e.g., VEGF-TKI, IO or VEGF/IO).

Results: Among 235 patients, median age was 65 years (33-90), 73% were male, and 65% were overweight or obese (BMI $\geq$ 25 kg/m^2). The majority of patients had undergone nephrectomy (86%). The most systemic therapy was VEGF-TKI (58%), followed by IO (17%) and VEGF/IO (25%). In patients treated with VEGF-TKI with low BMI, median OS was 25.0 months (95% CI: 18.7-31.2) versus 36.0 months (95% CI: 25.2-46.7) in patients with high BMI (P = 0.01). A similar result was found for patients treated with VEGF/IO, where median OS was 18.0 months (95% CI:10.0-25.9) for patients with low BMI versus 24.0 months (95% CI: 14.8-33.2) in patients with high BMI (P = 0.01). However, patients treated with IO with low BMI, median OS was 55.0 months (95% CI: 33.7-76.7) versus 22.9 months (95% CI: 17.7-28.1) in patients with high BMI (P = 0.33).

Conclusions: High BMI was associated with improved OS in patients with mRCC treated with VEGF-TKI or VEGF/IO, but the inverse trend was observed among patients receiving IO. In addition to validating previous findings associating VEGF-TKI, BMI and clinical outcome, our data highlight the need to reassess this phenomenon in the context of IO-based regimens.

Legal entity responsible for the study: City of Hope.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

895P Advanced treatment line (ATL) with lenvatinib and everolimus (Len+Eve) for metastatic renal cell carcinoma (mRCC): Analysis of a national early access program (EAP)

A. Peer[1], M. Kolin[1], K. Rouvinov[2], D. Keizman[3], D. Sarid[4], R. Leibowitz-Amit[5], R. Berger[5], A. Sella[6], A. Rasco[6], E. Rosenbaum[7], C. Maurice-Dror[1], A. Neumann[1], V. Neiman[7]

[1]Oncology, Rambam Health Care Center, Haifa, Israel, [2]Oncology, Soroka University Medical Center, Beer Sheva, Israel, [3]Oncology, Meir Medical Center, Kfar Saba, Israel, [4]Oncology, Tel Aviv Sourasky Medical Center-(Ichilov), Tel Aviv, Israel, [5]Oncology, Chaim Sheba Medical Center, Ramat Gan, Israel, [6]Oncology, Asaf Harofeh Medical Center, Zerifin, Israel, [7]Oncology, Rabin Medical Center Davidoff Cancer Centre, Beilinson Campus, Petah Tikva, Israel

Background: VEGFR inhibition is a mainstay in the treatment of mRCC. In recent years third generation TKIs offer advantages in treatment efficacy while combinations further improve clinical activity. Treatment with Len+Eve is approved based on a randomized phase 2 study in the second line setting. Data on activity and efficacy of this combination as ATL beyond second line is limited. We aimed to report the activity of Len+Eve in mRCC patients (pts) treated per a national EAP.

Methods: Records from consecutive mRCC (pts) treated with Len+Eve in ATL per a national EAP in 7 centers, were retrospectively reviewed. We report the clinical benefit, progression free survival (PFS), overall survival (OS), and toxicity.

Results: Between 11/2016 – 12/2017, 39 mRCC pts were treated with Len+Eve. Median age 60 (39-82), male 72%. Majority of the pts (82%) underwent nephrectomy. Heng risk was good/intermediate/poor in 13% (n = 5)/41% (n = 16)/46% (n = 18). According to the treating physician, 69% (n = 27) of pts had high burden disease at treatment initiation. 13% (n = 5) were treated as second line, 51% (n = 20) as third and 36% (n = 14) as fourth line. All patients in the third and fourth line received prior immunotherapy. Clinical benefit (stable disease+ partial response) was 74% (54% partial response and 20% stable disease). Median PFS was 6 months (mos). After a median follow up time of 9 mos, 62% of the pts with a clinical benefit are still with a benefit and on treatment (range 5-16m). Most pts (72%, n = 28) are alive, with median OS not reached. Dose reduction was required in 49% of the patients due to mainly grade 3 toxicity. There were no treatment discontinuations due to toxicity.

Conclusions: Len+Eve as ATL in mRCC may benefit patients beyond second line treatment, and is associated with responses similar to those seen in a clinical trial setting in the ATL setting, with manageable toxicity.

Legal entity responsible for the study: Avivit Peer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

896P Predictive radiomics signature for treatment response to nivolumab in patients (pts) with advanced renal cell carcinoma (RCC)

H-W. Sim, A. Stundzia, S. Pierre, U. Metser, M. O'Malley, E. Elimova, S.S. Sridhar, A. Hansen

Department of Medical Oncology, Princess Margaret Cancer Center, Toronto, ON, Canada

Background: Although nivolumab has been widely adopted as a treatment for advanced RCC, only a minority of pts benefit. We aimed to use radiomics as a predictive biomarker. By extracting quantitative information from serial imaging, this non-invasive method captures the spatial and temporal heterogeneity of tumors, more than tissue biopsy. We hypothesized to find an imaging correlate of host immune recognition, characterized by infiltration of the invasive tumor margin by immune effector cells, that would identify pts to benefit from nivolumab.

Methods: We retrospectively identified all advanced RCC pts treated with nivolumab at our institution from 2013-2017. Pts were labelled as responders (CR / PR / durable SD) or non-responders based on clinical data. For each pt, lesions were contoured from pre-treatment and first on-treatment CT scans. All lesions were manually contoured in tandem by two trained investigators. This information was used to train a radial basis function support vector machine classifier to learn a prediction rule to distinguish responders versus non-responders. The classifier was internally validated by 10-fold nested cross-validation.

Results: 37 pts were identified. Excluded: imaging unavailable = 3, incompatible CT protocols = 7. 104 lesions were contoured from 27 pts. Median age 56 years, 78% male, 89% clear cell histology, 89% prior nephrectomy, 89% prior systemic therapy. 19 responders vs 8 non-responders. Lesions: 60% lymph nodes, 23% lung metastases, 17% renal/adrenal metastases. For the classifier trained on the baseline CT scans, 69% accuracy was achieved. For the classifier trained on the first on-treatment CT scans, 66% accuracy was achieved.

Conclusions: Based on preliminary computations, the radiomics signature could discriminate nivolumab responders from non-responders. Additional texture feature analysis with over 72 billion calculations is underway to improve the classifier performance to discriminate tumor responses to immunotherapy. External validation against the comprehensive patient dataset from the International Metastatic Renal Cell Cancer Database Consortium is planned.

Legal entity responsible for the study: Dr Hao-Wen Sim and Dr Aaron Hansen.

Funding: Awarded $40,000 from peer-reviewed 2017 GUMOC Astellas Research Grant.

Disclosure: All authors have declared no conflicts of interest.

897P A phase Ib study of safety and preliminary efficacy of extracranial stereotactic body radiation therapy (SBRT) in patients with metastatic renal cell carcinoma (mRCC) treated with systemic therapy

N. Dengina[1], T. Mitin[2], S. Gamayunov[3], S. Safina[4], Y. Kreinina[5], I. Tsimafeyeu[6]

[1]Radiotherapy Department, Ulyanovsk Regional Clinical Cancer Center, Ulyanovsk, Russian Federation, [2]Radiation Medicine, Oregon Health & Science University, Portland, OR, USA, [3]Thoracic and Abdominal Surgery Department, Republical Clinical Cancer Center, Cheboksary, Russian Federation, [4]Medical Oncology, Republical Clinical Cancer Center, Kazan, Russian Federation, [5]Brachytherapy Department, Russian Scientific Center of Roentgen Radiology, Moscow, Russian Federation, [6]Russian Society of Clinical Oncology, Moscow, Russian Federation

Background: Tyrosine kinase inhibitors (TKI) and checkpoint inhibitors (CI) have been established as effective treatment for mRCC, but only a minority of patients achieves complete response and additional strategies are necessary to improve the efficacy of these agents. We have designed a prospective phase 1b "Volga" study to determine the safety and efficacy of extracranial SBRT in patients with clear-cell mRCC.

Methods: Patients were included if they had stable disease for at least 4 months on TKI or CI. SBRT was delivered to an organ with multiple comparable lesions, where one lesion was in the treatment target (target lesion) and the other one was intentionally left untreated (control lesion). Dose of radiation and number of fractions were determined based on target lesion localization and the proximity of organs at risk. Response in both target and control lesions was scored using RECIST 1.1 criteria at least 2 months after completion of SBRT.

Results: 17 patients were enrolled, 12 of them received TKI and 5 patients received nivolumab. SBRT was delivered to lungs (n = 5), bones (n = 4), lymph nodes (n = 4), liver (n = 1), primary RCC (n = 1), and locally recurrent RCC (n = 2). Equivalent Dose (EQD) with alpha/beta ratio of 2.6 was 114 Gy (range, 40-276 Gy). With a median follow-up of 8 months (range, 3-18), cumulative rate of SBRT-related toxicity (grade 1) was 12% (n = 2), consisting of esophagitis (n = 1) and skin erythema (n = 1). No grade 2 or higher toxicity was detected. Radiographic response in the target lesion was seen in 13 patients (76%), with complete response in 5 (29%) patients and partial response in 8 (47%) including abscopal effect in 1 patient. Control lesions were stable in 16 patients. The difference between response in target and control lesions as judged by mean sizes of these lesions before and at 2 months after SBRT was statistically significant (P < 0.01). Fraction size of equal to or greater than 10 Gy was associated with complete response in the target lesion.

Conclusions: Extracranial SBRT in patients with mRCC treated with TKI or CI is well tolerated and could be effective. This approach will be studied in an expanded cohort of patients.

Clinical trial identification: NCT02864615.

Legal entity responsible for the study: Kidney Cancer Research Bureau.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

898P VOTRAGE study pazopanib in a population of "frail" elderly patients after geriatric assessment: A phase I study with geriatric criteria

L. Mourey[1], A. Ravaud[2], L. Digue[2], B. Cabarrou[3], C.A. Gomez-Roca[4], T. Valentin[1], P. Olivier[5], A. Fabre[6], M. Mounier[6], L. Balardy[7], T. Filleron[3]

[1]Medical Oncology, Institut Universitaire du Cancer de Toulouse - Oncopole, Toulouse, France, [2]Medical Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France, [3]Biostatistic Unit, Institut Universitaire du Cancer de Toulouse - Oncopole, Toulouse, France, [4]Medical Oncology, Institut Universitaire du Cancer de Toulouse - Oncopole, Toulouse, Haute-Garonne, France, [5]Pharmacology Department, CHU Toulouse, Toulouse, France, [6]Clinical Research Unit, Institut Universitaire du Cancer de Toulouse - Oncopole, Toulouse, France, [7]Geriatric Medicine, CHU Toulouse Hôpital Purpan, Toulouse, France

Background: Efficacy and toxicity of targeted therapies don't seem to vary with age, but the impact of side effects in frail elderly patients ($\geq$ 75 years-old) (EP) is a major concern for clinicians. Our study aims to explore an original method to find the maximum tolerated dose of Pazopanib (P), in a population of EP, classified as "frail" after comprehensive geriatric assessment (CGA), using a phase I methodology, integrating a geriatric criterion for DLT (2 points drop in Activity of Daily Living Score (ADL)). Pharmacokinetic and pharmacogenomic studies were planned.

Methods: Open-label, multicenter (2), non-randomized, phase 1 dose escalation clinical trial (standard 3 + 3 design) to determine MTD and DLT of P in a population of frail EP, selected after CGA. Tested dose levels of P were 400, 600 and 800 mg /day. Toxicity was assessed during the first cycle (28days). Patients received P until progression. The MTD was defined as the highest dose level for which 6 patients are treated with a maximum of one patient (~20%) presenting a DLT. Main inclusion criteria • Age $\geq$ 75 • Metastatic solid cancers (kidney, lung, pancreatic-neuroendocrine, sarcoma, ovary, thyroid, bladder or breast) • "Frail" by CGA.

Results: From 11/2012 to 09/2017, 18 pts were included. Median age was of 82.5 (range 75-91). No DLT was reported at 400mg/day. There was 1 DLT (asthenia Grade 3) at 600 mg/day. At 800 mg/day, 3/6 patients experienced a DLT. Two patients had treatment interruption longer than two weeks due to side effects and one experienced a grade 3 hypertension. Diarrhea, fatigue and hypertension were the most frequently treatment related toxicity.

Conclusions: Our study used an original way to assess feasibility of an approved treatment in population of frail EP ($\geq$ 75 years-old). The results demonstrate that it is probably deleterious to initiate a treatment with P in this vulnerable population at the approved dose level of 800mg/day. The treatment should be initiated at a lower dose (600mg/day). Our results reinforce the need to proceed to geriatric assessment in EP before initiation of cancer treatment to individualize their management.

Clinical trial identification: EudraCT: 2011-005012-29.

Legal entity responsible for the study: Institut Claudius Regaud.

Funding: Novartis.

Disclosure: L. Mourey: Honoraria, travel expenses and research funding: Novartis. All other authors have declared no conflicts of interest.

899P A phase II study investigating the safety and efficacy of neoadjuvent atezolizumab in muscle invasive bladder cancer (ABACUS)

D. Castellano[1], I. Duran[2], A. Rodríguez-Vida[3], S.J. Crabb[4], M.S. van der Heijden[5], A. Font Pous[6], G. Gravis[7], U. Anido Herranz[8], A. Protheroe[9], A. Ravaud[10], D. Maillet[11], M.J. Mendez-Vidal[12], C. Suarez[13], A. Lorch[14], C.N. Sternberg[15], M. Linch[16], S-J. Sarker[17], J. Notta[17], K. Mousa[17], T.B. Powles[17]

[1]Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain, [2]Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain, [3]Medical Oncology, Hospital del Mar, Barcelona, Spain, [4]Southampton Experimental Cancer Medicine Centre, University of Southampton, Southampton, UK, [5]Medical Oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, [6]Medical Oncology, Institut Català d' Oncologia, Badalona, Barcelona, Spain, [7]Medical Oncology, Institute Paoli Calmettes, Marseille, France, [8]Medical Oncology Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, La Coruña, Spain, [9]Medical Oncology Department, Churchill Hospital University of Oxford, Oxford, UK, [10]Medical Oncology Department, CHU Bordeaux Hopital St. André, Bordeaux, France, [11]Medical Oncology Department, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [12]Medical Oncology Department, Reina Sofia University Hospital, Cordoba, Spain, [13]Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [14]Genitourinary Medical Oncology, Universitätsklinikum Düsseldorf, Düsseldorf, Germany, [15]Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy, [16]Medical Oncology Department, UCL Cancer Institute, London, UK, [17]Barts Cancer Institute, Queen Mary University of London, London, UK

Background: Atezolizumab is a PD-L1 inhibitor, which is licenced in metastatic urothelial cancer. This study investigates the efficacy and safety of neoadjuvant atezolizumab given prior to cystectomy in operable muscle invasive transitional cell carcinoma of the bladder.

Methods: This single arm phase 2 study investigated 2 cycles of atezolizumab (1200mg Q3) prior to cystectomy in muscle invasive transitional cell cancer (T2-4N0M0). Pathological complete response (pCR) occurring in $\geq$ 20% of patients was the primary endpoint. Biomarker analysis on sequential tissue was a co-primary endpoint. Cross sectional imaging was performed at baseline and prior to cystectomy which occurred 4 - 8 weeks after starting atezolizumab. Radiological response was assessed. Adverse events (AEs) and surgical complications were assessed using CTCAE v4.03 and the Clavien-Dindo classification. Updated analysis with 75 patients will be presented. IMCORE provided biomarker analysis.

Results: At baseline pT2, T3, T4 disease occurred in 73%, 20% and 7% of patients respectively. 16 (21%) patients had only 1 cycle (9 due to AEs). 7 patients did not have cystectomy (1 disease progression, 2 treatment related AE). There was 1 potential treatment related death during treatment/perioperative period (cardiovascular disease). Treatment related grade 3/4 toxicity occurred in 12% of patients. Grade 3 or 4 surgical complications occurred in 31% of pt. The pCR rate was 20/68 (29%) [95%CI: 19% to 42%] (pT0 24%, Tis 6%, T1 9% T2 24% T3 22% T4 15% stage at surgery). 39% of patients were down staged to non-muscle invasive disease. 3/20 (15%) of the pCR patients had pT3/4 disease at baseline. 47% patients were positive for PD-L1 ($\geq$5% IC SP142); pCR rates were 38% and 27% in PD-L1 positive and negative tumours respectively (n = 62). 47 patients had sequential imaging and radiologically measurable disease at baseline. 28% [95%CI, 16% to 43%] and 17% [95%CI, 8% to 31%] of these patients radiologically responded and progressed respectively.

Conclusions: Neoadjuvant atezolizumab is safe and associated with a meaningful pathological CR rate at this interim stage. Further exploration is justified.

Clinical trial identification: NCT02662309.

Legal entity responsible for the study: Queen Mary University of London.

Funding: F. Hoffmann - La Roche Ltd.

Disclosure: I. Duran: Consulting or advisory role: roche/Genentech, MSD Oncology, Bayer, Bristol-Myers Squibb; Travel, accommodation, expenses: Roche/Genentech; Honoraria: Bristol-Myers Squibb, Ipsen, Roche/Genentech; Research funding: Roche/Genentech (institution). S.J. Crabb: Consulting or Advisory role: Roche, Clovis Oncology, Bayer, Janssen-Cilag; Travel, accommodation, expenses: Bayer, Merck, Ipsen, Bristol-Myers Squibb, Roche, Janssen-Cilag; Honoraria: Novartis, Roche, Janssen-Cilag; Research funding: AstraZeneca, Astex Pharmaceuticals, Plexxikon, Clovis Oncology. M.S. van der Heijden: Consulting or advisory role (institution): Roche/Genentech, Astellas Pharma, AstraZeneca/MedImmune, Bristol-Myers Squibb; Travel, accommodation, expenses: Novartis, Astellas Pharma, MSD Oncology; Research funding: Astellas Pharma (institution). G. Gravis: Travel, accommodation, expenses: Novartis, Sanofi, Janssen Oncology, Bristol-Myers Squibb, Astellas Pharma, Takeda. U. Anido Herranz: Consulting or advisory role: Bayer; Travel, accommodation, expenses: Astellas Pharma; Honoraria: Pfizer, Novartis, Bayer. A. Ravaud: Consulting or advisory role: Pfizer, Novartis, Bristol-Myers Squibb, Ipsen, Roche; Travel, accommodation, expenses: Pfizer, Novartis, Bristol-Myers Squibb; Honoraria: Pfizer, Bristol-Myers Squibb, Novartis; Research funding (institution): Pfizer, Novartis. C. Suarez: Consulting or advisory role: Bristol-Myers Squibb, Ipsen, Sanofi, Pfizer; Travel, accommodation, expenses: Bristol-Myers Squibb; Honoraria: Roche. A. Lorch: Consulting or advisory role: Bristol-Myers Squibb, Novartis, AstraZeneca, Roche; Travel, accommodation, expenses: Novartis, Ipsen; Honoraria: Astellas Scientific and Medical Affairs Inc, Ipsen. C.N. Sternberg: Consulting or advisory role: Bristol-Myers Squibb, Novartis, Janssen, Bayer, Eisai, MSD, Lilly, Clovis Oncology, Ferring; Honoraria: Pfizer, Astellas Pharma, Sanofi, Ipsen, AstraZeneca. T.B. Powles: Consulting or advisory role: Roche/Genentech, Bristol-Myers Squibb, Merck, Novartis, AstraZeneca; Honoraria: Roche/Genentech, Bristol-Myers Squibb, Merck; Research funding: AstraZeneca/MedImmune, Roche/Genentech; Other relationship: Ipsen, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

900P Interim results of fight-201, a phase II, open-label, multicenter study of INCB054828 in patients (pts) with metastatic or surgically unresectable urothelial carcinoma (UC) harboring fibroblast growth factor (FGF)/FGF receptor (FGFR) genetic alterations (GA)

A. Necchi[1], D. Pouessel[2], R. Leibowitz-Amit[3], A. Flechon[4], S. Gupta[5], P. Barthelemy[6], M. Maio[7], X. Zhu[8], E. Asatiani[9], G. Serbest[10], H. Zhen[11], Y. Loriot[12]

[1]Department of Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Department d'Oncologie Médicale, Institut Claudius Régaud – IUCT Oncopôle, Toulouse, France, [3]Cancer Research Center, Chaim Sheba Medical Center, Ramat Gan, Israel, [4]Departement de Cancers Urologiques, Centre Léon Bérard, Lyon, France, [5]Department of Medicine, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA, [6]Department of Medical Oncology, C.H.U. Strasbourg-Nouvel Hopital Civil, Strasbourg, France, [7]Dipartimento Oncologico, A.O.U. Senese Policlinico Santa Maria alle Scotte, Siena, Italy, [8]Medical Oncology, Northwell Cancer Institute, Lake Success, NY, USA, [9]Clinical Development, Incyte Corporation, Founex, Switzerland, [10]Clinical Development, Incyte Corporation, Willmington, DE, USA, [11]Biostatistics, Incyte Corporation, Willmington, DE, USA, [12]Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France

Background: FGFR3 GA are implicated in the pathogenesis of UC; ≈ 15% of pts with advanced UC have mutations and 6% have translocations. INCB054828, a selective, potent, oral inhibitor of FGFR1, 2, and 3, has shown efficacy in pts with FGF/FGFR GA tumors.

Methods: This study (NCT02872714) is enrolling pts with metastatic or unresectable UC who failed $\geq$ 1 therapy or are platinum ineligible and have FGFR3 mutations/fusions (cohort A, n = 100) or other FGF/FGFR GAs (cohort B, n = 40). Pts receive oral INCB054828 13.5 mg once daily on a 21-day cycle (2 wk on, 1 wk off) until disease

progression or unacceptable toxicity. The primary endpoint is overall response rate (ORR) in cohort A, assessed by independent review per RECIST v1.1. Secondary endpoints include ORR in cohort B, duration of response, progression-free survival, overall survival, and safety/tolerability. The primary objective of this interim analysis is to evaluate the efficacy and safety of INCB054828 in pts in cohort A who had ≥ 1 postbaseline tumor assessment or discontinued the study.

Results: As of data cutoff (7 Feb 2018), 64 and 36 pts were enrolled in cohorts A and B, respectively. In cohort A, 84% (54/64) had ECOG PS ≤ 1, 39% (25/64) received ≥ 3 prior therapies, and 36% (23/64) had a prior PD-1/L1 inhibitor. Of 64 pts, 51 had ≥ 1 postbaseline scan or discontinued. Best overall responses in cohort A were 7 confirmed partial responses (PRs), 6 unconfirmed PRs (ongoing), and 17 stable disease (10 ongoing). ORR, including unconfirmed PRs, was 25% (95% CI, 14%–40%). In cohort B, 1 pt with FGF10 amplification had an unconfirmed PR. Common treatment-emergent adverse events (TEAEs) in all pts were diarrhea (40%), alopecia (32%), fatigue (29%), constipation (28%), and dry mouth (28%). Grade ≥ 3 TEAEs in > 5% of pts were urinary tract infections (7%) and fatigue (6%). Hyperphosphatemia (any postbaseline serum phosphate > 5.5 mg/dL) was 68% in cohort A and 64% in all pts.

Conclusions: INCB054828 was generally well tolerated and showed preliminary efficacy in previously treated pts with UC and FGFR3 GA. Updated data will be presented.

Clinical trial identification: NCT02872714.

Editorial acknowledgement: Medical writing assistance was provided by Ann Yeung, CMPP, PhD, of Scientific Pathways, Inc, and funded by Incyte.

Legal entity responsible for the study: Incyte Corporation.

Funding: Incyte Corporation.

Disclosure: A. Necchi: Consultancy (incl. expert testimony): Roche, Merck, AstraZeneca, Incyte, Clovis Oncology, Bioclin Therapeutics, Janssen, Bayer; Research funding: Merck, AstraZeneca; Honoraria: Roche, Merck, AstraZeneca, Incyte, Clovis Oncology, Bioclin Therapeutics, Janssen, Bayer. D. Pouessel: Consultancy (incl. expert testimony): Janssen, Astellas, Sanofi, AstraZeneca, Pfizer, Novartis; Honoraria: Janssen, Astellas, Sanofi, AstraZeneca, Pfizer; Travel and accommodation expenses: Sanofi, Astellas. R. Leibowitz-Amit: Consultancy (Includes expert testimony): Janssen, Bayer, Roche; Honoraria: Bristol-Myers Squibb, MSD; Membership on any entity's Board of Directors or advisory committees; Pfizer. A. Flechon: Honoraria: Pfizer, Novartis, Ipsen, Astellas, Sanofi, Janssen, Roche, MSD, Bristol-Myers Squibb; Travel and accommodation support: Pfizer, Novartis, Ipsen, Astellas, Sanofi, Janssen, Roche, MSD, Bristol-Myers Squibb. S. Gupta: Research support to Institution: Pfizer, Five Prime Therapeutics, Hoosier Oncology Group, Rexahn Pharmaceuticals, Incyte, Bristol-Myers Squibb, Novartis, LSK, Mirati, Merck; Personal: Spouse is equity holder of Salarius Pharmaceuticals. P. Barthelemy: Consultancy (incl. expert testimony): Bristol-Myers Squibb, Novartis, Pfizer, Roche, MSD; Honoraria: Janssen, Cilag, Sanofi, Astellas. M. Maio: Honoraria: Bristol-Myers Squibb, GlaxoSmithKline, AstraZeneca, Roche, MSD, Incyte; Served on Advisory Committees: Bristol-Myers Squibb, GlaxoSmithKline, AstraZeneca, Roche, MSD, Incyte. E. Asatiani, G. Serbest: Employment: Incyte; Equity Ownership: Incyte. H. Zhen: Employment: Incyte; Equity ownership: Incyte stock. Y. Loriot: Consultancy (incl. expert testimony): Seattle Genetics, Astellas, Roche, AstraZeneca, MSD, Bristol-Myers Squibb; Research funding: Sanofi, Janssen; Honoraria: Sanofi, Pfizer. All other authors have declared no conflicts of interest.

901P Impact of prognostic factors and risk groups on overall survival (OS) in patients treated with pembrolizumab vs investigator's choice chemotherapy for advanced urothelial cancer (UC): Post hoc analysis of KEYNOTE-045

J. Bellmunt[1], R. de Wit[2], D.J. Vaughn[3], Y. Fradet[4], J.L. Lee[5], L. Fong[6], N.J. Vogelzang[7], M.A. Climent[8], D. Petrylak[9], T.K. Choueiri[10], A. Necchi[11], W.R. Gerritsen[12], H. Gurney[13], D.I. Quinn[14], S. Culine[15], C.N. Sternberg[16], E. Jensen[17], T. Frenkl[17], R.F. Perini[17], D. Bajorin[18]

[1]Medical Oncology, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain, [2]Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [3]Medical Oncology, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA, [4]Medical Oncology, CHU de Québec-Université Laval, Québec City, QC, Canada, [5]Medical Oncology, Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea, [6]Medicine, University of California, San Francisco, CA, USA, [7]Medical Oncology, Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA, [8]Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [9]Medical Oncology, Smilow Cancer Hospital at Yale University, New Haven, CT, USA, [10]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [11]Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [12]Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands, [13]Medical Oncology, Westmead Hospital and Macquarie University, Macquarie Park, Australia, [14]Medical Oncology, University of Southern California Norris Comprehensive Cancer Center and Hospital, Los Angeles, CA, USA, [15]Medical Oncology, Hôpital Saint-Louis, Paris, France, [16]Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy, [17]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [18]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: Well-defined prognostic factors (PF) and risk groups have been shown to impact OS in first- and second-line chemotherapy (chemo) for UC. Post hoc analysis of survival outcome per level of risk was conducted using data from the phase 3 KEYNOTE-045 trial (NCT02256436).

Methods: Data from the Oct 26, 2017 data cut were included. The presence or absence of 4 predefined criteria applied at study randomization was noted for each patient: ECOG PS (0 vs 1 or 2), hemoglobin level (<10 g/dL vs ≥ 10 g/dL), liver metastases (yes vs no), and time from prior chemotherapy (<3 months vs ≥ 3 months). Patients were grouped per the number of PFs they had (0, 1, 2, or 3/4), and OS was estimated for each risk group receiving pembrolizumab (pembro) or chemo, using Kaplan-Meier (K-M) statistics.

Results: Data from 529/542 patients were included. Stratified randomization ensured that the distribution of risk levels was similar between the 2 treatment arms. Overall, OS decreased with increasing numbers of PFs for pembro (from 19 to 5 months) and chemo (from 18 to 3 months) (Table). Within the chemo arm, the results of the K-M survival profiles were consistent with previously published data, in which each risk group had different outcomes. Within the pembro arm, outcomes of pts with 0 and 1 PF were distinct from those with 2 and 3/4 PF groups. OS was longer with pembro than with chemo across all PF subgroups.

Conclusions: OS within the pembro and chemo arms decreased with increasing numbers of PFs. OS of patients treated with pembro was longer than those receiving chemo across the risk groups. Patients treated with pembro who had 2 or 3/4 PFs had overall similar outcomes. Additional analyses are needed to characterize novel risk models for patients treated with immunotherapies.

Clinical trial identification: NCT02256436, trial initiation date: October 3, 2014.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Matthew Grzywacz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: J. Bellmunt: Consultant/advisory: Pierre Fabre, Astellas, Pfizer, Merck, Genentech, Novartis, AstraZeneca, BMS; Travel: Pfizer, MSD Oncology; Research funding: Millennium, Sanofi. R. de Wit: Consultant/advisory: Sanofi, Merck, Lilly,

Table: 901P

	0 PFS		1 PF		2 PFs		3 or 4 PFs	
OS	Pembro n = 54	Chemo n = 45	Pembro n = 97	Chemo n = 97	Pembro n = 66	Chemo n = 80	Pembro n = 45	Chemo n = 45
Median (95% CI),months	18.5 (14.1-NE)	17.6 (10.2-24.2)	12.6 (8.1-18.9)	8.8 (7.4-11.2)	5.1 (2.8-8.7)	4.7 (3.5-6.1)	4.6 (2.3-7.4)	3.4 (2.4-4.6)
24-month OS, %	41.4	36.7	35.3	17.8	12.6	5.6	13.7	NR
30-month OS, %	41.4	31.6	25.9	13.7	NR	5.6	11.4	NR
HR for OS	0.81 (0.49-1.36)		0.67 (0.48-0.93)		0.82 (0.57-1.16)		0.61 (0.39-0.97)	

Roche/Genentech; Honoraria: Sanofi, Lilly, Roche/Genentech, Merck; Research funding: Sanofi. D.J. Vaughn: Research funding: Merck, Roche, Genentech. Y. Fradet: Consultant/Advisory: Merck, Astellas, Roche, AstraZeneca; Research funding: Astellas; Travel: Roche. J.L. Lee: Consultant/Advisory: Astellas, AstraZeneca, Eisai; Honoraria: Pfizer, Astellas, Novartis, BMS; Research funding: Pfizer, Janssen, Novartis, Exelixis, BMS, Roche/Genentech. L. Fong: Consultant/Advisory: Atreca, Ideava Biosciences, MIODx; Research funding: BMS, Abbvie, Roche/Genentech, Janssen, Merck, Nektar. N.J. Vogelzang: Consultant/Advisory: Amgen, Pfizer, Bayer, Genentech/Roche, AstraZeneca, Caris Life Science, Tolero; Speakers' bureau: Bayer, Sanofi, BMS, Exelixis, AstraZeneca, Stock, Caris Life Sciences, Honoraria: Pfizer; Research funding: Endocyte, Merck. M.A. Climent: Honoraria: Roche, BMC, Bayer, Astella, Sanofi, Pfizer, Novartis; Consulting/Advisory: Janssen, Pfizer, Roche, Sanofi, Astellas Pharma, Bayer; Travel: Astellas, Janssen, Pfizer. D. Petrylak: Consultant/Advisory: Bayer, Johnson & Johnson, Exelixis, Ferring, Millennium, Medivation, Pfizer, Roche, Sanofi; Research funding: Johnson & Johnson, Sanofi, Endocyte, Genentech, Merck, Astellas, Novartis, AstraZeneca, Bayer, Lilly, Seattle Genetics. T.K. Choueiri: Consultant: Pfizer, Bayer, Novartis, GlaxoSmithKline, Merck, BMS Roche/Genentech, Eisai, AstraZeneca, Exelixis, Alligent; Honoraria: NCCN; Research funding: Pfizer, Novartis, Merck, Exelixis, GlaxoSmithKline, BMS, AstraZeneca, Roche/Genentech, Celldex. W.R. Gerritsen: Consultant/Advisory: BMS, Amgen, Merck, Aglaia Biomedical Ventures, Astellas, Bayer, Janssen-Cilag; Speakers' bureau: Astellas, Bayer, Janssen-Cilag; Travel: Amgen, Bayer. H. Gurney: Consultant/Advisory: BMS, Ipsen, Merck, AstaZeneca; Travel: Astellas, Sanofi; Honoraria: Roche, Astellas; Research funding: Pfizer. D.I. Quinn: Consultant/Advisory: Astellas, Pfizer, BMS, Genetech/Roche, Merck, Bayer, Exelixis, AstraZeneca, Sanofi; Honoraria: Bayer, Astellas, Pfizer, Genentech/Roche, Merck, BMS, AstraZeneca, Sanofi, Millennium, Genentech/Roche, GlaxoSmithKline. S. Culine: Consultant/Advisory: Roche, Janssen; Speakers bureau: Astellas, Roche, Merck; Travel: Amgen, Astellas, Janssen. C.N. Sternberg: Honararia: OncoGenex, Lilly, Janssen, Merck, BMS, AstraZeneca, Roche/Genentech; Research funding: Lilly, Janssen, Merck, BMS, AstraZeneca, Roche/Genentech. E. Jensen: Employment: Merck. T. Frenkl, R.F. Perini: Employment and stock. D. Bajorin: BMS, Novartis, Roche/Genentech, Merck, Lilly, Fidia Farmaceutici, Urogen Pharma, Lilly Pfizer, EMD Serono; Honoraria: Merck; Research funding: Dendreon, Novartis, Amgen. Genentech/Roche, Merck, BMS. All other authors have declared no conflicts of interest.

902P Biological features and clinical outcomes in atezolizumab (atezo)-treated patients (pts) with metastatic urothelial cancer (mUC) of the upper vs lower urinary tract (UTUC vs LTUC)

M.D. Galsky[1], R. Banchereau[2], E.E. Kadel, III[2], T. Ramirez-Montagut[2], S. Mariathasan[3], A. Thåström[2], J. Rosenberg[4], T. Powles[5], M.S. van der Heijden[6], A. Necchi[7]

[1]Hematology-Oncology, Mount Sinai Hospital, New York, NY, USA, [2]Genentech, Inc., South San Francisco, CA, USA, [3]Oncology Biomarker Department, Genentech, Inc., San Francisco, CA, USA, [4]Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [5]Experimental Cancer Medicine, Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, London, UK, [6]Molecular Carcinogenesis, Netherlands Cancer Institute, Amsterdam, Netherlands, [7]Medical Oncology, Medical Oncology, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy

Background: mUC arising from UTUC vs LTUC may involve distinct biology resulting in different treatment responses & outcomes. However, this hypothesis has not been comprehensively explored. Here, data from 2 prospective trials of atezo (anti–PD-L1) in platinum-treated mUC (IMvigor210 Cohort 2; IMvigor211) were used to explore relationships between UTUC/LTUC primary tumor site, objective response rate (ORR)/overall survival (OS) & biomarker status.

Methods: PD-L1 (VENTANA SP142 IHC assay), targeted DNA sequencing (FoundationOne) and RNA sequencing (Expression Analysis) were evaluated in archival samples. Microsatellite status (MSI) was determined at 114 loci, & tumor mutational burden (TMB) on 1.1 Mb sequenced DNA. Biomarker-evaluable pts had tumors with known baseline PD-L1 status & RNAseq profiles.

Results: 220 IMvigor210 & 339 IMvigor211 pts were efficacy evaluable (Table), of whom 24% & 28%, respectively, had UTUC. Numerically higher ORR was seen in LTUC vs UTUC (IMvigor210, 23% vs 14%; IMvigor211, 18% vs 10%); these differences were not statistically significant. In both cohorts LTUC pts had significantly higher TMB (IMvigor210 P = 0.05; IMvigor211 P = 0.02) & a trend toward higher PD-L1 expression. Lund molecular subtype distribution also differed between UTUC vs LTUC (IMvigor210 P = 0.005; IMvigor211 P = 0.098) with increased frequency of genomically unstable tumors in LTUC pts. FGFR3 alterations did not associate with UTUC vs LTUC or with response in these groups. In the combined IMvigor210 and IMvigor211 cohorts, MSI-high tumors occurred in 1/146 (< 1%) of UTUC and 5/413 (1%) of LTUC subgroups.

Conclusions: Our data suggest pts with LTUC may have improved outcomes with atezo vs pts with UTUC, although benefit was observed in both groups. Numerically higher ORR/OS in pts with platinum-treated LTUC may be partly related to non-overlapping underlying biology & warrants further study in different settings.

Table: 902P

	UTUC	LTUC
IMvigor210 (n = 220)[a]		
n	52	168
ORR (%)	13	23
Median OS (mo)	10.3	11.7
IMvigor211 (n = 339)[a]		
n	94	245
ORR (%)	11	18
Median OS (mo)	9.7	10.9

[a]Biomarker-evaluable pts from overall cohorts of 310 pts (IMvigor210 cohort 2) & 467 pts (IMvigor211). P values in the abstract are shown for descriptive purposes only based on this post hoc analysis.

Clinical trial identification: NCT02108652, NCT02302807.

Editorial acknowledgement: Medical writing support provided by Paige S. Davies, PhD, of Health Interactions.

Legal entity responsible for the study: F. Hoffmann-La Roche AG.

Funding: F. Hoffmann-La Roche AG.

Disclosure: M.D. Galsky: Advisory boards and research funding: Merck, Genentech, AstraZeneca, BMS; Advisory boards: Pfizer. R. Banchereau: Employee of Genentech. E.E. Kadel, III: Employee of Genentech/Roche; Stock: Roche, Compugen, Clinuvel, Epizyme, Mannkind, Merck; Immediate family member who owns stock in Gilead Sciences; Travel, accommodations, expenses: Genentech/Roche. T. Ramirez-Montagut, S. Mariathasan, A. Thåström: Employee and stock owner: Genentech. J. Rosenberg: Consultant: Merck, Roche/Genentech, AstraZeneca, BMS, Inovio, EMD-Serono, Bayer, Seattle Genetics, Astellas; Speaking fees: Chugai, AstraZeneca. Research sponsorship: Novartis, Roche/Genentech, Astellas, Seattle Genetics, Bayer, Mirati, Oncogenex, Incyte. T. Powles: Funding: AstraZeneca, Roche; Honoraria: AstraZeneca, Roche, Pfizer, Merck, BMS. M.S. van der Heijden: Consultancy fees and research funding: BMS, Astellas; Consultancy fees: Roche/Genentech, MSD, AstraZeneca/Medimmune, Seattle Genetics. A. Necchi: Research grants: AstraZeneca and Merck; Advisor: Merck, Incyte, Roche, AstraZeneca, Janssen, Clovis Oncology, BioClin Therapeutics, BMS.

903P Neuroendocrine carcinoma of the urinary bladder: A large analysis of the French GETUG consortium

M. Sroussi[1], M. Lorcet[2], M.P. Tardy[3], M. Guerin[4], F. Estrade[5], R. Delva[6], P. Barthelemy[7], P. Lavaud[8], Y. Neuzillet[9], N. Penel[10], N. Houede[11], D. Pouessel[12], E. Mussat[13], M. Gross Goupil[14], H. Gauthier[15], A. Gobert[16], O. Huillard[17], Y. Allory[18], R-T. Elaidi[1], S. Oudard[1]

[1]Medical Oncology Department, HEGP - European Georges Pompidou Hospital, Paris, France, [2]Medical Oncology Department, Léon Bérard Center, Lyon, France, [3]Medical Oncology Department, Antoine Lacassagne Center, Nice, France, [4]Medical Oncology Department, Paoli Calmettes Insitute, Marseille, France, [5]Medical Oncology Department, Eugène Marquis Center, Rennes, France, [6]Medical Oncology Department, Paul Papin Center, Angers, France, [7]Medical Oncology Department, University Hospital Center, Strasbourg, France, [8]Medical Oncology Department, Gustave Roussy Institute, Villejuif, France, [9]Urology Department, Hopital Foch, Suresnes, France, [10]General Oncology Department, Oscar Lambret Center, Lille, France, [11]Medical Oncology Department, Gard Cancerology Department, Nimes, France, [12]Medical Oncology Department, IUCT Oncopole, Toulouse, France, [13]Medical Oncology Department, Henri Mondor Hospital, Creteil, France, [14]Medical Oncology Department, St. André Hospital, Bordeaux, France, [15]Medical Oncology Department, St Louis Hospital, Paris, France, [16]Medical Oncology Department, Salpétrière Hospital, Paris, France, [17]Medical Oncology Department, Cochin Hospital, Paris, France, [18]Pathology Department, Curie Institute, Saint-Cloud, France

Background: Neuroendocrine carcinoma of the urinary bladder (NCUB) is a rare malignancy, accounting for <1% of bladder cancers. Despite high sensitivity to platinum-based chemotherapy (CT), prognosis remains poor.

Methods: We retrospectively reviewed patients treated for NCUB in 18 French institutions to determine clinical/biologic characteristics, treatment efficacy and outcomes. Patient characteristics, treatment, follow-up and histological data were obtained from medical records. Tissue samples were pooled for further biological analyses.

Results: From 1992 to 2017, we reviewed 234 NCUB cases (84% male, age 31–93 [median 67] years, ECOG PS 0–3 [median 1]). Small cell carcinoma was found in 47% of patients and large cell carcinoma in 9%; urothelial carcinoma was present in 51% of patients. Hematuria (71%) and pain (19%) were the main symptoms. Main metastatic sites at diagnosis of metastatic disease were lymph node (76%), liver (42%), bone (42%), pelvic recurrence (33%), lung (19%) or brain (12%). Of 230 patients evaluable for staging at diagnosis, 168 had stage I–III disease: stage I (3%), II (20%), III (34%), not evaluable (16%). They were treated with neoadjuvant CT (49%; mainly based on a

platinum-based agent + etoposide [85%]), surgery (74%), radiotherapy (24%), and/or adjuvant CT (24%). Ninety-nine patients (59%) had metastatic recurrence. Median time to relapse was 4 months, disease-free survival was 14 months (95% confidence interval [CI] 12–18]), and median overall survival (mOS) was 28 months (95% CI 20–32). Of 62 patients (27%) with metastases at diagnosis, first-line CT was based on platinum + etoposide (81%), platinum + other drug (15%), or taxanes (4%). For these patients, median progression-free survival (mPFS) was 7 months (95% CI 4–9). Only 28 patients had second-line CT with mPFS of 5.2 months and mOS of 11 months (95% CI 8–15).

Conclusions: This is, to our knowledge, the largest cohort of NCUB patients studied to date. Data emphasize the heterogeneity and aggressiveness of this disease. Future studies should investigate disease biology and the activity of targeted therapies in NCUB. Molecular characteristics based on tumor tissue analysis are underway.

Legal entity responsible for the study: HEGP (European Georges Pompidou Hopsital).

Funding: Pierre Fabre.

Disclosure: All authors have declared no conflicts of interest.

904P Impact of different programmed cell death ligand-1 (PD-L1) expression algorithms on patient selection and durvalumab efficacy in urothelial carcinoma (UC)

J. Walker[1], M. Zajac[1], J. Ye[2], M. Scott[3], M. Ratcliffe[1], P. Scorer[3], C. Barker[3], H. Al-Masri[4], M.C. Rebelatto[5], A. Gupta[2], P. Mukhopadhay[2], S. Ferro[2], T. Powles[6], J.A. Williams[1]

[1]Oncology Companion Diagnostics Unit, AstraZeneca, Cambridge, UK, [2]Biometrics and Information Sciences, GMD Unit, AstraZeneca, Gaithersburg, MD, USA, [3]Precision Medicine and Genomics, IMED Biotech Unit, AstraZeneca, Cambridge, UK, [4]Anatomic Pathology & Clinical Pathology, Hematogenix, Tinley Park, IL, USA, [5]Experimental Pathology, Translational Sciences-Research, MedImmune, Gaithersburg, MD, USA, [6]Barts & The London School of Medicine & Dentistry, Barts Cancer Center, London, UK

Background: Antibodies targeting programmed cell death-1/PD-L1 (PD-1/PD-L1) have shown clinical activity in advanced UC. The ability of PD-L1 to predict response has been investigated using different antibody clones and scoring algorithms. It is important to understand if these assays/algorithms identify the same patients and how they compare in predicting response.

Methods: Archival UC tumour samples from 335 patients from a commercial source were stained with VENTANA SP263, VENTANA SP142, PD-L1 IHC pharmDx 28-8 and PD-L1 IHC pharmDx 22C3 Assays; classified according to their respective algorithms: tumour cell (TC) or immune cell (IC) staining ≥25% (TC/IC≥25%), PD-L1 staining IC area ≥5% of tumour (IC ≥ 5%), TC staining ≥1% or combined positive score (CPS ≥10). Overlap between populations was assessed by overall percent agreement (OPA), negative percent agreement (NPA) and positive percent agreement (PPA). UC samples from study 1108 (NCT01693562) were stained using VENTANA SP263 and TC/IC≥25%, IC ≥ 5% and CPS≥10 algorithms were applied. Objective response rates (ORR; data cutoff Oct 2017) in patients classified as PD-L1 high or low by these algorithms were investigated.

Results: There was moderate overlap between populations identified by VENTANA SP263 (TC/IC≥25%) and PD-L1 IHC pharmDx 28-8 (TC ≥ 1%) or PD-L1 IHC pharmDx 22C3 (CPS≥10) and minimal overlap between VENTANA SP263 (TC/IC≥25%) and VENTANA SP142 (IC ≥ 5%) (Table). Applying different algorithms to data from study 1108 also gave differences in patient classification. ORR in patients determined as PD-L1 high vs low/negative were as follows: TC/IC≥25%: 28% vs 6%, IC ≥ 5%: 48% vs 14%, CPS≥10 25% vs 13%.

Conclusions: The TC/IC≥25% algorithm identifies a different population to IC ≥ 5% or CPS10. In CD-ON MEDI4736-1108, highest response rates were seen in PD-L1 high patients determined by IC ≥ 5%, whereas TC/IC≥25% was optimal in predicting non-responders to durvalumab.

Table: 904P Overall (OPA), negative (NPA) and positive percent agreement (PPA) between PD-L1 assays

Clinical Algorithm (assay)	VENTANA SP263 (TC/IC 25%) Assay used as reference, % agreement (95% CI[a])		
	OPA	PPA	NPA
CPS ≥1 (PD-L1 IHC pharmDx22C3	77.0% (72.9%)	90.7% (85.0%)	69.6% (64.0%)
CPS ≥10 (PD-L1 IHC pharmDx 22C3)	81.5% (77.6%)	62.7% (54.8%)	91.7% (87.9%)
TC ≥ 1% (PD-L1 IHC pharmDx 28-8)	75.5% (71.3%)	66.9% (59.1%)	80.2% (75.2%)
$IC_{TumorArea}$ ≥5% (VENTANA SP142)	69.9% (65.5%)	15.3% (10.1%)	99.5% (97.8%)

[a]For each metric, lower boundary of 95% confidence interval (CI) was calculated with no upper bound using the Clopper-Pearson method

Clinical trial identification: CD-ON MEDI4736-1108 NCT01693562.

Editorial acknowledgement: Editorial support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Anne-Marie Manwaring of Parexel, and was funded by AstraZeneca.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: J. Walker, M. Zajac, J. Ye, M. Scott, P. Scorer, C. Barker, A. Gupta, P. Mukhopadhay, S. Ferro, J.A. Williams: Employee and shareholder of AstraZeneca. M. Ratcliffe: Consultant for AstraZeneca. H. Al-Masri: Employee of Hematogenix. M.C. Rebelatto: Employee of Medimmune. T. Powles: Honoraria for advisory boards: Novartis, Roche and Pfizer, Bristol-Myers Squibb; Research grant: AstraZeneca.

905P CD103+ tissue-resident CD8+ T Cells correlate with protective anti-tumoral immune responses in muscle-invasive bladder cancer patients

Z. Liu, J. Zhang, B. Dai

Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: CD103+ Tissue-resident CD8+ T cells are previously reported as memory CD8+ T cells and thus could promote adaptive immune response. While immunotherapy shows a great potential in muscle-invasive bladder cancer (MIBC) treatment, it is urgent to discover which subgroup MIBC patients could benefit most from immunotherapy. We here tried to explore the prognostic and predictive value of CD103+ tissue-resident CD8+ T cells, and provide possible molecular explanations.

Methods: We selected 259 MIBC patients who underwent radical cystectomy between 2002 and 2014. CD103+ tissue-resident CD8+ T Cells were evaluated via immunofluorescence of CD103 and CD8 performed in our constructed tissue microarrays. Prognostic value of CD103+ CD8+ T cells in MIBC was assessed, and was further validated in TCGA-BLCA cohort using tissue-resident CD8+ T cell core signatures. 10 fresh MIBC specimens were analyzed by flow cytometry to explore the anti-tumoral immune response and immune check-point expression of tissue-resident CD8+ T cell.

Results: Patients with higher CD103+ tissue-resident CD8+ T cells infiltration had a significant better overall survival in both our study population and TCGA-BLCA cohort (HR = 0.504, 95%CI: 0.312-0.816; P = 0.005 and HR = 0.637, 95%CI: 0.444-0.913; P = 0.014). Further Cox regression indicated that CD103+ tissue-resident CD8+ T cells was an independent prognosticator in MIBC patients. Flow cytometry results revealed that CD103+ CD8+ T cells tended to express more IFN-γ and granzyme B than CD103- CD8+ T cells (P < 0.001 and P = 0.007, respectively) (n = 10). However, expression of perforin did not show significant differences between CD103+ CD8+ T cells and CD103- CD8+ T cells. We then analyzed PD-L1 and TIM3 expression in CD103+ tissue-resident CD8+ T cells. Surprisingly, there was no significant differences of PD-L1 expression between CD103+ CD8+ T cells and CD103- CD8+ T cells. Nonetheless, CD103+ CD8+ T cells had more TIM3+ phenotypes than CD103- CD8+ T cells (P = 0.034).

Conclusions: High CD103+ tissue-resident CD8+ T cells could predict better prognosis in MIBC patients. Patients with high infiltration of CD103+ tissue-resident CD8+ T cells might benefit most from anti-TIM3 immunotherapy.

Legal entity responsible for the study: Dai, Bo.

Funding: National Natural Science Foundation of China; Shanghai Municipal Natural Science Foundation; Shanghai Municipal Commission of Health and Family Planning Program; Guide Project of Science and Technology Commission of Shanghai Municipality; Shanghai Cancer Research Charity Center.

Disclosure: All authors have declared no conflicts of interest.

906P Immune-checkpoint inhibitors in previously treated patients with urothelial carcinoma: A systematic review and meta-analysis

E. De Luca[1], V. Di Nunno[2], C. Buttigliero[3], M. Tucci[3], F. Vignani[1], C. Zichi[1], A. Ardizzoni[2], F. Massari[2], M. Di Maio[1]

[1]Division of Medical Oncology, "Ordine Mauriziano" Hospital, Turin, Italy, [2]Division of Oncology, S.Orsola-Malpighi Hospital, Bologna, Italy, [3]Division of Medical Oncology, "San Luigi Gonzaga" Hospital, Orbassano, Turin, Italy

Background: Very few therapeutic options are available in patients with advanced or metastatic urothelial carcinoma progressed or unfit to platinum based therapy. After decades of failures, a new classes of agents: the immune-checkpoint inhibitors seem to be a new promising hope for these patients. However, to date of the two randomized studies comparing these compounds to standard chemotherapy only one trial showed a clear survival advantage in this setting.

Methods: We performed a systematic review and meta-analysis to assess the efficacy, in terms of overall survival, of single agent immune-checkpoint inhibitors vs. single agent chemotherapy as second-line treatment. Moreover, we evaluated the assessed ORR of single-agent immune-checkpoint inhibitors in patients with advanced urothelial cancer exploring the predictive value of patients' selection according to PD-L1 expression. To do this, we reviewed clinical trials published on Pubmed/Medline, Cochrane library and clinical abstracts presented on main International meeting between 2014 and 2018.

Results: Systematic review included randomized (n = 2) and non-randomized (n = 9) clinical trials. We restricted meta-analysis to trials exploring immune-checkpoint inhibitors in previously platinum treated patients.In randomized trials, immune checkpoint inhibitors were associated with a significant improvement of overall survival compared to chemotherapy in unselected patients, with pooled Hazard Ratio 0.80 (95% confidence interval 0.69 – 0.93, p = 0.003), while the difference was not statistically significant in the subgroup of patients selected for the highest PD-L1 expression (Hazard Ratio 0.72, 95% confidence interval 0.48 – 1.09, p = 0.12). Polled probability of objective response was 0.18 (95% confidence interval 0.16 – 0.20) in unselected patients and 0.27% (95% confidence interval 0.25 – 0.32) in patients selected for the highest expression of PD-L1.

Conclusions: Immunotherapy showed a significant survival advantage in patients not selected for PD-L1 expression while both OS and ORR analysis suggested that the predictive value of PD-L1 expression is far from being optimal.

Legal entity responsible for the study: Francesco Massari.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

907P Match-adjusted indirect comparison of durvalumab and chemotherapy for locally advanced or metastatic urothelial carcinoma (UC) following failure of platinum-based therapy

C.K. Hoyle[1], A.B. Klein[1], K.A. Patel[1], N. Shire[1], H. Wang[1], B.C. Chu[2], M. Ouwens[1], B.L. Nordstrom[2], L. Horne[3], H-T. Arkenau[4]

[1]Health Economics & Payer Analytics, AstraZeneca, Cambridge, UK, [2]Real-World Evidence, Evidera, Waltham, MA, USA, [3]Oncology Business Unit, AstraZeneca, Gaithersburg, MD, USA, [4]Sarah Cannon Research Institute SCRI UK, London, UK

Background: Durvalumab gained FDA approval for locally advanced or metastatic UC following failure of platinum-based chemotherapy (CTx) based on the open-label, single arm study 1108. Real-world evidence can be used to enable comparative analyses by matching patients' baseline characteristics from independent datasets. Overall survival (OS) of patients on durvalumab vs CTx was evaluated by comparing patients in the phase 1/2 study 1108 (NCT01693562) with a real-world dataset.

Methods: Data from patients on durvalumab were compared with data from patients in the Flatiron oncology electronic medical record database treated with physician's choice of 2nd line CTx. All patients had progressed following platinum-based CTx. Patients were matched on propensity score to adjust for differences in baseline demographics and disease characteristics. Treatment effect for OS was estimated using Cox proportional hazards models. Prognostic impact of expression of programmed cell death ligand-1 (PD-L1) (≥25% of tumour cells [TC]/immune cells [IC] [high] or < 25% TC/IC [low/negative]) on OS was also evaluated. As PD-L1 expression was only available for patients in study 1108, PD-L1 subgroups were compared to otherwise-matched CTx patients.

Results: After adjustment for baseline differences between the 2 groups, durvalumab demonstrated a statistically significant improvement in OS vs CTx (n = 158/arm; HR = 0.634, 95% CI 0.479-0.839; median OS 11.2 vs 8.19 months). Treatment effect of durvalumab was greater in the PD-L1 high subgroup (n = 91 /arm; HR = 0.434, 95% CI 0.292-0.645; median OS 19.9 vs 7.84 months) vs matched CTx patients. There was no significant difference in OS for the PD-L1 low/negative subgroup for durvalumab vs CTx (n = 74/arm; HR = 0.989, 95% CI 0.679-1.440; median OS 4.86 vs 7.20 months).

Conclusions: This indirect, match-adjusted comparison of durvalumab vs CTx suggests that durvalumab provides a statistically significant improvement in OS vs CTx for patients with locally advanced or metastatic UC who progressed after platinum-based CTx; treatment effect was more pronounced in the PD-L1 high subgroup vs the PD-L1 low/negative subgroup.

Clinical trial identification: CD-ON-MEDI4736-1108 (NCT01693562).

Editorial acknowledgement: Editorial support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Anne-Marie Manwaring of Parexel, and was funded by AstraZeneca.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: C.K. Hoyle, A.B. Klein, K.A. Patel, N. Shire, H. Wang, M. Ouwens: Employee and shareholder of AstraZeneca. B.C. Chu: Employee of Real-world Evidence, Evidera. B.L. Nordstrom: Employee of Real-world Evidence, Evidera. L. Horne: Contractor and Shareholder: AstraZeneca. All other authors have declared no conflicts of interest.

908P Comparative effectiveness of neoadjuvant chemotherapy followed by cystectomy versus cystectomy followed by adjuvant chemotherapy versus palliative chemotherapy versus cystectomy for node-positive bladder cancer: A retrospective analysis: KCSG GU 17-03

J.H. Byun[1], H.A. Jung[2], W-K. Bae[3], H-J. Lee[4], S.H. Park[2], H.J. Kim[5], C.H. Maeng[6], I. Park[7], B.S. Sohn[8], J.A. Kim[9], K.H. Lee[10], D.H. Im[11], J.H. Kim[12], H. Jang[13], S.M. Kim[14]

[1]Division of Oncology, Department of Internal Medicine, Incheon St. Mary's Hospital, Incheon, Republic of Korea, [2]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [3]Hemato-Oncology, Chonnam National University Medical School & Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea, [4]Department of Internal Medicine, Chungnam National University College of Medicine, Daejeon, Republic of Korea, [5]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Republic of Korea, [6]Medical Oncology, Kyung Hee University Hospital, Seoul, Republic of Korea, [7]Medical Oncology, Gachon University Gil Medical Center, Incheon, Republic of Korea, [8]Department of Internal Medicine, Inje University Sanggye Paik Hospital, Seoul, Republic of Korea, [9]Medical Oncology, Kangdong Kyung Hee University Hospital, Seoul, Republic of Korea, [10]Yeungnam University College of Medicine, Department of Internal Medicine, Daegu, Republic of Korea, [11]Division of Hematology-Oncology, Department of Medicine, Dankook Univ. Hospotal, Cheonan, Republic of Korea, [12]Division of Hematology-Oncology, Department of Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea, [13]Medical Oncology, International St. Mary's Hospital, Incheon, Republic of Korea, [14]Division of Hematology-Oncology, Department of Medicine, Samsung Changwon Hospital, Changwon, Republic of Korea

Background: In the AJCC 7th edition, bladder cancer with lymph node metastasis is classified into stage IV regardless of the extent or number of lymph node metastasis. T1A-T4a, N1, and M0 were changed to stage IIIA, and T1a-T4a, N2-N3, and M0 were changed to stage IIIB in the AJCC 8th edition revised in 2018. Therefore, it is necessary to think about treatment strategy for clinically node positive bladder cancer. The aim of this study was to compare the treatment outcomes of chemotherapy, surgery, and combination therapy in patients with lymph node-positive bladder cancer.

Methods: From January 01, 2010 to December 31, 2015, patients with bladder cancer with clinically local lymph node metastasis at the time of diagnosis and were treated with neoadjuvant chemotherapy followed by cystectomy or cystectomy followed by adjuvant chemotherapy or palliative chemotherapy or cystectomy were retrospectively analyzed based on the clinical indices and survival time based on the medical record review.

Results: Of 230 patients with bladder cancer, 44(19.1%) were treated with palliative chemotherapy, 30(13.0%) with neoadjuvant chemotherapy followed by cystectomy, 129(56.1%) with cystectomy followed by adjuvant chemotherapy, and 27(11.7%) with cystectomy alone. Median survival was 30.4 months retrospectively. In palliative chemotherapy group, median OS was 19.3 months. Median OS for neoadjuvant chemotherapy followed by cystectomy was 49.1 months and for cystectomy followed by adjuvant chemotherapy was 42.6 months. Cystectomy show 11.2 months of median OS. The prognosis was different according to stage of lymph node in each groups (42.6 months for N1 vs 21.3 months for N2-3), especially survival rate of cystectomy followed by adjuvant chemotherapy was good in N1 stage.

Conclusions: This study is meaningful in understanding the actual clinical treatment patterns of lymph node - positive bladder cancer and comparing the results according to each treatment group.

Legal entity responsible for the study: KCSG.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

909P Plasma miR-371a-3p for detection of non-teratomatous viable germ cell tumor in testicular cancer

L. Nappi[1], M. Thi[2], B.J. Eigl[1], A. Lum[3], D. Huntsman[4], C. Martin[5], B. O Neil[5], D.J. Khalaf[1], K.N. Chi[1], M.E. Gleave[6], A. So[2], P. Black[2], S. Daneshmand[7], C.R. Nichols[8], C.K. Kollmannsberger[1]

[1]Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, [2]Urologic Science, Vancouver Prostate Centre, Vancouver, BC, Canada, [3]Department of Molecular Oncology, British Columbia Cancer Research Centre, Vancouver, BC, Canada, [4]Department Pathology and Laboratory Medicine, British Columbia Cancer Agency, Vancouver, BC, Canada, [5]Surgery, Huntsman Cancer Institute, Salt Lake City, UT, USA, [6]Urologic Science, University of British Columbia Faculty of Medicine, Vancouver, BC, Canada, [7]Urology, University of South California, Los Angeles, CA, USA, [8]Testicular Cancer Commons, Salt Lake City, UT, USA

Background: Active surveillance for CSI testicular cancer is currently based on serial radiological imaging and classic tumor markers (β-HCG, AFP, LDH). The management of borderline suspicious tumor markers negative enlarging nodes and of the post-chemotherapy residual disease is challenging, and currently relies on clinical follow-up with imaging to establish patterns of growth or pathological confirmation with biopsy or retroperitoneal lymphadenectomy (RPLND). A blood-based approach to reliably identify patients with non teratoma viable GCT (NTVGCT) would be valuable.

Methods: Plasma miR-371a-3p (miR371) of pts with GCT was analyzed by RT-PCR. Spike-in cel-miR-39-3p and miR-30b-5p as internal controls. miR-451a and miR-23a-

3p were used as quality control for the hemolysis. The miR371 expression was used to calculate its area under the ROC curve, sensitivity and specificity in detecting viable NTGCT.

Results: One hundred samples from 79 patients (44 CSI and 35 metastatic) were analyzed. Nineteen CSI pts presented suspicious enlarging nodes ($\geq$ IIA) during surveillance and 8/19 had confirmed relapse. miR371 predicted the clinical relapse in 6/8 of pts while the 11 CSI pts with unconfirmed enlarging nodes were all negative for miR-371. miR371 was expressed in all the pre-chemotherapy metastatic pts and negative after chemotherapy (n = 25). miR371 was negative in all the pts with post-chemotherapy residual radiographic findings (n = 24). No residual NTVGCT was detected in any of these 24 pts by either pathology at resection (n = 16) or clinical follow-up (n = 8). The area under the ROC curve was 0.94, the sensitivity and specificity were 89% and 98%, respectively. The results showed a high concordance comparing 2 independent experiments conducted in house and in an outside lab (r = 0.98 and 0.87, respectively).

Conclusions: Detectable circulating miR371 expression predicts the presence of NTVGCT. If validated in larger real world settings, this may result in significant change in the practice for all patients with germ cell tumors by moving it to a biological rather than radiological decision base. These encouraging findings inform upcoming North American trials for further definition of miR371 operating characteristics in GCTs.

Legal entity responsible for the study: Lucia Nappi.

Funding: GUMOC research grant 2017.

Disclosure: All authors have declared no conflicts of interest.

910P Increased risk of non-germ cell second cancer (SC) after cisplatin-based chemotherapy (CBCT) in 1-year testicular cancer (TC) survivors (TCS)

R. Hellesnes[1], Ø. Kvammen[2], R.M. Bremnes[3], A. Karlsdottir[4], T.Å. Myklebust[5], H. Negaard[6], T. Tandstad[7], T. Wilsgaard[8], S.D. Fosså[9], H.S. Haugnes[1]

[1]Department of Oncology, University Hospital of North Norway, Tromso, Norway, [2]Department of Oncology, Ålesund Hospital, Ålesund, Norway, [3]Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway, [4]Department of Oncology, Haukeland University Hospital, Bergen, Norway, [5]Department of Registration, Cancer Registry of Norway, Oslo, Norway, [6]Department of Oncology, Oslo University Hospital, Oslo, Norway, [7]The Cancer Clinic, St. Olavs Hospital, Trondheim, Norway, [8]Institute of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway, [9]National Advisory Unit on Late Effects after Cancer Treatment, Oslo University Hospital, Radiumhospitalet, Oslo, Norway

Background: Previous studies have documented that TCS have a 1.7 to 3.5-fold increased risk of developing SC compared with an age-matched general population after chemotherapy (CT) and/or radiotherapy (RT), but no increased risk after surgery only. Previous studies lack treatment details, and/or include patients treated before the introduction of cisplatin.

Methods: All Norwegian 1-year TCS diagnosed with their first TC 1980-2009 and with no prior history of cancer (n = 5625), were identified through the Cancer Registry of Norway (CRN). Clinical parameters, including detailed information on all cancer treatment given initially and in case of a relapse, were extracted from medical records and linked with data from CRN. The TCS were categorized into treatment groups: Surgery only (24.8%), CT (43.9%), RT (27.4%) and CT and RT combined ((CT + RT) 3.9%). Age-adjusted Cox regression models were performed to evaluate the impact of cancer treatment on the risk of SC, stratified according to decade of diagnosis.

Results: Median observation time was 16.6 years (IQR 10.9-23.8), during which 572 TCS (10.2%) were diagnosed with a non-germ cell SC. Median time to SC was 18.1 years (IQR 11.1-24.2). Overall, compared with surgery only, there was an elevated risk of SC after RT (Hazard Ratio (HR) 1.36, 95% CI 1.07-1.73) and RT + CT (HR 1.64 95% CI 1.10-2.46). When excluding TCS with <10 years observation time, all treatment groups had increased risks for SC (CT: HR 1.57, 95% CI 1.14-2.16; RT: HR 1.77, 95% CI 1.31-2.39; RT + CT: HR 1.83, 95% CI 1.14-2.96). There was an increased risk for SC with increasing number of cisplatin-based CT (CBCT), significant for 4 cycles (HR 1.35, 95% CI 1.01-1.81) and $\geq$5 cycles (HR 1.69, 95% CI 1.06-2.70). The risk for bladder cancer increased after CBCT (HR 3.81, 95% CI 1.29-11.21) and RT (HR 2.93, 95% CI 1.00-8.60). RT + CT was associated with elevated risks for leukemia (HR 13.82, 95% CI 1.20-159.67) and cancers of the stomach (HR 6.79, 95% CI 1.60-28.70) and thyroid (HR 8.71, 95% CI 1.56-52.08).

Conclusions: Cytotoxic treatment increases the risk of SC in TCS. After CBCT, the risk significantly increases after $\geq$4 cycles. Long-term follow-up of TCS focusing on prevention and early detection of SC seem to be important.

Legal entity responsible for the study: Translational Cancer Research Group, Deapartment of Clinical Medicine, UiT The Arctic University of Norway.

Funding: Helse Nord RHF.

Disclosure: All authors have declared no conflicts of interest.

911P Vascular damage and pulmonary function in very long-term survivors of testicular cancer (TC) treated with cisplatin-based chemotherapy (CT)

J. Stelwagen[1], S. Lubberts[1], L.C. Steggink[1], G. Steursma[1], L.M. Kruyt[1], J.W. Donkerbroek[1], A.M. van Roon[2], A.I. van Gessel[2], S.C. van de Zande[2], C. Meijer[1], J.B. Wempe[3], C.H. Gräfin zu Eulenburg[4], J. Nuver[1], A.M.E. Walenkamp[1], J.D. Lefrandt[2], J.A. Gietema[1]

[1]Medical Oncology, University Hospital Groningen (UMCG), Groningen, Netherlands, [2]Internal Medicine, University Hospital Groningen (UMCG), Groningen, Netherlands, [3]Pulmonology, University Hospital Groningen (UMCG), Groningen, Netherlands, [4]Epidemiology, University Hospital Groningen (UMCG), Groningen, Netherlands

Background: Late effects are a source of long term cardiovascular and pulmonary morbidity in testicular cancer (TC) survivors. The objective was to assess vascular damage and pulmonary function in TC survivors more than 20 years after cisplatin-bleomycin combination CT and compare this to age-matched patients treated for TC with surgery only (SU) as well as healthy male controls (CO).

Methods: Aortic stiffness was measured by the gold standard of aortic pulse-wave velocity (aPWV) from the carotid to femoral artery. aPWV is considered an accurate predictor of cardiovascular risk. Additional blood markers for vascular damage were assessed, including factor VIII, v-WF and fibrinogen. Pulmonary function including Diffusion Capacity Carbon Monoxide (DLCO) was assessed according to international guidelines using spirometry, body-plethysmography and the single breath-holding method parameters.

Results: After a mean follow-up duration of 28 years (range: 20-42), aPWV and DLCO was assessed in 118 TC survivors (63 CT patients and 55 SU patients) and 56 controls. aPWV (m/s) was higher in the CT group as compared to the SU and CO group (geometric mean 8.49 vs 7.69 and 7.64 respectively, P = 0.005). DLCO (% predicted) was significantly reduced in CT patients compared to SU patients (87% vs 94%, P = 0.02).A significant reduction in DLCO (defined as < 80% of predicted) occurred in 27% and 13% for CT and SU patients, respectively (X^2; P = 0.055). In the CT patient group, aPWV and DLCO were associated (r = 0.3, P = 0.03). Furthermore, in the CT patient group, DLCO and endothelial activation markers were associated (vWF r=-0.30, P = 0.02; F-VIII r=-0.31, P = 0.01; fibrinogen r=-0.27, P = 0.03).

Conclusions: TC survivors treated with cisplatin-bleomycin combination chemotherapy have an increased aortic stiffness and reduced DLCO more than 20 years after treatment. This implicates an increased risk of cardiovascular morbidity and impaired pulmonary function. Association between markers for vascular damage and reduced DLCO suggests a role of vascular damage in the etiology of pulmonary dysfunction for TC survivors.

Clinical trial identification: NCT02572934.

Legal entity responsible for the study: University Medical Center Groningen, The Netherlands (PI: Prof. Dr. J.A. Gietema).

Funding: Dutch Cancer Society, Grant no. RUG2011-5267.

Disclosure: J.A. Gietema: Research funding to institute: Roche, Abbvie, Siemens. All other authors have declared no conflicts of interest.

912P Sexual function and quality of life in a national cohort of bilateral testicular cancer survivors

M. Bandak[1], J. Lauritsen[1], C. Johansen[1], M.B. Kreiberg[1], J.W. Skøtt[1], M. Agerbaek[2], N.W. Holm[3], K.G. Daugaard[1]

[1]Department of Oncology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [2]Department of Oncology, Aarhus University hospital, Aarhus, Denmark, [3]Department of Oncology, Odense University Hospital, Odense, Denmark

Background: Sexual function and quality of life remain unexplored in long-term survivors of bilateral testicular cancer (TC). The aim was to investigate sexual function, fatigue, anxiety and depression in long-term survivors of bilateral TC (unilateral TC with contralateral germ cell neoplasia in situ (TC+GCNIS) or bilateral TC (BTC)).

Methods: Cross-sectional study of 2479 long-term TC survivors of whom 126 were treated with contralateral radiotherapy due to GCNIS, 93 were treated with bilateral orchiectomy due to BTC and 2260 had unilateral TC (reference group). Outcomes were assessed with validated questionnaires with a median time since diagnosis of 17 years (interquartile range (IQR) 12-23 years). Results in TC+ GCNIS and BTC were compared with the reference group. Adjustment was made for age and treatment for disseminated disease.

Results: The age-adjusted risk of anxiety was significantly increased in BTC survivors (odds ratio 1.7 (1.1-2.8) p = 0.002). Apart from increased risk of reduced motivation in survivors with TC+GCNIS there were no other significant differences between the groups. Limitations include the few cases with symptoms of depression.

Conclusions: Survivors of BTC had increased risk of anxiety but did not experience impairment of other aspects of quality of life. These results are of importance for evidence-based information on late effects for bilateral TC patients.

Legal entity responsible for the study: Danish Testicular Cancer Group (Dateca).

Funding: Copenhagen University Hospital Rigshospitalet.

Disclosure: All authors have declared no conflicts of interest.

913P The prognostic value of DNA damage level in peripheral blood lymphocytes in germ cell cancer patients

M. Mego[1], Z. Sestakova[2], K. Kalavska[1], L. Hurbanova[2], D. Jurkovicova[2], J. Gursky[2], M. Chovanec[1], D. Svetlovska[1], V. Miskovska[3], J. Obertova[1], P. Palacka[4], K. Rejlekova[1], Z. Sycova-Mila[1], J. Mardiak[1], M. Chovanec[2]

[1]Department of Oncology, National Cancer Institute(Národn Onkologick Ustav), Bratislava, Slovak Republic, [2]Department of Genetics, Cancer Research Institute, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovak Republic, [3]Oncology, St. Elisabeth Cancer Institute, Bratislava, Slovak Republic, [4]Department of Outpatient Chemotherapy, National Cancer Institute(Národn Onkologick Ustav), Bratislava, Slovak Republic

Background: Germ cell tumors (GCTs) are extraordinarily sensitive to cisplatin (CDDP)-based chemotherapy. DNA damage represents one of the most important factors contributing to the toxic effects of CDDP-based chemotherapy. Previously, in a pilot study, we observed prognostic value of the DNA damage level in peripheral blood lymphocytes (PBLs) from chemo-naïve GCT patients. This study was aimed to validate the prognostic value of the DNA damage level in PBL in chemo-naïve, as well as chemotherapy pre-treated GCT patients.

Methods: PBLs isolated from 123 GCT patients (101 chemotherapy-naïve and 22 chemotherapy pre-treated) baseline and before 2nd cycle of chemotherapy were included into this prospective study. The DNA damage levels in PBLs were evaluated by the Comet assay and scored as percentage of DNA in tail by the Metafer-MetaCyte analyzing software. The DNA damage level in PBL was categorized as 'low' or 'high' according to the cut-off level of the mean.

Results: The mean ± SEM (standard error of the mean) of the endogenous DNA damage level was 5.25 ± 0.64. Chemotherapy-naïve patients with "low" DNA damage levels at baseline had significantly better progression-free survival (PFS) (hazard ratio [HR] = 0.05 95%CI (0.02 – 0.17), P = 0.0001) and overall survival (OS) (HR = 0.00, P = 0.0002, no death occurred in patients with "low" DNA damage level) compared to patients with "high" DNA damage levels. In multivariate analysis, prognostic value of the DNA damage level in PBL was significantly associated with PFS and OS independently of IGCCCG risk group. Moreover, there was significant correlation between the DNA damage level and response to treatment, non-pulmonary visceral metastases, number of metastatic sites, presence of mediastinal lymph nodes metastases and serum tumor markers level. There was no prognostic value of DNA damage level in PBL before 2nd cycle of chemotherapy and/or in pre-treated GCTs.

Conclusions: These data suggest that the DNA damage levels in PBLs of GCT patients are a novel prognostic marker timely identifying patients with poor outcome. We hypothesize that altered DNA damage level in PBLs could be induced by GCTs similarly to cancer-related immunosuppression and is abolished by administration of chemotherapy.

Legal entity responsible for the study: Michal Mego.

Funding: VEGA 1/0043/18, APVV-15-0086.

Disclosure: All authors have declared no conflicts of interest.

914P Intermediate prognosis in metastatic germ cell tumors (IPGCT): Outcome and prognostic stratification

C. Seidel[1], K.G. Daugaard[2], A. Tryakin[3], A. Necchi[4], G. Cohn Cedermark[5], O. Ståhl[6], M. Hentrich[7], M. Brito[8], C. Albany[9], F. Taza[9], A. Gerl[10], K. Oechsle[1], C. Oing[1], C. Bokemeyer[1]

[1]Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, UKE Universitätsklinikum Hamburg-Eppendorf KMTZ, Hamburg, Germany, [2]Department of Oncology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [3]Department of Clinical Pharmacology and Chemotherapy, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [4]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [5]Department of Oncology-Pathology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden, [6]Department of Oncology, Lund University Hospital, Lund, Sweden, [7]Department of Medicine III, Red Cross Hospital Munich, Munich, Germany, [8]Francisco Gentil de Lisboa, Instituto Portugues de Oncologia, Lisbon, Portugal, [9]Hematology/Oncology, Indiana University School of Medicine, Indianapolis, IN, USA, [10]Oncology Practice, Ludwig-Maximilians University Munich, Munich, Germany

Background: Germ cell tumor patients with intermediate prognosis (IPGCT) according to the IGCCCG classification represent a heterogeneous group exhibiting a variety of clinical features. We established a registry to identify prognostic markers to further characterize IPGCT.

Methods: A retrospective observational study was performed. Eligibility criteria were intermediate prognosis according to IGCCCG criteria, male sex, age ≥16 years. Patients were diagnosed from 1979 to 2014. Clinical characteristics were evaluated with uni- and multivariate analyses to detect new prognosticators. AFP and HCG were available in 85% and LDH levels in 72% of the cases, respectively. Overall survival (OS) was the primary endpoint.

Results: The database included n = 707 IPGCT with a median follow-up of 8.6 years (IQR: 14.4). First line cisplatin-based chemotherapy was administered to 701 patients (99%) and the 5-year OS rate was 87%. First diagnosis in the 1980s (n = 115), the 1990s (n = 158), and after 2000 (n = 434) were associated with 5-year OS rates of 81%, 85%, and 89%, respectively. Statistical analyses revealed AFP and LDH, but not HCG levels prior chemotherapy as prognosticators. A patient stratification according to AFP levels <1000 IU/ml (n = 360), 1000 to 2000 IU/ml (n = 77), >2000 to 5000 IU/ml (n = 93) and >5000 (n = 74) IU/ml prior first course of chemotherapy, revealed a significant correlation between AFP levels and OS, associated with 5-year OS rates of 89%, 87%, 86% and 82%, respectively (p = 0.037). LDH levels prior chemotherapy also correlated with outcome, associated with five-year OS rates of 92% for <2 ULN (n = 289), 88% for ≥2 to 3 ULN (n = 91), 80% for >3 to 4 ULN (n = 37), and 78% for >4 ULN (n = 89), respectively (p = 0.011). In multivariate analysis cut-off values of AFP levels >6000 IU/ml (p = 0.036; HR 2.096) and LHD levels >2 ULN (p = 0.02; HR 2.121) or > 3 ULN (p = <0.001; HR 2.305) were independent prognosticators for OS.

Conclusions: Prognostication according to LDH and AFP levels prior chemotherapy could offer a new approach to stratify IPGCT. The largest fraction of patients had AFP levels <2000 IU/ml and LDH <2 ULN associated with an outcome similar to the good prognosis category. These results need to be confirmed in the upcoming IGCCCG reclassification.

Legal entity responsible for the study: Christoph Seidel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

915P Long term follow-up of the MRC TE23 randomized phase II trial of intensive induction chemotherapy (CBOP/BEP) in poor prognosis germ cell tumours (GCT) (CRUK/05/014; ISRCTN53643604)

R.A. Huddart[1], F. Cafferty[2], J. White[3], J. Shamash[4], I.M. Hennig[5], M. Cullen[6], S. Stenning[2]

[1]Radiotherapy and Imaging, Royal Marsden Hospital Institute of Cancer Research, Sutton, UK, [2]MRC Clinical Trials Unit at UCL, UCL, London, UK, [3]Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK, [4]Dept of Medical Oncology, St Bartholomew's Hospital, London, UK, [5]Department of Clinical Oncology, Nottingham University Hospitals NHS Trust-City Hospital Campus, Nottingham, Nottinghamshire, UK, [6]Dept of Medical Oncology, Queen Elizabeth-University Hospital Birmingham NHS Foundation Trust, Birmingham, UK

Background: Up to 50% of men with poor prognosis non-seminoma GCT die with standard BEP chemotherapy. An intensive regimen, CBOP/BEP (carboplatin, bleomycin, vincristine, cisplatin/BEP), met response targets in a phase II, multicentre, open-label, randomized trial (74% with complete response or partial response marker negative, 90% CI 61% to 85%; primary outcome). Here, we report long term outcomes and prognostic factors.

Methods: Patients with extracranial GCT and IGCCCG poor prognosis features were randomised to 4xBEP or CBOP/BEP (2xCBOP, 2xBO, 3xBEP with bleomycin dose 15,000iu). Low-dose, stabilising chemotherapy prior to entry was permitted. This analysis focuses on progression-free survival (PFS), overall survival (OS) and toxicity (all secondary outcomes), and exploratory analysis of prognostic factors and the impact of marker decline (as defined in GETUG13).

Results: 89 patients (43 CBOP/BEP) were randomised. After median 63 months follow-up, 3-year PFS is 55.7% (95% CI 39.7%, 69.0%) for CBOP/BEP arm, 38.7% (24.7%, 52.4%) for BEP (HR 0.59 (0.33, 1.06), p = 0.079). 3-year OS is 65.0% (48.8%, 77.2%) and 58.5% (43.0%, 71.2%) respectively (HR 0.79 (0.41, 1.52), p = 0.49). 12-month toxicity was affected by subsequent treatments, with no clear differences between arms. There was no grade ≥3 toxicity in the CBOP/BEP arm. In multivariate models, use of pre-protocol chemotherapy was the only factor associated with poorer PFS (HR2.09 (1.14, 3.81), p = 0.017). Mediastinal primary (HR 2.13 (1.02, 4.46), p = 0.045) and use of pre-protocol chemotherapy (HR 3.40 (1.74, 6.63), p < 0.001) were associated with poorer OS. Unfavourable marker decline, in 60 (70%) patients, was not associated with other prognostic factors, nor with long term outcomes (HR 0.82 (0.44, 1.53), p = 0.54 for PFS).

Conclusions: The trial was not powered to compare PFS and OS, but PFS results for CBOP/BEP are promising, and similar to the intensive arm of GETUG13. Impact on OS was less clear (and will be affected by subsequent therapy). Use of pre-protocol chemotherapy was associated with poorer outcomes. Further study in an international phase III trial is warranted.

Clinical trial identification: ISRCTN53643604.

Legal entity responsible for the study: Medical Research Council, UK.

Funding: Cancer Research UK (grant no CRUK/05/014).

Disclosure: R.A. Huddart: Stock or other ownership interests: Cancer Centre London LLP; Consulting or advisory role: MSD, Roche, Bristol-Myers Squibb; Speaker's bureau: Roche, Elekta; Research funding: MSD, Elekta; Travel expenses: Roche, MSD. All other authors have declared no conflicts of interest.

916P Sunitinib tolerance following an initial exposure period: Results of longitudinal PRO data from S-TRAC study

D.J. George[1], R. Figlin[2], R.J. Motzer[3], J. Paty[4], M.J. Lechuga Frean[5], G. Zanotti[6], H. Bhattacharyya[7], K. Ramaswamy[7], L. Deannuntis[8], A. Ravaud[9]

[1]Medical Oncology, Duke University Medical Center, Durham, NC, USA, [2]Medicine - Hematology Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [3]Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [4]Real World & Analytic Solutions, IQVIA, New York, NY, Pittsburgh, USA, [5]Oncology, Pfizer Italy, Milan, Italy, [6]Global HEOR, Oncology, Pfizer, Inc., New York, NY, USA, [7]Oncology, Pfizer Inc., New York, NY, USA, [8]Worldwide Safety and Regulatory, Pfizer Inc., Collegeville, PA, USA, [9]Medical Oncology, CHU Bordeaux University Hospital St. André, Bordeaux, France

Background: Sunitinib (SU) was FDA-approved for adjuvant treatment of patients (pts) with renal cell carcinoma (RCC) at high risk of recurrence post nephrectomy, based upon a 24% reduction in disease-free survival with up to 1 year of SU treatment vs placebo (PBO) (S-TRAC trial). The analysis of patient-reported outcomes (PRO) data showed a statistically significant difference favoring PBO in most EORTC QLQ-C30 scales, and in the symptoms appetite loss and diarrhea, a clinically meaningful difference ($\geq$ 10 points) favoring PBO was observed. Recognizing that some pts did not tolerate SU early on, with higher discontinuation and dose reduction rates for SU than PBO, we describe a baseline reset analysis to assess the longitudinal PRO profile of pts who were able to tolerate and stay on treatment beyond the first 2 cycles (C).

Methods: After censoring the data from C1 and 2, and resetting a new baseline at C 3, the baseline reset analysis described here used the same statistical analysis done for PRO data in S-TRAC. For each scale, comparison of the two treatment arms was carried out using longitudinal repeated measures mixed effect.

Results: Of the 615 pts enrolled in S-TRAC, 580 were included in the PRO analyses. Of these, 506 pts had PRO data at C 3 and were included in this analysis. The longitudinal between treatment comparison resulted in statistically significant differences favoring PBO in 6 of the 15 scales with no clinically meaningful differences ($\geq$10 points) (see Table). The discontinuation rates of the 2 treatment groups were comparable from C 3 onward.

Table: 916P Summary results: EORTC QLQ-C30: Scores between treatment comparison intent-to-treat population (cycles 3-9)

	Sunitinib (n = 241) Model Estimated Mean	Placebo (n = 265) Model Estimated Mean	Difference (Sunitinib – Placebo)
EORTC QLQ-C30			
Global Health status/QoL (large values better)	69.87	72.20	-2.32*
Functional scales (large values better)			
Physical functioning	85.12	86.18	-1.06
Role functioning	80.84	83.49	-2.65*
Emotional functioning	81.52	82.49	-0.97
Cognitive functioning	85.59	86.35	-0.76
Social functioning	83.10	85.31	-2.22*
Symptom items/scales (large values worse)			
Fatigue	27.40	24.55	2.85*
Nausea and vomiting	6.50	5.30	1.21
Pain	20.78	18.68	2.10
Dyspnea	14.36	14.04	0.32
Insomnia	20.71	20.89	-0.18
Appetite loss	12.21	7.74	4.47 *
Constipation	10.46	10.63	-0.17
Diarrhea	18.67	10.67	8.00 *
Financial difficulties	14.10	13.53	0.58

A repeated measures longitudinal analysis with an intercept term, and treatment, time, treatment by time, and baseline as covariate over all cycles.

*P < 0.05

P-values not adjusted for multiplicity.

Conclusions: These analyses suggest that for pts who are able to tolerate SU for > 2 cycles (3 months), PRO profiles for SU are similar to PBO pts with similar discontinuation rates. Some pts do not tolerate SU early on in the adjuvant setting, but for the majority who do, long term tolerance may be more acceptable than originally thought.

Clinical trial identification: NCT00375674.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer.

Disclosure: D.J. George: Honoraria & Consulting: Sanofi, Exelixis, Bayer; Consulting: Merck, Sanofi; Grants: Genentech/Roche, Novartis, Astellas, Celldex, Acerta; Grants & Consulting: Exelixis, Janssen, Pfizer, Innocrin Pharma, BMS. R. Figlin: Funding: Merck, Pfizer, Peloton, Calithera; Consulting fees: Pfizer. R.J. Motzer: Consulting fees: Pfizer, Eisai, Novartis, Exelixis; Clinical trial support to institution: Pfizer, Eisai, Novartis, Bristol-Myers Squibb, Genentech/Roche, Exelixis. M.J. Lechuga Frean, G. Zanotti, H. Bhattacharyya, K. Ramaswamy, L. Deannuntis: Employee of and owns stock in Pfizer. A. Ravaud: Advisory boards: Pfizer, Novartis, GSK, Roche, BMS; Institutional support grants: Pfizer, Novartis; Housing and transportation for meetings and speeches: Pfizer, Novartis, BMS. All other authors have declared no conflicts of interest.

917TiP Phase II study of paclitaxel and TAK-228 in metastatic urothelial carcinoma and the impact of PI3K-mTOR pathway genomic alterations

A. Rodríguez-Vida[1], J.L. Pérez-Gracia[2], A. Taus[1], T. Bonfill[3], F.J. Vázquez-Mazón[4], S. Galtes[1], B. Pons[1], L. Cano[1], S. Macia[5], P. Maroto[6], J. Bellmunt[1]

[1]Medical Oncology, Hospital del Mar, Barcelona, Spain, [2]Medical Oncology, Clínica Universitaria de Navarra, Pamplona, Spain, [3]Medical Oncology, Hospital Parc Taulí, Barcelona, Spain, [4]Medical Oncology, Hospital General de Elche, Elche, Spain, [5]Medical Department, Pivotal, La Florida, Madrid, Spain, [6]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Background: Metastatic urothelial carcinoma (mUC) is an aggressive disease associated with poor outcomes. Despite the recent incorporation of several immunotherapy agents targeting the PD-1 pathway, most patients will ultimately experience progressive disease. Moreover, there are no available predictive biomarkers to these novel agents. Clinical studies testing new anticancer drugs embedded with biomarkers analysis are still urgently needed for mUC. Mammalian target of rapamycin (mTOR) is a key intracellular target involved in several cellular signaling pathways, promoting cell proliferation and tumor angiogenesis. TAK-228 is a new investigational mTOR inhibitor of both TORC1 and TORC2. TAK-228 is currently being investigated in several phase II studies as treatment for advanced cancers. Paclitaxel, a taxane chemotherapy that stabilizes microtubules interfering with normal cell division, is a valid treatment option in mUC progressing to platinum-based chemotherapy. The combination of TAK-228 and paclitaxel has shown synergistic activity in bladder cancer cell lines, xenograft models and a phase I trial in advanced solid tumors.

Trial design: This is a single-arm open-label phase II study evaluating the efficacy and safety of TAK-228 (given orally on days 2 – 4, 9 – 11, 16 – 18 and 23 – 25 of 28-day cycles) in combination with paclitaxel (given on days 1, 8 and 15). Eligibility criteria include patients with mUC, performance status 0 – 1, prior platinum-based chemotherapy with no limit in number of lines, adequate organ function and measurable disease. The primary endpoint of the study is objective response rate (ORR). Secondary endpoints include safety, tolerability, progression-free survival and overall survival. As an exploratory endpoint, PI3K/AKT/mTOR pathway mutations will be characterized and correlated with clinical outcomes. A maximum of 52 patients will be enrolled in order to obtain 40 evaluable patients. The combination will be considered for further testing should the ORR increase from a historical 10% to $\geq$ 26%. A sample size of 40 patients will have a 90% power to detect this change with a 10% alpha risk. The trial is open, and enrollment is ongoing.

Clinical trial identification: EudraCT: 2017-004486-27.

Legal entity responsible for the study: APRO.

Funding: Takeda.

Disclosure: All authors have declared no conflicts of interest.

918TiP EV-201: A single-arm, open-label, multicenter study of enfortumab vedotin for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor therapy

J.E. Rosenberg[1], A. Balar[2], P.H. O'Donnell[3], E.I. Heath[4], N.M. Hahn[5], N.M. Cavazos[6], A. Melhem-Bertrandt[7], D.P. Petrylak[8]

[1]Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]Departments of Medical Oncology and Urology, NYU Langone Medical Center, New York, NY, USA, [3]Department of Medicine, University of Chicago, Chicago, IL, USA, [4]Oncology, Karmanos Cancer Center, Detroit, MI, USA, [5]Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, MD, USA, [6]Clinical Research, Seattle Genetics, Bothell, WA, USA, [7]Astellas Pharma USA, Northbrook, IL, USA, [8]Medical Oncology, Yale University School of Medicine Medical Oncology, New Haven, CT, USA

Background: Most patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC) will not respond to immune checkpoint inhibitors (CPIs) in the post-platinum or first-line cisplatin ineligible setting. Enfortumab vedotin (EV), an antibody-drug conjugate, delivers the microtubule-disrupting agent monomethyl auristatin E to tumors expressing Nectin-4, which is highly expressed in 97% of mUC pt samples

(Petrylak ASCO 2017). In a phase 1 study (NCT02091999), EV monotherapy was generally well tolerated at the recommended dose of 1.25 mg/kg. In this study, 29% of mUC pts had liver metastasis, and most had prior treatment with a CPI (79%), platinum (94%), and/or taxanes (29%). Interim results in mUC pts treated at 1.25 mg/kg showed a confirmed objective response rate (ORR) of 41% (46 of 112) and an ORR of 40% in pts previously treated with a CPI (36 of 89). The most common treatmentrelated adverse events (AEs) among pts with mUC were fatigue (54%), alopecia (45%), and decreased appetite (40%). There were no treatment-related Grade $\geq$3 AE in $\geq$ 5% of mUC pts. Four possibly treatmentrelated fatal AEs were reported: respiratory failure, urinary tract obstruction, diabetic ketoacidosis, and multiorgan failure. These encouraging results along with a favorable safety and tolerability profile warrant further investigation of EV as a monotherapy.

Trial design: This single-arm, open-label, multicenter phase 2 study (NCT03219333) evaluates the antitumor activity and safety of EV monotherapy in la/mUC pts with prior CPI treatment. The study will enroll ~100 platinum-treated pts (Cohort 1) and ~100 platinum-naive and cisplatin-ineligible pts (Cohort 2). The primary objective is to determine antitumor activity of EV as measured by ORR assessed per RECIST v1.1. Secondary objectives include assessment of duration of response, disease control rate, PFS, OS, safety, and tolerability. Pts must have tumor tissue available for exploratory analyses. Study enrollment began in Sep 2017.

Clinical trial identification: NCT03219333.

Editorial acknowledgement: Editoral Assistance provided by Heather Brignull, PhD at Seattle Genetics.

Legal entity responsible for the study: Seattle Genetics, Inc. and Astellas, Inc.

Funding: Seattle Genetics, Inc. and Astellas, Inc.

Disclosure: J.E. Rosenberg: Consultant: Agensys, AstraZeneca/MedImmune, Bayer, Bristol-Myers Squibb, EMD Serono, Inovio Pharmaceuticals, Lilly, Merck, Roche/Genentech, Sanofi, Seattle Genetics; Equity ownership: Illumina, Merck & Co.; Honoraria: AstraZeneca, Bristol-Myers Squibb, Medscape, Peerview, Up To Date, Vindico; Patents on a 'predictor of platinum sensitivity; Research funding: Agensys, Genentech, Genentech/Roche, Incyte, Mirati Therapeutics, Novartis, Oncogenex, Viralytics; Travel expenses: Bristol-Myers Squibb, Genentech/Roche. A. Balar: Consultant: AstraZeneca/MedImmune, Cerulean Pharma, Genentech/Roche, Incyte, Merck, Pfizer/EMD, Serono; Honoraria: Genentech/Roche, Merck; Research funding grants: AstraZeneca/MedImmune, Genentech/Roche, Merck, Seattle Genetics. P.H. O'Donnell: Equity ownership: Allergan; Honoraria: Algeta ASA, American Medical Forum, Astellas Pharma, AstraZeneca, Genentech/Roche, Harrison Consulting, Inovio Pharmaceuticals, Janssen Biotech, Kantar Health, Merck, Novartis, Parexel, Quintiles, Seattle Genetics, Xcenda; Named as co-inventor on a pending patent for a genomics-based system for prescribing medication; Research funding grants: Acerta Pharma, AstraZeneca/MedImmune, Boehringer Ingelheim, Genentech/Roche, Janssen, Merck, Seattle Genetics; Travel expenses: Merck; Expert testimony: Tera, Triage Cancer. E.I. Heath: Consultant: Agensys; Honoraria: Bayer, Dendreon, Sanofi; Research funding grants: Agensys, Celgene, Celldex, Dendreon, Genentech/Roche, Inovio Pharmaceuticals, Millennium, Seattle Genetics, Tokai Pharmaceuticals; Speaker's Bureau: Sanofi. N.M. Hahn: Consultant: AstraZeneca/MedImmune, Bristol-Myers Squibb, Genentech/Roche, Health Advances, Incyte, Inovio Pharmaceuticals, Merck, Oncogenex, Pieris Pharmaceuticals, Seattle Genetics; Research funding grants: Acerta Pharma, AstraZeneca/MedImmune, Bristol-Myers Squibb, Genentech/Roche, Heat Biologics, Merck, Mirati Therapeutics, Novartis, Oncogenex, Principa Biopharma. N.M. Cavazos: Employee ownership interest: Seattle Genetics. A. Melhem-Bertrandt: Employed: Astellas Pharma USA. D.P. Petrylak: Consultant: Bayer, Bellicum Pharmaceuticals, Dendreon, Exelixis, Ferring, Johnson & Johnson, Medivation, Millennium, Pfizer, Roche, Sanofi, Tyme Pharmaceuticals; Equity Ownership: Bellicum Pharmaceuticals, Tyme, Inc.; Research funding: Agensys, Astellas Medivation, AstraZeneca, Bayer, Dendreon, Endocyte, Genentech, Innocrin Pharma, Johnson & Johnson, Lilly, MedImmune, Merck, Millineum, Novartis, Oncogenex, Pfizer, Progenics, Roche, Sanofi, Seattle Genetics, Sotio; Expert testimony: Celgene, Sanofi.

919TiP The potential of patient reported outcomes in urothelial cancer patients receiving immuno- or chemotherapy: A feasibility study of electronic reporting in an aging and comorbid population

G.A. Taarnhøj[1], H. Lindberg[2], H. Pappot[1], L.H. Dohn[2], C. Johansen[1]

[1]Oncology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [2]Oncology, Copenhagen University Hospital Herlev, Herlev, Denmark

Background: Worldwide urothelial cancer (UC) is one of the most common malignant diseases and causes of death. Patients with UC often have comorbidities, troubling completion of treatment, thus enhancing the need for better supportive instruments during treatment. Patient-reported outcomes (PROs) have been suggested as such, although the use of these has not yet been demonstrated feasible in this aging and comorbid population. Furthermore the literature is sparse on toxicities and quality of life (QoL) during treatment for UC patients outside of clinical trials. This study shall demonstrate the feasibility of electronic reporting of PROs and describe toxicities and QoL in the UC population.

Trial design: From February 2018, inclusion of patients with UC stage T2-T4NxMx was initiated. All patients initiating chemo- or immunotherapy outside a clinical trial at Rigshospitalet and Herlev Hospital, Denmark, are approached. Recruitment continues until 40 patients are enrolled. All patients will at baseline and weekly during treatment complete four e-questionnaires: EORTC QLQ-C30 & QLQ-BLM30, HADS, selected PRO-CTCAE^{TM} questions and finally three general health questions. Reminders to complete the questionnaires are sent to patients electronically. Clinicians will in turn have an overview of the patients' answers categorized into groups of severity. The overview is automatically incorporated into the electronic medical charts. The study will evaluate the feasibility of electronic reporting and describe toxicities, QoL, rate of completion and hospital admissions. The results of this study will contribute to the content of a randomized patient-reported outcomes study in the UC population initiated this autumn (2018).

Legal entity responsible for the study: Helle Pappot.

Funding: Danish Cancer Society.

Disclosure: All authors have declared no conflicts of interest.

920TiP Erdafitinib compared with vinflunine or docetaxel or pembrolizumab in patients (pts) with metastatic or surgically unresectable (M/UR) urothelial carcinoma (UC) and selected fgfr gene alterations (FGFRalt): The phase III THOR study

Y. Loriot[1], A. Necchi[2], S.H. Park[3], R.A. Huddart[4], E. Burgess[5], B. Zhong[6], A. Santiago-Walker[7], S. Little[8], T. Roccia[9], P. De Porre[10], A.O. Siefker-Radtke[11]

[1]Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [2]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Hematology-Oncology, Samsung Medical Center, Seoul, Republic of Korea, [4]Radiotherapy, Institute of Cancer Research, Sutton, UK, [5]Medical Oncology, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA, [6]Biostatistics, Janssen Research & Development, Spring House, PA, USA, [7]Oncology Translational Research, Janssen Research & Development, Spring House, PA, USA, [8]Clinical Oncology, Janssen Research & Development, Spring House, PA, USA, [9]Clinical Oncology, Janssen Research & Development, Buckinghamshire, UK, [10]Clinical Oncology, Janssen Research & Development, Beerse, Belgium, [11]Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: Pts with M/UR UC have poor prognoses. Programmed death (ligand)-1 (PD-[L]1) inhibitors have improved outcomes in some pts, but responses vary based on genotypic subtype. FGFRalt are present in 20% of pts with UC, and may reflect an immunologically "cold" tumor that does not respond well to immunotherapy (Siefker-Radtke ASCO GU 2018). In early phase 2 data, the pan-FGFR (1-4) inhibitor erdafitinib (ERDA, 8 mg/d continuous) demonstrated tolerability and a favorable 42% objective response rate (ORR) in pts with M/UR UC and FGFRalt; uptitration to 9 mg/d was feasible. Activity of single-agent ERDA will be compared with chemo or pembrolizumab in pts with M/UR UC in this randomized phase 3 study.

Trial design: Adult pts (ECOG performance status $\leq$ 2 and adequate bone marrow, liver, and renal function; no uncontrolled cardiovascular disease, known HIV, hepatitis B or C, or baseline phosphate persistently above the upper limit of normal allowed) with stage 4 M/UR UC and specific pathogenic FGFRalt (FGFR3 mutations or FGFR2/3 fusions) who have received 1 line of prior systemic therapy are eligible. Pts will be screened for FGFRalt and randomized 1:1 to cohort 1 or 2. In cohort 1 (n ~280), pts with prior chemo and PD-(L)1 inhibitor (prior PD-[L]1 inhibitor alone allowed for cisplatin-ineligible pts) in combination or in maintenance setting will receive 8 mg/d continuous ERDA vs chemo (1:1) with docetaxel or vinflunine. In cohort 2, pts (n ~350) with prior chemo but no prior PD-(L)1 inhibitor will receive 8 mg/d ERDA vs pembrolizumab (1:1). Uptitration of ERDA to 9 mg/d is recommended in pts with serum phosphate $\leq$ 9 mg/dL. Primary end point: overall survival. Secondary end points: progression-free survival, ORR, duration of response, pt-reported outcomes, safety, and pharmacokinetics. PD-L1 expression level per immunohistochemistry and UC subtype per RNA sequencing or other methods are exploratory end points. Pts are being enrolled at sites in 25 countries. For additional information on specific sites/countries: https://clinicaltrials.gov/ct2/show/NCT03390504.

Clinical trial identification: NCT03390504.

Editorial acknowledgement: Editorial assistance was provided by Tamara Fink, PhD, of PAREXEL (Hackensack, NJ, USA), with funding from Janssen Global Services, LLC (Raritan, NJ, USA).

Legal entity responsible for the study: Janssen Research & Development.

Funding: Janssen Research & Development.

Disclosure: Y. Loriot: Consulting/advisory role: Janssen, Astellas, Roche, Ipsen, Sanofi, AstraZeneca, MSD, Seattle Genetics; Research funding: Sanofi, Janssen; Travel expenses: Roche, MSD, AstraZeneca. A. Necchi: Consulting/advisory capacity: Merck Sharp & Dohme, Roche, Bayer, AstraZeneca, Clovis Oncology; Travel expenses: Roche, Merck Sharp & Dohme, Pierre Fabre; Research funding: Amgen, Merck Sharp & Dohme, AstraZeneca. S.H. Park: Consulting/advisory role and in Speaker's bureaus: Eli Lilly. R.A. Huddart: Consulting/advisory role: MSD, Roche, Bristol-Myers Squibb; Stock or other ownership interests: Cancer Centre London, LLP; Speaker's bureaus: Roche, Elekta; Research funding: MSD, Elekta; Travel expenses: Roche, MSD. E. Burgess: Consulting/advisory role: Janssen, Roche/Genentech, Bayer, Pfizer; Stock or other interests: Exelixis, Becton Dickinson, Calithera Biosciences, Gilead Sciences, McKesson, Medtronic; Speaker's bureaus: Janssen, Exelixis; Research funding: Pfizer, Astellas; Travel expenses: Janssen, Exelixis, Pfizer. B. Zhong, A. Santiago-Walker, S. Little, T. Roccia, P. De Porre: Employed by Janssen Research & Development; Stock in Johnson & Johnson. A.O. Siefker-Radtke: Consulting/advisory role: Janssen, Merck,

NCCN, Eisai, Genentech, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, EMD Serono, Inovio Pharmaceuticals; Research funding: Janssen, NIH, the Michael and Sherry Sutton Fund for Urothelial Cancer, Takeda; Patents, royalties or other intellectual property titled, "Methods of characterizing and treating molecular subsets of muscle-invasive cancer".

921TiP An open-label phase II study to evaluate PT2977 for the treatment of von hippel-lindau disease associated renal cell carcinoma

E. Jonasch[1], E. Park[2], S. Thamake[2], M. Hirmand[2], R. Srinivasan[3]

[1]GU Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Clinical Development, Peloton Inc., San Francisco, CA, USA, [3]Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Background: In VHL disease, renal cell carcinomas (RCC) are known to be of clear cell histology (ccRCC). HIF-2α has been established as an oncogenic driver in ccRCC, where VHL deficiency is the underlying genomic alteration. In this setting of VHL gene inactivation, HIF-2α accumulates under normoxic conditions, driving the expression of genes associated with progression of ccRCC, including vascular endothelial growth factor A (VEGFA), cyclin D1 and other factors that contribute to tumor growth and proliferation. Clinical management of VHL disease-associated renal tumors involves active surveillance until surgery is required for tumors larger than 3 cm to prevent metastasis. Repeated surgical procedures can carry significant morbidity. Systemic therapy options that can delay or obviate the need for surgery by reducing tumor size are needed.

Trial design: This open-label Phase 2 study will evaluate the efficacy and safety of PT2977, a highly selective small molecule inhibitor of HIF-2α, in patients with VHL disease who have at least 1 measurable ccRCC (as defined by RECIST 1.1). PT2977 will be administered orally at a dosage of 120 mg once daily. Key inclusion criteria include a germline VHL alteration and at least 1 measurable solid ccRCC but no tumor >3.0 cm that requires immediate surgical intervention. Patients may have VHL disease-associated tumors in other organ systems. Key exclusion criteria include prior systemic therapy for VHL disease, an immediate need for surgical intervention, evidence of metastatic disease, and history of a non-VHL disease-associated invasive malignancy in the past 2 years. The primary efficacy endpoint is objective response rate (ORR) of ccRCC tumors per RECIST 1.1. Secondary efficacy endpoints include duration of response (DOR), time to response (TTR), progression-free survival (PFS), and time to surgery (TTS) for ccRCC tumors as well as efficacy evaluations for non-ccRCC VHL disease-associated tumors. Safety/tolerability and pharmacokinetics of PT2977 in this trial will also be evaluated. Patient recruitment is ongoing.

Clinical trial identification: NCT03401788; EudraCT: 2018-000125-30.

Legal entity responsible for the study: Peloton Therapeutics, Inc.

Funding: Peloton Therapeutics, Inc.

Disclosure: E. Jonasch, R. Srinivasan: Research support: Peloton Inc. E. Park, S. Thamake, M. Hirmand: Employee of Peloton Inc.

922TiP EV-301: An open-label, randomized phase III study to evaluate enfortumab vedotin versus chemotherapy in patients with previously treated locally advanced or metastatic urothelial cancer (la/mUC)

D.P. Petrylak[1], J. Rosenberg[2], I. Duran[3], Y. Loriot[4], G. Sonpavde[5], C. Wu[6], E. Gartner[7], A. Melhem-Bertrandt[8], T. Powles[9]

[1]Medical Oncology and Urology, Yale University School of Medicine, New Haven, CT, USA, [2]Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3]Medical Oncology, Hospital Universitario "Marqués de Valdecilla", Santander, Spain, [4]Medical Oncology, Institut Gustave Roussy, Paris, France, [5]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [6]Biostatistics, Astellas Pharma US, Inc., Northbrook, IL, USA, [7]Experimental Medicine, Seattle Genetics, Inc., Bothell, WA, USA, [8]Development Medical Sciences - Oncology, Astellas Pharma US, Inc., Northbrook, IL, USA, [9]Barts Cancer Institute, Queen Mary University of London, London, UK

Background: Standard first-line treatment for patients (pts) with la/mUC is cisplatin-based chemotherapy or carboplatin-based chemotherapy for pts unfit for cisplatin. Recently, immune checkpoint inhibitors (CPIs) have become standard treatment options for pts who progressed during/after platinum-based chemotherapy or are ineligible for cisplatin. While some pts with la/mUC achieve durable responses with CPIs, only a minority respond. Following failure with CPI, no therapies are approved. Enfortumab vedotin (EV) is a fully humanized monoclonal antibody that delivers the microtubule-disrupting agent monomethyl auristatin E to tumors expressing Nectin-4, which is highly expressed in 97% of mUC patient samples (Petrylak ASCO 2017). In a phase 1 study (EV-101; NCT02091999), single-agent EV at the established recommended phase 2 dose of 1.25 mg/kg was generally well tolerated and demonstrated a confirmed objective response rate of 41% (n = 46/112) across the overall population of pts with mUC; in pts with prior CPI therapy, a confirmed ORR of 40% (n = 36/89) was observed.

Trial design: EV-301 is a global, multicenter, open-label phase 3 trial (NCT03474107) enrolling adult pts with la/mUC and an ECOG score ≤1, who have received one prior platinum-containing chemotherapy, and have experienced disease progression during or following treatment with a CPI. Approximately 550 pts will be randomized 1:1 to receive EV 1.25 mg/kg (Arm A) or chemotherapy (Arm B); randomization will be stratified by ECOG score, regions of the world, and liver metastases at baseline. Patients in Arm A will receive EV on Days 1, 8, and 15 of each 28-day cycle; pts in Arm B will receive either docetaxel, paclitaxel, or vinflunine (determined by investigator) on Day 1 of every 21-day cycle. Patients will continue to receive study treatment until disease progression, intolerance, or other discontinuation criterion is met. The primary endpoint is overall survival; secondary endpoints include progression-free survival, duration of response, and overall response rate, as well as assessment of safety/tolerability, and quality-of-life parameters.

Clinical trial identification: NCT03474107.

Editorial acknowledgement: Medical writing and editorial support was provided by Regina Switzer, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: Astellas Pharma, Inc.

Funding: Astellas Pharma, Inc.

Disclosure: D.P. Petrylak: Grants, personal fees, or other support: Astellas, AstraZeneca, Bayer, Bellicum, Dendreon, Exelixis, Ferring, Johnson & Johnson, Lilly Medivation, Millenium, Pfizer, Roche Laboratories, Sanofi Aventis, Agensys, Clovis, Eli Lilly, Endocyte, Genentech, Innocrin, Lilly, Medimmune, Medivation, Merck, Novartis, Sanofi Aventis, Sotio, Bellicum, Tyme. J. Rosenberg: Grants or personal fees: Astellas, Roche, Seattle Genetics, Merck, BMS, AstraZeneca, Bayer, Lilly, Sanofi, EMD Serono. I. Duran: Personal fees: Seattle Genetics, outside the submitted work. Y. Loriot: Personal fees: Astellas, Seattle Genetics, during the conduct of the study; Grants and personal fees: Janssen, Sanofi, MSD, AstraZeneca, Roche, outside the submitted work. G. Sonpavde: Grants or personal fees: Boehringer-Ingelheim, Bayer, Onyx-Amgen, Celgene, Pfizer, Merck, Genentech, Novartis, Argos, Sanofi, Agensys/Astellas, Clinical Care Options, AstraZeneca, Uptodate, Biotheranostics, Exelixis, Bristol-Myers-Squibb, Janssen, Amgen, Eisai, NCCN, Physicians Education Resource, Onclive, Research to Practice, QUILT/Oncotherapeutics symposium, EMD Serono. C. Wu, A. Melhem-Bertrandt: Employee of Astellas. E. Gartner: Employee of Seattle Genetics. T. Powles: Personal fees or grants: AstraZeneca, Roche, Pfizer, Novartis, Merck, BMS.

923TiP A phase III study of INCB054828 as adjuvant therapy in patients (pts) with high-risk urothelial carcinoma (UC) harboring fibroblast growth factor receptor 3 (FGFR3) genomic alterations

A. Necchi[1], J.L. Pérez-Gracia[2], Y. Loriot[3], W. Witjes[4], F. Montorsi[5], A. Bjartell[6], S.F. Shariat[7]

[1]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Medical Oncology, Clínica Universitaria de Navarra, Pamplona, Spain, [3]Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [4]Research Foundation, European Association of Urology, Arnhem, Netherlands, [5]Urological Research Institute (URI), IRCCS San Raffaele, Milan, Italy, [6]Urology, Skåne University Hospital Malmö, Malmö, Sweden, [7]Urology, Medical University of Vienna, Vienna, Austria

Background: After neoadjuvant chemotherapy (NAC), about 20% of pts with muscle-invasive UC are found to have advanced pT-stage or lymph node involvement and 5-year overall survival (OS) of them is < 30%. Tumor samples from these pts may provide information about chemotherapy resistance, and may predict for the activity of new drugs given postoperatively. Alterations of FGFR3 gene represent a therapeutic target in UC and FGFR3 mutations/fusions are enriched in UC Luminal-1 subtype. The pan-FGFR inhibitor INCB054828 has shown promising results in chemotherapy-treated patients with genomic alterations of FGFR3 in tumor tissue and is currently being evaluated in an international phase 2 study (fight-201, NCT02872714). Our study aims to assess the safety and efficacy of adjuvant INCB054828 in pts with FGFR3 mutations/fusions.

Trial design: This is an open-label, single-arm, phase 2 study. Subjects will receive INCB054828 at a once-daily (QD) dose of 13.5 mg on a 2-weeks-on and 1-week-off schedule. Treatment should start within 60 days of surgery and will continue until 12 months, or until the evidence of disease recurrence or unacceptable toxicity onset. Key inclusion criteria are predominant UC histology, FGFR3 mutations/fusions (FoundationOne), bladder or upper tract UC, previous radical cystectomy or nephroureterectomy, previous administration ≥3 cycles of CDDP-based NAC, pT3-4 and/or pN1-3 stage. Relapse-free survival (RFS) is the primary endpoint, assessed every 9 weeks until disease recurrence or death. No interim analyses are planned. It is expected that about 30% of the total screened pts will harbor FGFR3 aberrations. In a single-stage design, with 90% power and one-sided alpha at 0.10, the total enrolled pts will be 56 (H0: 2-y RFS: 30%; H1: 2-y RFS: 45%). Translational research on tissue samples will include associations of immune-inflamed phenotype with next-generation sequencing results and outcome of treatment, and response to any subsequent immunotherapy. The study is sponsored by the EAU-Research Foundation and will involve 15 centers in Europe (EudraCT number 2017-004426-15).

Clinical trial identification: EudraCT: 2017-004426-15.

Legal entity responsible for the study: European Association of Urology Research Foundation.

Funding: Incyte Inc.

Disclosure: A. Necchi: Consultant role for Incyte Inc. W. Witjes: Employee of EAU-RF. All other authors have declared no conflicts of interest.

924TiP A phase I study of HERV-E TCR transduced autologous T Cells (HERV-E TCR T Cells) in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC)

R. Nadal[1], E. Cherkasova[1], S. Barisic[1], D. Granadier[1], G. Aue[1], B. Wells[1], G. Hawks[1], T. Hughes[1], R. Shalabi[1], D. Stroncek[2], S. Highfill[2], G. Scurti[3], L. Chen[1], R. Reger[1], M. Nishimura[1], R. Childs[1]

[1]Laboratory of Transplantation Immunotherapy, National Heart, Lung, and Blood Institute. NIH, Bethesda, MD, USA, [2]Transfusion Medicine Department, National Institutes of Health, Bethesda, MD, USA, [3]Tumor Immunology and Immunotherapy, Loyola University, Chicago, IL, USA

Background: Our team isolated cytotoxic T lymphocyte (CTL) lines from a patient who had sustained mccRCC regression after an allogeneic transplant that showed specific killing of ccRCC. Utilizing these CTL and cDNA expression cloning, we discovered: transcripts encoding antigens targeted by these CTL were derived from a novel human endogenous retrovirus (HERV-E); selective HERV-E expression was present in most ccRCC tumors but not in normal tissues and VHL inactivation lead to transcription of HERV-E in ccRCC. Using HERV-E reactive CTL, we cloned a TCR that recognizes a HERV-E HLA-A11 restricted peptide (CT-RCC-1) into a retroviral vector containing a truncated CD34 cassette for enrichment of transduced cells. Transduced T cells acquired selective killing of HLA-A11+ ccRCC cells. A GMP method to manufacture enriched HERV-E TCR T cells was developed that incorporated cytokine stimulation of PBMCs followed by CD4+ depletion, T cell transduction, CD34 enrichment & ex vivo expansion. A scale up of this manufacturing process in 3 healthy donors showed transduced T cells: > 90% CD34+ and had > 90% CT-RCC-1 tetramer specificity. When co-cultured with HERV-E+ ccRCC cells, T cells secreted high levels of IFN-γ and killed ccRCC cells (Table).

Trial design: Phase 1 (3 + 3 design) cell dose-escalation study (1×10^6, 5×10^6, 1×10^7 and 5×10^7 cells/kg) to determine the MTD of HERV-E TCR T cells in mccRCC. Pts first receive cyclophosphamide and fludarabine conditioning, followed by single infusion of HERV-E TCR T cells & moderate-dose IL-2. Eligibility criteria: histologically-confirmed ccRCC, progressive disease and 2 prior lines of therapy. Primary endpoint: safety by day 21. Adverse events assessed using CTCAEv5. Biomarker objectives: persistence of HERV-E TCR T cells in blood, T cell lineage/functionality of these cells over time; cytokine profiles & HERV-E expression and presence of HERV-E TCR T cells in tumor tissue.

Table: 924TiP

	HERV-E TCR T cells (n = 3 donors)	Method
Cell number after ex vivo expansion (range)	7.55×10^8 (1.34×10^8-6.34×10^9)	Cellometer-based
CD34+, % (range)	96.4 (96.1-96.8)	Flow
CT-RCC-1 tetramer+, % (range)	93.2 (91.3-94.5)	Flow
Tumor Specific lysis, % (SD)	46 ± 8.5	LDH assay
IFN-γ secretion, pg/ml (range)	1635 (1555-1750)	ELISA

Clinical trial identification: NCT03354390.

Legal entity responsible for the study: National Heart, Lung, and Blood Institute.

Funding: National Institutes of Health.

Disclosure: All authors have declared no conflicts of interest.

925TiP Phase Ib/II study to evaluate the safety, tolerability and pharmacokinetics of rogaratinib in combination with atezolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer and FGFR mRNA overexpression

J. Rosenberg[1], A. Necchi[2], R.F. Sweis[3], K. Nakajima[4], C. Lu[5], H. Nogai[6]

[1]Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Medical Oncology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [3]Section of Hematology/Oncology - Department of Medicine, University of Chicago, Chicago, IL, USA, [4]Clinical Development, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, [5]Clinical Statistics, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, [6]Oncology, Bayer AG, Berlin, Germany

Background: PD-(L)1 inhibitors have been shown to be effective in patients with metastatic urothelial cancer (UC) who are ineligible to receive cisplatin-based chemotherapy, with the PD-L1 inhibitor atezolizumab being FDA-approved. Dysregulation of fibroblast growth factor receptors (FGFR) has been shown to play a role in UC development and progression, and FGFR3 overexpression/molecular alterations are associated with a non-T-cell inflamed tumor microenvironment. Rogaratinib, an oral pan-FGFR 1-4 inhibitor, has shown promising efficacy in a phase I study in UC patients selected based on FGFR1-3 overexpression, including patients who rapidly progressed on immunotherapy. The aim of this study is to explore the clinical safety and benefit of combining rogaratinib with atezolizumab.

Trial design: This is a multicenter, phase 1b/2 study of rogaratinib in combination with atezolizumab in patients with FGFR-positive locally advanced or metastatic UC. The primary objectives of the single-arm phase 1b portion are to determine the safety, tolerability, recommended phase-2 dose (RP2D) and pharmacokinetics of rogaratinib in combination with atezolizumab. The primary objective of the randomized phase 2 portion is to compare progression-free survival (PFS) of rogaratinib plus atezolizumab versus placebo plus atezolizumab in chemotherapy-untreated patients with FGFR-positive locally advanced or metastatic UC. Patients will be tested for FGFR1/3 mRNA expression levels in archival tumor samples (RNAscope®) and patients with FGFR-positive UC will enter into screening, regardless of the presence of FGFR mutations or translocations. Eligible patients will be treated with a starting dose of daily rogaratinib 800 mg po bid together with a fixed dose of 1200 mg atezolizumab iv on day 1 of a 21-day cycle. Following determination of the RP2D, patients will be randomized 1:1 to rogaratinib plus atezolizumab versus placebo plus atezolizumab. The primary efficacy variable is PFS based on assessment of blinded independent central review. Approximately 160 patients will be enrolled.

Clinical trial identification: NCT03473756.

Legal entity responsible for the study: Bayer AG.

Funding: Bayer AG.

Disclosure: K. Nakajima, C. Lu, H. Nogai: Employee: Bayer. All other authors have declared no conflicts of interest.

926TiP Neo-adjuvant ipilimumab and nivolumab in high risk resectable bladder urothelial cancer (NABUCCO)

N. van Dijk[1], C.U. Blank[1], P. Kvistborg[2], T.N. Schumacher[2], E. Hooijberg[3], K. Sikorska[4], B.V. Rhijn[5], M.S. van der Heijden[6]

[1]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [2]Molecular Oncology and Immunology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [3]Pathology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [4]Biometrics, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [5]Surgical oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, [6]Medical Oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands

Background: Although muscle-invasive urothelial cancer (UC) can be cured by surgery, recurrence rates are high. Despite impressive response rates to neo-adjuvant cisplatin-based chemotherapy, the absolute overall survival benefit is only 5%. Immunotherapy targeting the PD-1/PD-L1-axis has shown promising activity in UC, particularly when combined with anti-CTLA-4, and patients with lymph node only disease treated with frontline immunotherapy appear to benefit most. Since responses to immunotherapy often appear to be durable, neo-adjuvant immunotherapy may improve prognosis, particularly for high risk N+ disease. Preliminary data on neo-adjuvant pembrolizumab showed remarkable pCR rates (38.9%) and a manageable toxicity profile after 3 cycles of pembrolizumab in resectable T2-3N0 UC, underpinning the potential of neo-adjuvant combination trials for high risk UC.

Trial design: This is a single-arm phase 1B trial to establish whether sequenced pre-operative ipilimumab and nivolumab is safe and effective in high risk UC, defined as upper/lower tract cT3-4aN0 OR ≥T1, cN+ OR ≥T1, any N, resectable retroperitoneal lymph node metastasis. Patients are eligible if they are ≥ 18 years with WHO performance 0-1. Patients must be cisplatin ineligible or refuse cisplatin-based chemo with no previous treatment with PD-(L)1 and CTLA-4 immunotherapy. To mitigate the risk of immune-related toxicity, patients are treated with a mitigated schedule (based on Meerveld-Eggink et al., Ann Oncol 2017): ipi 3 mg/kg (day 1), ipi 3 mg/kg + nivo 1 mg/kg (day 22) and nivo 3 mg/kg (day 43) followed by radical cystectomy or nefro/ureterectomy (day 57-71) with appropriate LN dissection. Six patients will undergo a re-TUR for in-depth analysis of T cell infiltrates. The primary endpoint of this trial is the percentage of patients having surgery <12 weeks after study enrollment. Secondary endpoints are efficacy (pCR) and translational. In total 24 patients will be included. At the time of abstract submission, 5 patients were included.

Clinical trial identification: NCT03387761.

Legal entity responsible for the study: The Netherlands Cancer Institute.

Funding: BMS.

Disclosure: All authors have declared no conflicts of interest.

927TiP A phase III, randomized, placebo-controlled trial of adjuvant nivolumab plus ipilimumab in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after radical or partial nephrectomy (CheckMate 914)

A. Bex[1], V. Grünwald[2], P. Russo[3], Y. Tomita[4], E. Berghorn[5], M.B. McHenry[6], R.J. Motzer[7]

[1]Department of Urology, Netherlands Cancer Institute, Amsterdam, Netherlands, [2]Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany, [3]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [4]Department of Molecular Oncology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [5]Global Clinical Research, Bristol-Myers Squibb, Princeton, NJ, USA, [6]Global Biometeric Sciences, Bristol-Myers Squibb Company, Princeton, NJ, USA, [7]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background: Surgery is the standard treatment for non-metastatic RCC. Unfortunately, pts with stage II or III RCC have high risk of relapse with 5-year survival rates of 20% to 53%; prevention of recurrence is an unmet need. In CheckMate 214, the nivolumab + ipilimumab treatment combination demonstrated significant improvement in overall survival (OS) in first-line treatment of pts with advanced or metastatic RCC, with a manageable safety profile. This phase III multinational study will evaluate adjuvant nivolumab + ipilimumab vs placebo in pts with high risk of relapse after nephrectomy (NCT03138512).

Trial design: Key inclusion criteria: Radical or partial nephrectomy with negative surgical margins >4 weeks and ≤12 weeks before randomization; predominantly clear primary tumor cell histology; pathologic TNM staging T2a (grade [G] 3 or 4), T2b (any G), T3 (any G), or T4 (any G) N0M0, or any T (any G) N1M0; Eastern Cooperative Oncology Group performance status ≤1, no clinical/radiological evidence of macroscopic residual disease or distant metastases post-nephrectomy, and tumor tissue obtained ≤3 months pre-enrollment. Key exclusion criteria: Pts with conditions requiring corticosteroid or immunosuppressive systemic treatment, autoimmune disease, prior treatment with drugs specifically targeting T-cell co-stimulation or checkpoint pathways, and prior systemic treatment for RCC. Pts are randomized 1:1 to receive nivolumab and ipilimumab at the specified dose on specified days for 24 weeks, or placebo infusions on the same schedule for 24 weeks or until recurrence, unacceptable toxicity, or withdrawal of consent. Stratification factors: TNM staging and type of nephrectomy procedure. Primary endpoint: Disease-free survival per blinded independent central review. Secondary endpoints: OS, safety, and tolerability. Tertiary/exploratory endpoints include disease-related symptoms based on the Functional Assessment of Cancer Therapy-Kidney Symptom Index, and changes in global health status based on EuroQoL's EQ-5D-3L. Enrollment began July 2017 with a target of 800 pts.

Clinical trial identification: NCT03138512.

Editorial acknowledgement: Professional medical writing and editorial assistance were provided by Juan Sanchez-Cortes, PhD, and Lawrence Hargett of PPSI (a PAREXEL company), funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb and Ono Pharmaceutical Company Limited.

Disclosure: A. Bex: Honoraria: Bristol-Myers Squibb, Pfizer, Roche, Eisai, Ipsen; Consulting or Advisory role: Bristol-Myers Squibb, Pfizer, Roche, Eisai, Ipsen; Research funding: Pfizer. V. Grünwald: Honoraria: Bristol-Myers Squibb; Consulting or Advisory role: Bristol-Myers Squibb, Novartis, Pfizer, Bayer; Speakers' bureaus: Bristol-Myers Squibb, Novartis, Pfizer. Y. Tomita: Honoraria: Pfizer, Novartis, Ono Pharmaceutical Co., Ltd.; Consulting or Advisory role: Ono Pharmaceutical Co., Ltd., Novartis, Taiho; Research funding (Inst): Takeda, Pfizer, Ono Pharmaceutical Co., Ltd., Astellas. E. Berghorn, M.B. McHenry: Employment: Bristol-Myers Squibb Stock or Other ownership: Bristol-Myers Squibb. R.J. Motzer: Consulting or Advisory role: Eisai, Exelixis, Genentech/Roche, Merck, Novartis, Pfizer; Research funding: Bristol-Myers Squibb, Eisai, Exelixis, Novartis, Pfizer. All other authors have declared no conflicts of interest.

928TiP ATLAS: A phase II, open-label study of rucaparib in patients (pts) with locally advanced (unresectable) or metastatic urothelial carcinoma

S. Chowdhury[1], S. Feyerabend[2], Y. Loriot[3], A. Necchi[4], S. Gupta[5], D.H. Josephs[6], A. Rodríguez-Vida[7], S. Srinivas[8], Y. Zakharia[9], D. Nepert[10], K. Wride[11], D. Thomas[12], A. Loehr[13], A.D. Simmons[13], P. Grivas[14]

[1]Medical Oncology, Guy's Hospital and Sarah Cannon Research Institute, London, UK, [2]Urologic Oncology, Studienpraxis Urologie, Nürtingen, Germany, [3]Department of Cancer Medicine, Gustave Roussy Cancer Campus, Villejuif, France, [4]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [5]Genitourinary Oncology Program, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA, [6]Department of Medical Oncology, Guy's and St. Thomas' Hospital, London, UK, [7]Genitourinary Cancer Unit, Hospital del Mar, Barcelona, Spain, [8]Urologic Oncology Clinic, Stanford University School of Medicine, Stanford, CA, USA, [9]Division of Hematology, University of Iowa and Holden Comprehensive Cancer Center, Iowa City, IA, USA, [10]Clinical Science, Clovis Oncology, Inc., Boulder, CO, USA, [11]Biostatistics, Clovis Oncology, Inc., Boulder, CO, USA, [12]Clinical Operations, Clovis Oncology, Inc., Boulder, CO, USA, [13]Translational Medicine, Clovis Oncology, Inc., Boulder, CO, USA, [14]Dept. of Medicine, Division of Oncology, University of Washington, Seattle, WA, USA

Background: There are currently no standard treatment options for pts with metastatic urothelial carcinoma (mUC) who have progressed on or after platinum (cisplatin/carboplatin)–based chemotherapy (PBC) and/or immune checkpoint inhibitors (ICIs). Analysis of The Cancer Genome Atlas bladder cancer dataset suggests that approximately 60% of bladder tumours have homologous recombination deficiency (HRD), as identified by a deleterious mutation in a homologous recombination pathway gene or high genomic loss of heterozygosity (LOH). Poly(ADP-ribose) polymerase (PARP) inhibitors have demonstrated clinical activity and are approved in other indications for tumours with HRD. We hypothesise that PARP inhibition has antitumour activity in mUC. The ATLAS (NCT03397394) trial is evaluating the efficacy and safety of the PARP inhibitor rucaparib as monotherapy treatment for pts with locally advanced (unresectable) or metastatic UC previously treated with PBC and/or ICI.

Trial design: Eligible pts must have received 1–2 prior standard-of-care treatments (eg, PBC and/or ICI) and have radiographic progression, measurable disease (RECIST v1.1) and adequate organ function. Confirmation of HRD status before enrolment is not required; however, fresh tumour or recently obtained archival tissue is mandatory for central HRD profiling. Prior PARP inhibitor treatment is exclusionary. All pts will receive rucaparib monotherapy (600 mg BID) until disease progression or other reason for discontinuation. The coprimary endpoints are confirmed objective response rate (investigator-assessed per RECIST v1.1) in the HRD-positive (signature based on tumour genomic LOH) and intent-to-treat populations. Secondary endpoints include response duration, progression-free survival, overall survival, safety and pharmacokinetics. Exploratory endpoints include evaluation of molecular biomarkers associated with response and resistance to rucaparib, including changes in plasma and tumour samples. Pts are being enrolled in 6 countries (target, N = 200). The study has >90% power to reject the null hypothesis (P = 0.10) at a 5% significance level if the true response rate for rucaparib is 20%.

Clinical trial identification: NCT03397394.

Editorial acknowledgement: Writing and editorial support, funded by Clovis Oncology, Inc. (Boulder, CO, USA) was provided by Ritu Pathak, PhD, and Shannon Davis of Ashfield Healthcare Communications (Middletown, CT, USA).

Legal entity responsible for the study: Clovis Oncology, Inc.

Funding: Clovis Oncology, Inc.

Disclosure: S. Chowdhury: Consulting or advisory role and/or on speakers bureaus: Clovis Oncology, Sanofi, Pfizer, Astellas Pharma, Janssen; Honoraria: GlaxoSmithKline, Novartis; Research funding: Sanofi, Johnson & Johnson. S. Feyerabend: Advisory boards: Janssen, Boehringer Ingelheim Pharma, Aventis; Honorarium: Janssen; Travel and accommodation expenses: Aventis. Y. Loriot: Consulting or advisory role: Janssen, Astellas, Roche, MSD, Seattle Genetics, Pfizer, Bristol-Myers Squibb, AstraZeneca; Research funding: Sanofi, Johnson & Johnson, Merck Sharp & Dohme. S. Gupta: Research support for clinical trials: Pfizer, Five Prime Therapeutics, Hoosier Oncology Group, Rexahn Pharmaceuticals, Incyte, Bristol-Myers Squibb, Novartis, LSK BioPharma, Mirati, Merck; Spouse holds stock/equity in Salarius Pharmaceuticals. D.H. Josephs: Unbranded educational speaker program with Pfizer; Travel and accommodation expenses: EUSA Pharma, Ipsen. A. Rodríguez-Vida: Consulting or advisory role and/or on Speakers bureaus: Clovis Oncology, Merck Sharp & Dohme, Pfizer, BMS, Astellas, Janssen, Bayer, Roche; Honoraria: AstraZeneca, Sanofi Aventis; Research funding from Takeda, Pfizer, Merck Sharp & Dohme. Y. Zakharia: Advisory boards: Novartis, Amgen, Roche Diagnostics, Eisai, Exelixis, Castle Bioscience. D. Nepert, K. Wride, D. Thomas, A. Loehr, A.D. Simmons: Employee of Clovis Oncology and may own stock or have stock options in that company. P. Grivas: Consulting or advisory role with Clovis Oncology, Genentech, Bristol-Myers Squibb, Merck & Co, AstraZeneca, EMD Serono, Exelixis, Dendreon, Biocept, Seattle Genetics, Foundation Medicine, Driver Inc.; Unbranded educational speaker program (with direct input in slide content): Genentech, Bristol-Myers Squibb within the previous 2 years. All other authors have declared no conflicts of interest.

929TiP BAYOU: Phase II study of efficacy and safety of durvalumab plus olaparib as first-line therapy in cisplatin-ineligible patients (pts) with stage iv urothelial cancer (UC)

J.E. Rosenberg[1], D.F. Bajorin[1], A. Smith[2], C. D'Cruz[3], M. Lanasa[3]

[1]Genitourinary Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]Biometrics & Information Sciences, AstraZeneca, Cambridge, UK, [3]GMed Cancer Immunotherapy, AstraZeneca, Gaithersburg, MD, USA

Background: UC is platinum-responsive and hypothesized to be sensitive to targeted DNA-damaging agents such as PARP inhibitors (PARPi). Cisplatin (cis)-ineligible pts with metastatic/unresectable primary UC have limited effective treatment options. Immune checkpoint blockade may increase the proportion of pts that respond to PARPi. Durvalumab is a selective, high-affinity, engineered, human IgG1 monoclonal Ab that blocks PD-L1 binding to PD-1 and CD80. In UC, the combination of olaparib (a PARPi) + durvalumab may broaden the therapeutic effect of monotherapy given their different mechanisms of action, with potentially enhanced benefit for pts with metastatic/unresectable UC and DNA repair deficiencies (mutations in homologous recombination repair genes [HRRm]).

Trial design: BAYOU is a double-blind, randomized, placebo-controlled, multicenter phase 2 study designed to assess the efficacy and safety of durvalumab + olaparib vs durvalumab + placebo in cis-ineligible pts with stage IV UC. Adult pts ($\geq$18 years) who are cis-ineligible with histologically/cytologically confirmed unresectable stage IV UC, WHO performance status 0-2, and with known HRRm status will be enrolled. Pts with active/prior autoimmune disorders, brain metastases, prior PARPi/immune therapy, current/prior immunosuppressive agents, non-UC invasive malignancies, and concomitant use of strong CYP3A inhibitors/inducers are excluded. All pts will be randomized (1:1) to durvalumab (1500 mg intravenous, every 4 weeks) + placebo or durvalumab + olaparib (tablet) until disease progression. Olaparib dose will be 300 mg twice daily in pts with CrCl >50 mL/min and 200 mg twice daily in pts with CrCl $\geq$31 to $\leq$ 50 mL/min. The primary endpoint is progression-free survival in HRRm patients (investigator assessed, RECIST v1.1). Secondary endpoints are overall survival (OS), duration of response, objective response rate, proportion of pts alive and progression free at 6 months, and OS at 18 months. Safety, pharmacokinetics, and immunogenicity will also be assessed. The trial is currently enrolling pts.

Editorial acknowledgement: Editorial assistance, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Ingrid Monteiro of Cactus Communications (Mumbai, India).

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: J.E. Rosenberg: Stockholder: Ilumina; Advisory board: Merck, BMS, AstraZeneca, EMD-Serono, Roche/Genentech, Inovio; Corporate-sponsored research: Roche/Genentech, Seattle Genetics, Astellas, Novartis. D.F. Bajorin: Advisory board or board of directors: Merck, Genentech, Bristol-Myers Squibb, Urogen, Novartis; Corporate-sponsored research: Merck, Novartis. A. Smith, C. D'Cruz, M. Lanasa: Employment: AstraZeneca; Stockholder: AstraZeneca.

930TiP Phase II/III study of rogaratinib versus chemotherapy in patients with locally advanced or metastatic urothelial carcinoma selected based on FGFR1/3 mRNA expression

C.N. Sternberg[1], J. Bellmunt[2], H. Nishiyama[3], D.P. Petrylak[4], D.I. Quinn[5], K. Nakajima[6], C. Lu[7], A. Holynskyj[6]

[1]Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy, [2]Medical Oncology, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain, [3]Urology, University of Tsukuba, Tsukuba, Japan, [4]Medical Oncology, Yale University School of Medicine Medical Oncology, New Haven, CT, USA, [5]Translation and Clinical Science Program / Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [6]Clinical Development, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, [7]Clinical Statistics, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA

Background: Long-term survival is poor for patients with locally advanced or metastatic urothelial carcinoma (UC) receiving chemotherapy and/or immunotherapy following progression with platinum-containing chemotherapy. Genetic alterations of fibroblast growth factor receptors (FGFR) have been shown to play a role in UC development and progression. Non-genetic and epigenetic activation of FGFR gene expression have also been described. Rogaratinib, an oral pan-FGFR 1-3 inhibitor, has shown promising activity and a manageable safety profile in a phase I study in patients with UC who were selected based on FGFR1-3 mRNA overexpression and/or activating mutations in the FGFR3 gene.

Trial design: This is a randomized, open-label, phase 2/3 study to evaluate the efficacy and safety of rogaratinib compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic UC who have received prior platinum-containing chemotherapy. The primary objective is to show superiority of rogaratinib over chemotherapy in prolonging overall survival (OS) of UC patients with FGFR-positive tumors. Secondary objectives include: objective response rate (ORR), progression-free survival, disease control rate, duration of response, and safety. Testing for FGFR1 and 3 mRNA over expression will be conducted centrally using an RNA in situ hybridization (RNA-ISH) in archival samples. Eligible patients will be randomized 1:1 to rogaratinib (800 mg po bid) or iv chemotherapy Q3W (docetaxel 75 mg/m^2; paclitaxel 175 mg/m^2; or 320 mg/m^2 vinflunine). Randomization will be stratified according to PIK3CA and/or RAS activating mutations, prior immunotherapy, and modified 4-factor Bellmunt risk score. The objective for the phase 2 part of the study is ORR. A total of 116 patients in PIK3CA and RAS WT patients will be enrolled to the phase 2 part of the study to rule out a low difference in ORR between rogaratinib and chemotherapy as futility. The phase 3 portion of the study is powered to detect an increase in median OS in PIK3CA and RAS WT patients. Total patient enrollment expected to be approximately 400 patients.

Clinical trial identification: NCT03410693.

Legal entity responsible for the study: Bayer AG.

Funding: Bayer AG.

Disclosure: K. Nakajima, C. Lu, A. Holynskyj: Bayer employment. All other authors have declared no conflicts of interest.

931TiP PRISM: A randomised phase II trial of nivolumab in combination with alternatively scheduled ipilimumab in first-line treatment of patients with advanced or metastatic renal cell carcinoma

F. Collinson[1], S. Brown[1], H. Buckley[1], G. Ainsworth[1], H. Howard[1], H. Poad[1], G. Carr[1], R.E. Banks[2], J. Brown[2], G. Velikova[3], J. Larkin[4], P. Nathan[5], T.B. Powles[6], N.S. Vasudev[3]

[1]Leeds Clinical Trials Research Unit, University of Leeds, Leeds, UK, [2]Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK, [3]St James's Institute of Oncology, St. James's University Hospital Leeds, Leeds, UK, [4]Department of Medical Oncology, Royal Marsden NHS Foundation Trust, London, UK, [5]Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, Middlesex, UK, [6]Department of Oncology, St. Bartholomew's Hospital, London, UK

Background: Initial results from the CheckMate 214 randomised phase III study demonstrate an overall survival advantage for combination ipilimumab plus nivolumab over sunitinib in front-line treatment of patients with intermediate/poor risk metastatic renal cell carcinoma (mRCC). However, the safety profile of nivolumab-plus-ipilimumab could be further optimised: 46% (250/547) of patients experienced a Grade 3-4 adverse reaction (AR), 22% (118/547) discontinued therapy due to ARs and (35%) (152/436) patients needed high dose steroids to resolve immune-mediated ARs. The aim of the PRISM trial is to explore safer and more tolerable scheduling of these agents. We hypothesise that 12-weekly rather than standard 3-weekly dosing of ipilimumab, in combination with nivolumab, will result in lower rates of grade 3-4 ARs whilst maintaining treatment efficacy.

Trial design: PRISM is a multi-centre phase II trial randomising patients (1:2) to nivolumab 3mg/kg combined with ipilimumab 1mg/kg every 3 weeks for 4 doses, followed by nivolumab 240mg flat-dose every 2 weeks (standard arm) versus nivolumab 3mg/kg combined with ipilimumab 1mg/kg at weeks 1, 13, 25 & 37 (4 doses) with single-agent 2-weekly nivolumab 240mg given in intervening weeks (experimental arm). Patients with untreated metastatic clear cell RCC will form the study population and patients with good, intermediate and poor prognosis disease, as per IMDC criteria, are eligible. The primary endpoint of the study is the rate of grade 3 or 4 ARs within the initial 12 months of treatment. Progression-free survival (PFS) at 12 months forms a key secondary endpoint, to exclude the PFS rate of no interest and support further investigation in a subsequent definitive phase III trial. Other secondary endpoints include treatment discontinuation rates, quality of life, overall response rate and duration of response. An exploratory objective is to examine circulating and tissue-based biomarkers of response. The study aims to recruit 189 patients across 15 UK centres over a 2-year period and opened in March 2018. To date, 4 patients have been recruited.

Clinical trial identification: EudraCT: 2017-001476-33.

Legal entity responsible for the study: University of Leeds.

Funding: Bristol Myers Squibb.

Disclosure: All authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii332–viii358, 2018
doi:10.1093/annonc/mdy285

GYNAECOLOGICAL CANCERS

932O Phase III trial of lurbinectedin versus PLD or topotecan in platinum-resistant ovarian cancer patients: Results of CORAIL trial

S. Gaillard[1], A. Oaknin[2], I.L. Ray-Coquard[3], I.B. Vergote[4], G. Scambia[5], N. Colombo[6], S.A. Ghamande[7], A. Soto-Matos[8], C.M. Fernandez[8], C. Kahatt[8], J. Gomez[8], A. Nieto[8], N. Torres[8], B. Pardo-Burdalo[9], Z. Papai[10], R.S. Kristeleit[11], D.M. O'Malley[12], I. Benjamin[13], P. Pautier[14], D. Lorusso[15]

[1]Gynecologic Cancer Trials, Duke University Medical Center, Baltimore, MD, USA, [2]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [3]Medical Oncology, University Claude Bernard Lyon I & GINECO, Lyon, France, [4]Gynaecology, University Hospitals Leuven, Leuven, Belgium, [5]Oncology, Policlinico Universitario A. Gemelli, Rome, Italy, [6]Gynecologic Oncology, Istituto Europeo di Oncologia, Milan, Italy, [7]Gynecologic Oncology, Georgia Cancer Center at Augusta University, Augusta, GA, USA, [8]Clinical, PharmaMar, Madrid, Spain, [9]Oncology, Institut Catala Oncologia-Hospital Duran i Reynals, Barcelona, Spain, [10]Oncology, Magyar Honvedseg Egeszsegugyi Kozpont, Budapest, Hungary, [11]Academic Department of Oncology, UCL Cancer Institute, London, UK, [12]Clinical Research Gynecologic Oncology, The Ohio State University, Wexner Medical Center, Columbus, OH, USA, [13]Oncology, Arizona Center for Cancer Care, Peoria, IL, USA, [14]Medical Oncology, Institute Gustave Roussy & GINECO, Villejuif, France, [15]Gynecologic Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

933O Carboplatin/pegylated liposomal doxorubicin/bevacizumab (CD-BEV) vs. carboplatin/gemcitabine/bevacizumab (CG-BEV) in patients with recurrent ovarian cancer: A prospective randomized phase III ENGOT/GCIG-Intergroup study (AGO study group, AGO-Austria, ANZGOG, GINECO, SGCTG)

J. Pfisterer[1], A.P. Dean[2], K. Baumann[3], J. Rau[4], P. Harter[5], F. Joly[6], J. Sehouli[7], U. Canzler[8], B. Schmalfeldt[9], C. Shannon[10], A. Hein[11], D.U. Reimer[12], L.C. Hanker[13], T. Petit[14], F. Marmé[15], A. El-Balat[16], R. Glasspool[17], N. de Gregorio[18], S. Mahner[19], J-E. Kurtz[20]

[1]Gyn Onc, AGO Study Group & Gynecologic Oncology Center, Kiel, Germany, [2]Gynaecological oncology, AGO Study Group & St. John of God Hospital, Subiaco, Australia, [3]Gynaecology, AGO Study Group & Klinikum der Stadt Ludwigshafen am Rhein gGmbH, Ludwigshafen, Germany, [4]Coordinating Centre for Clinical Trial, AGO Study Group & Coordinatoring Center for Clinical Trials Philipps-University of Marburg, Marburg, Germany, [5]Gynecology & Gynecologic Oncology, AGO Study Group & Kliniken Essen Mitte Evang. Huyssens-Stiftung, Essen, Germany, [6]Gynaecology, GINECO & Centre Francois Baclesse Caen, Caen, France, [7]Gynaecology, AGO Study Group & Department of Gynecology, Charité, Campus-Virchow-Klinikum, Berlin, Germany, [8]Gynaecology, AGO Study Group & Medical Faculty and University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany, [9]Gynaecology, AGO Study Group & Technical University of Munich - Klinikum rechts der Isar; University of Medical Center Hamburg-Eppendorf, Hamburg, Germany, [10]Oncology Department, ANZGOG & Mater Cancer Care Centre, Brisbane, Australia, [11]Gynaecology, AGO Study Group & Erlangen University Hospital, Erlangen, Germany, [12]Gynaecology, AGO Austria & Innsbruck Medical University, Innsbruck, Austria, [13]Gynaecology, AGO Study Group & University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany, [14]Gynaecology, GINECO & Paul Strauss Cancer Center and University of Strasbourg, Strasbourg, France, [15]Gynaecology, AGO Study Group & National Center for Tumor disease, University of Heidelberg, Heidelberg, Germany, [16]Gynaecology, AGO Study Group & University Hospital Frankfurt, Frankfurt, Germany, [17]Gynaecology, AGO Study Group & Beatson West of Scotland Cancer Centre, Glasgow, UK, [18]Gynaecology, AGO Study Group & University of Ulm, Ulm, Germany, [19]Gynaecology, AGO Study Group & University Medical Center Hamburg-Eppendorf and University of Munich, Ludwig-Maximilians-University Munich; University of Munich, Munich, Germany, [20]Haematology-oncology, GINECO & CHRU de Strasbourg Hôpital Civil, Strasbourg, France

934O Alienor/ENGOT-ov7 randomized trial exploring weekly paclitaxel (wP) + bevacizumab (bev) vs wP alone for patients with ovarian sex cord tumors (SCT) in relapse

I.L. Ray-Coquard[1], P. Harter[2], D. Lorusso[3], C. Dalban[4], I.B. Vergote[5], K. Fujiwara[6], L. Gladieff[7], H-J. Lueck[8], A. Floquet[9], A.F. Lesoin[10], A. Schnelzer[11], S. Pignata[12], F. Selle[13], J. Sehouli[14], F. Brocard[15], G. Mangili[16], P. Pautier[17], U. De Giorgi[18], M. Provansal[19], P-E. Heudel[20]

[1]Medical Oncology, Centre Léon Bérard, Lyon, France, [2]Gynecology & Gynecologic Oncology, Kliniken Essen Mitte Evang. Huyssens-Stiftung, Essen, Germany, [3]Gynecologic Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [4]Medical Oncology, Centre Léon Bérard, Lyon, France, [5]Gynaecology, University Hospitals Leuven, Leuven, Belgium, [6]Gynecologic Oncology, Saitama Medical University Internatl Medical Centre, Saitama, Japan, [7]Gynecologic Oncology, Institut Universitaire du Cancer - Toulouse- Oncopole, Toulouse, Haute-Garonne, France, [8]Gynecologic Oncology, Gynäkologisch-onkologische Praxis, Hamburg, Germany, [9]Oncologie Médicale, Institute Bergonié, Bordeaux, France, [10]Gynecologic Oncology, Centre Oscar Lambret, Lille, France, [11]Oncologie Médicale, Klinikum rechts der Isar, Munchen, Germany, [12]Urology and Gynecology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [13]Medical Oncology, APHP, CancerEst, Tenon University Hospital, Paris, France, [14]Gynecology, Department of Gynecology, Charité, Campus-Virchow-Klinikum, Berlin, Germany, [15]Oncologie Médicale, Centre d'Oncologie de Gentilly, Nancy, France, [16]Medical Oncology, Ospedale San Raffaele, Milan, Italy, [17]Medecine, Gustave Roussy, Villejuif, France, [18]Medical Oncology, Istituto Tumori della Romagna I.R.S.T., Meldola, Forlì-Cesena, Italy, [19]Oncologie Médicale, Institut Paoli Calmettes, Marseille, France, [20]Oncologie Médicale, Centre Léon Bérard, Lyon, France

940O OVPSYCH2: A randomised study of psychological support versus standard of care following chemotherapy for ovarian cancer

S. Blagden[1], G. Bertelli[2], E. Frangou[3], C. Butcher[4], S. Love[3], M. Mackean[5], R.M. Glasspool[6], A. Cook[7], S. Nicum[8], R. Lord[9], M. Ferguson[10], R.L. Roux[1], M. Martinez[11], S. Black[12], A. James[12], H. Palmer[13], S. Hughes[12], C. Marriott[13], L. Howells[14]

[1]Department of Oncology, Churchill Hospital University of Oxford, Oxford, UK, [2]Oncology, Sussex Cancer Centre, Brighton, UK, [3]Centre for Statistics and Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK, [4]Oncology Clinical Trials Office, University of Oxford, Oxford, UK, [5]Oncology, Edinburgh Cancer Centre Western General Hospital, Edinburgh, Midlothian, UK, [6]Department of Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK, [7]Department of Oncology, Gloucester Oncology Centre, Cheltenham, UK, [8]Oncology, Churchill Hospital University of Oxford, Oxford, UK, [9]Department of Oncology, Clatterbridge Cancer Center, Wirral, Merseyside, UK, [10]Medical Oncology, Ninewells Hospital, Dundee, UK, [11]Surgery and Cancer, Imperial College London, London, UK, [12]Research Team, Maggie's Swansea, Swansea, UK, [13]Research Team, Maggie's Oxford, Oxford, UK, [14]Research Team, Maggie's Centres, London, UK

936PD **A phase II study of durvalumab, a PD-L1 inhibitor and olaparib in recurrent ovarian cancer (OvCa)**

J-M. Lee[1], C.M. Annunziata[1], N. Houston[1], E.C. Kohn[1], S. Lipkowitz[1], L. Minasian[1], E. Nichols[1], J. Trepel[2], K. Trewhitt[1], F. Zia[1], A.D.S. Zimmer[2]

[1]Women's Malignancies Branch, National Cancer Institute, Rockville, MD, USA, [2]Developmental Therapeutics Branch, National Cancer Institute, Rockville, MD, USA

935PD **Preliminary safety, efficacy, and PK/PD characterization from GARNET, a phase I clinical trial of the anti–PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-H endometrial cancer**

A. Oaknin[1], S.L. Ellard[2], C. Leath III[3], V. Moreno[4], R. Kristeleit[5], W. Guo[6], S. Lu[7], D. Jenkins[8], K. McEachern[8], K. Yu Jen[9], S. Dunlap[9], E. Im[10], L. Gilbert[11]

[1]Medical Oncology, Vall d'Hebron University Hospital; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [2]Medical Oncology, British Columbia Cancer Agency and University of British Columbia, Vancouver, BC, Canada, [3]Obstetrics & Oncology, University of Alabama at Birmingham, Birmingham, AL, USA, [4]Medical Oncology, START Madrid-FJD, Hospital Fundacion Jimenez Diaz, Madrid, Spain, [5]Oncology, University College London UCL Cancer Institute, London, UK, [6]Biostatistics, Tesaro, Inc., Waltham, MA, USA, [7]Clinical Pharmacology, Tesaro, Inc., Waltham, MA, USA, [8]Translational Research, Tesaro, Inc., Waltham, MA, USA, [9]Clinical Science, Tesaro, Inc., Waltham, MA, USA, [10]Oncology Clinical Research, Tesaro, Inc., Waltham, MA, USA, [11]Obstetrics and Gynecology, McGill University Health Centre, Montreal, QC, Canada

937PD **A phase II trial of combination nivolumab and bevacizumab in recurrent ovarian cancer**

J.F. Liu[1], C. Herold[1], W. Luo[2], R. Penson[3], N. Horowitz[4], P. Konstantinopoulos[1], C. Castro[3], J. Curtis[1], U.A. Matulonis[1], S. Cannistra[5], D.S. Dizon[6]

[1]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [2]Biostatistics, Dana Farber Cancer Institute, Boston, MA, USA, [3]Medical Oncology, Massachusetts General Hospital, Boston, MA, USA, [4]Gynecologic Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [5]Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA, [6]Medical Oncology, Lifespan Cancer Institute, Providence, RI, USA

938PD **Need for a stratified analysis in stage I malignant ovarian germ cell tumors (MOGCT): Prospective survival analysis of cases collection from the French rare malignant ovarian tumors (TMRO) network & GINECO group**

T. de la Motte Rouge[1], F. Derquin[1], A. Floquet[2], J. Edeline[1], J-P. Lotz[3], J. Alexandre[4], P. Pautier[5], G. Ferron[6], E. Boissier[7], C. Lefeuvre-Plesse[1], H. Vegas[8], A. Patsouris[9], E. Kalbacher[10], D. Berton-Rigaud[11], A-C. Hardy Bessard[12], V. Lavoué[13], I.L. Ray-Coquard[14]

[1]Medical Oncology, Centre Eugene - Marquis, Rennes, France, [2]Oncologie Médicale, Institute Bergonié, Bordeaux, France, [3]Medical Oncology, APHP, CancerEst, Tenon University Hospital, Paris, France, [4]Medical Oncology, Hôpital Cochin, Paris, France, [5]Medecine, Gustave Roussy, Villejuif, France, [6]Surgical Department, Centre Claudius-Regaud, Toulouse, France, [7]Medical Oncology, European George Pompidou Hospital, Paris, France, [8]Medical Oncology, CHRU Bretonneau, Tours, France, [9]Medical Oncology, Centre Paul Papin, Angers, France, [10]Medical Oncology, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [11]Medical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [12]Medical Oncology, Hôpital Privé des Côtes d'Armor, Plérin, France, [13]Gynaecology Department, CHU Anne-de-Bretagne, Rennes, France, [14]Medical Oncology, Centre Léon Bérard, Lyon, France

939PD **Quality of life and symptoms in longterm survivors with ovarian cancer: It's still an issue. Expression VI – Carolin meets HANNA – holistic analysis of long-term survival with ovarian cancer: The international NOGGO, ENGOT and GCIG survey**

H. Woopen[1], I. Braicu[1], R. Richter[1], K. Schnuppe[2], P. Krabisch[3], T. Boxler[4], G. Emons[5], J. Glajzer[6], M. Rose[7], L. Erdur[7], R. Lindhorst[8], M. Endres[9], P. Hühnchen[9], I.B. Vergote[10], R. Berger[11], C. Marth[12], J. Sehouli[1]

[1]Gynecology, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [2]NOGGO, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [3]Gynecology, Klinikum Chemnitz, Chemnitz, Germany, [4]Gynecology, Klinikum Fuerth, Fuerth, Germany, [5]Gynecology, University of Göttingen, Göttingen, Germany, [6]Deprtment for Gynecology, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [7]Psychosomatics, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [8]Cardiology, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [9]Neurology, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [10]Gynaecology, University Hospitals Leuven, Leuven, Belgium, [11]Gynecologic Oncology, Medical University of Innsbruck, Innsbruck, Austria, [12]Gynecologic Oncology, University Hospital Innsbruck, Innsbruck, Austria

941PD **A prospective evaluation of tolerability of niraparib dosing based upon baseline body weight (wt) and platelet (blplt) count: Blinded pooled interim safety data from the PRIMA Study**

A. Gonzalez[1], M.R. Mirza[2], I. Vergote[3], Y. Li[4], S. Hazard[5], R. Clark[5], W. Graybill[6], B. Pothuri[7], B.J. Monk[8]

[1]Medical Oncology, Grupo Español de Investigación en Cáncer de Ovario (GEICO) & Clinica Universidad de Navarra, Madrid, Spain, [2]Department of Oncology, The Nordic Society of Gynecological Oncology (NSGO) & Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark, [3]Gynecological Oncology, Belgian Gynecological Oncology (BGOG) & University Hospitals Leuven, Leuven, Belgium, [4]Biostatistics, Tesaro Inc., Waltham, MA, USA, [5]Clinical Science, Tesaro Inc., Waltham, MA, USA, [6]Gynecologic Oncology, Medical University of South Carolina, Charleston, SC, USA, [7]Obstetrics & Oncology, NYU Langone Medical Center, New York, NY, USA, [8]Gynecologic Oncology, Division of Gynecologic Oncology, Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Phoenix Creighton University School of Medicine at St. Joseph's Hospital, Phoenix, AZ, USA

943PD **Response to neoadjuvant chemotherapy in ICON8: A GCIG phase III randomised trial evaluating weekly dose-dense chemotherapy integration in first-line epithelial ovarian/ fallopian tube/ primary peritoneal carcinoma (EOC) treatment**

A.R. Clamp[1], I.A. McNeish[2], A. Dean[3], D. Gallardo-Rincon[4], J-W. Kim[5], D.M. O'Donnell[6], J. Hook[7], S. Blagden[8], J.D. Brenton[9], R. Naik[10], T.J. Perren[7], S. Sundar[11], A.D. Cook[12], E.C. James[13], H. Gabra[14], R. Lord[15], M. Hall[16], G. Dark[17], R.S. Kaplan[13], J.A. Ledermann[18]

[1]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [2]Department of Surgery and Cancer, Imperial College London, London, UK, [3]Medical Oncology, Saint John of God Hospital Subiaco, Subiaco, Australia, [4]Gynecology Oncology Clinic, Instituto Nacional de Cancerologia - Mexico, Ciudad De México, Mexico, [5]Gynecologic Oncology, KGOG & Seoul National University, Seoul, Republic of Korea, [6]Medical Oncology, Cancer Trials Ireland, Dublin, Ireland, [7]Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [8]Oncology, Churchill Hospital University of Oxford, Oxford, UK, [9]Li Ka Shing Centre, Cancer Research UK, Cambridge Research Institute Addenbrooke's Hospital, Cambridge, UK, [10]Northern Gynaecological Oncology Centre, Gateshead Health NHS Foundation Trust, Gateshead, UK, [11]Birmingham Gynaecological Cancer Centre, University of Birmingham, Birmingham, UK, [12]MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology-UCL, London, UK, [13]MRC, Institute of Clinical Trials and Methodology-UCL, London, UK, [14]Surgery and Cancer, Imperial College London - Hammersmith Hospital, London, UK, [15]Clatterbridge Cancer Centre, The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK, [16]Medical Oncology, Mount Vernon Cancer Centre, Northwood, Middlesex, UK, [17]Northern Cancer for Cancer Care, Newcastle University, Newcastle, UK, [18]Cancer Trials Centre, University College London Cancer Institute, London, UK

944P QUADRA: A phase II, open-label, single-arm study to evaluate niraparib in patients (pts) with relapsed ovarian cancer (ROC) in 4th or later line of therapy: Results from the tBRCAmut subset

K.N. Moore[1], A.A. Secord[2], M. Geller[3], D.S. Miller[4], N.G. Cloven[5], G.F. Fleming[6], A.E. Wahner Hendrickson[7], M. Azodi[8], P. DiSilvestro[9], A. Oza[10], M. Cristea[11], J.S. Berek[12], J.K. Chan[13], B.J. Rimel[14], Y. Li[15], K. Luptakova[16], R. Clark[16], U.A. Matulonis[17], B.J. Monk[18]

[1]Gynecologic Oncology, Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK, USA, [2]Gynecologic Oncology, Duke University Medical Center, Duke Cancer Institute, Durham, NC, USA, [3]Obstetrics, Gynecology and Women's Health, University of Minnesota Medical School, Minneapolis, MN, USA, [4]Obstetrics & Gynecology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [5]Gynecologic Oncology, Texas Oncology - FortWorth, Fort Worth, TX, USA, [6]Gynecologic Oncology, The University of Chicago Medicine, Chicago, IL, USA, [7]Medical Oncology, Mayo Clinic, Rochester, NY, USA, [8]Obstetrics, Gynecology & Reproductive Sciences, Smillow Cancer Hospital at Yale and Yale University, New Haven, CT, USA, [9]Gynecologic Oncology, Women and Infants Hospital, Providence, RI, USA, [10]Medical Oncology and Hematology, University Health Network and Princess Margaret Cancer Centre, Toronto, ON, Canada, [11]Medical Oncology & Therapeutics Research, City of Hope National Medical Center, Duarte, CA, USA, [12]Obstetrics & Gynecology, Stanford Women's Cancer Center, Stanford, CA, USA, [13]Gynecologic Oncology, Sutter Health, San Francisco, CA, USA, [14]Obstetrics and Gynecology, Cedars-Sinai Medical Center, West Hollywood, CA, USA, [15]Biostatistics, Tesaro, Inc., Waltham, MA, USA, [16]Clinical Science, Tesaro, Inc., Waltham, MA, USA, [17]Medical Oncology, Harvard Medical School, Boston, MA, USA, [18]Division of Gynecologic Oncology, Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Phoenix Creighton University School of Medicine at St. Joseph's Hospital, Phoenix, AZ, USA

Background: Therapeutic options in late line ROC offer limited efficacy, especially for pts who are considered platinum (plat) resistant (res) or refractory (ref). Pts whose cancers harbor *BRCA* mutations (*BRCA*mut) have been included in poly (ADP-ribose) polymerase inhibitor (PARPi) trials and derived modest benefit from treatment (ORR ≈25% for plat-res and 0-14% for plat-ref pts). QUADRA evaluated niraparib monotherapy in ROC pts regardless of their plat and biomarker status.

Methods: Eligible pts received treatment with single agent niraparib in 4th or later line of therapy. Pts were evaluated for *BRCA*mut and HRD status (MyChoice HRD Test). Pts received niraparib 300 mg once daily until progression; treatment emergent adverse events (AEs) were managed with dose reduction to 200 or 100 mg. The primary endpoint was ORR per RECIST v1.1.

Results: 463 pts were treated. Median age was 65 years (range: 29-91). 162 pts were plat ref (defined as progression within 28 days of the last dose of plat); 152 plat res (defined as less than 6 months between last dose of plat and subsequent progression); 118 plat sensitive; 31 unknown. Results in HRD+ pts have been presented at a prior congress. We focus here on the t*BRCA*mut (both germline and somatic) PARPi-naïve subgroup. ORR for 4th line or later, PARPi-naïve t*BRCA*mut pts (n = 55) was 31% (95% CI: 19-45), including 18 plat-sensitive pts (ORR 39%), 21 plat-res pts (ORR 33%), and 16 plat-ref pts (ORR 19%). The combined ORR in the plat-res and -ref pts (n = 37) was 27%. The median DOR among all t*BRCA*mut pts was 9.2 months, with an estimated 43% of responding pts maintaining their response at 24 months. In the entire study cohort, 197 pts (42.5%) experienced a serious AE (SAE) and 91 pts (19.7%) a treatment-related SAE. The most frequent treatment-emergent SAEs were gastrointestinal disorders (19.9%), thrombocytopenia (8.4%), small intestinal obstruction (6.6%), and vomiting (5.1%).

Conclusions: Niraparib demonstrated meaningful and durable responses among the difficult-to-treat patient population, including platinum resistant and refractory t*BRCA*mut patients.

Clinical trial identification: NCT02354586.

Editorial acknowledgement: Writing and editorial support, funded by Tesaro, Inc. (Waltham, MA, USA) and coordinated by Ted Paunescu, PhD of TESARO, Inc., was provided by Nicole Renner, PhD and Dena McWain of Ashfield Healthcare Communications (Middletown, CT, USA).

Legal entity responsible for the study: Tesaro, Inc.

Funding: Tesaro, Inc.

Disclosure: K.N. Moore: Honorarium and served on advisory boards: Tesaro, Genentech Roche, Clovis, Astra Zeneca (for agents not involved in the SOLO-a Study), Immunogen, VBL Therapeutics, Janssen. M. Geller: Advisory Role, Speakers' bureau & Research funding: Tesaro Inc. D.S. Miller: Advisory role: Eisai, ImmunoGen, Tesaro, Clovis Oncology, Genentech, AstraZeneca, Guardant Health, Alexion. Speakers' bureau: Genentech, Clovis; Research funding: Tracon, AstraZeneca, Tesaro, Janssen, Aeterna Zentaris, Genentech, Pfizer, Aprea AB, ImmunoGen, Takeda, Xenetic Biosciences. N.G. Cloven: Employment: Texas Oncology. G.F. Fleming: Research funding: Corcept Therapeutics. P. DiSilvestro: Advisory role: Tesaro, AstraZeneca; Research funding: AstraZeneca, Tesaro, Abbvie, Genentech, Roche, Janssen. A. Oza: Steering Committees for PARPi trials: Tesaro, Clovis, AstraZeneca; Honoraria: Intas Pharma. M. Cristea: Research funding: Trovagene. J.S. Berek: Advisory role: Atara Biotherapeutics; Research funding: Tesaro. J.K. Chan: Advisory role: Roche/Genentech, AstraZeneca, Janssen Oncology, Clovis, Mateon, Biodesix, Tesaro; Spearkers' bureau and Honoraria: Roche/Genentech, AstraZeneca, Clovis, Tesaro. Y. Li, K. Luptakova, R. Clark: Employment and stock and other ownership interests: Tesaro Inc. U.A. Matulonis: Advisory role: Merck KGaA, AstraZeneca, Immunogen, Tesaro, Genentech. B.J. Monk: Advisory role: GSK, Merck, Tesaro, Roche/Genentech, AstraZeneca,Gradalis, Advaxis, Verastem, Cerulean Pharma, Amgen, Vermillion, Immunogen, Bayer, NuCana BioMed, Insys Therapeutics, Clovis, Oxigene, Pfizer, Mateon, Precision, Perthera, Biodesix, Abbvie, Myriad, Incyte; Spearkers' bureau: Roche/Genentech, AstraZeneca, Janssen, Clovis, Tesaro; Honoraria: GSK, Merck, Tesaro, Roche/Genentech, AstraZeneca, Gradalis, Advaxis, Veraste, Cerulean, Amgen Vermillion, Bayer, NuCana BioMed, Insys Therapeutics, Clovis, Oxigene, Pfizer Mateon, Precision, Perthera, Biodesix, Abbvie, Myriad, Incyte, Janssen. All other authors have declared no conflicts of interest.

945P A phase I/II study of chemo-immunotherapy with durvalumab (durva) and pegylated liposomal doxorubicin (PLD) in platinum-resistant recurrent ovarian cancer (PROC)

R.E. O'Cearbhaill[1], A. Wolfer[2], P. Disilvestro[3], D.M. O'Malley[4], P. Sabbatini[1], L. Shohara[5], P.O. Schwarzenberger[5], T. Ricciardi[5], M. Macri[5], A. Ryan[5], R.R. Venhaus[5], J.K. Bryan[6], P. Wong[7], K. Homicsko[8], L. Kandalaft[9], S. Rusakiewicz[9], A. Harari[9], B.J. Monk[10], G. Coukos[11]

[1]Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA, [2]Medical Oncology, University Hospital and University of Lausanne, Lausanne, Switzerland, [3]Gynecologic Oncology, Women and Infants Hospital of Rhode Island, Providence, RI, USA, [4]Clinical Research Gynecologic Oncology, Ohio State University College of Medicine and Ohio State University, James Cancer Center, Columbus, OH, USA, [5]Clinical Research, Ludwig Cancer Research, New York, NY, USA, [6]Research, Novella Clinical, Seattle, WA, USA, [7]Ludwig Center for Cancer Immunotherapy, Zuckerman Research Center and Memorial Sloan Kettering Cancer Center, New York, NY, USA, [8]Oncology, University Hospital and University of Lausanne, Lausanne, Switzerland, [9]Clinical Research, University Hospital of Lausanne and Lausanne Branch, Ludwig Institute for Cancer Research, Lausanne, Switzerland, [10]Gynecologic Oncology, Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA, [11]Medical Oncology, University Hospital of Lausanne and Lausanne Branch, Ludwig Institute for Cancer Research, Lausanne, Switzerland

Background: Programmed cell death ligand 1 (PD-L1) expression and preliminary evidence of antitumor activity with anti-PD-1 therapy have been reported in ovarian cancer. PLD, a pegylated, liposomal form of doxorubicin, is a standard option for this population; durva is an anti-PD-L1 antibody. The primary objectives of this study are to determine the safety of the combination and to evaluate clinical efficacy by progression-free survival rate at 6 months (PFS6) using RECIST 1.1.

Methods: This is a phase 1/2, multicenter, open-label study (NCT02431559) of durva in patients (pts) with PROC, scheduled to receive PLD. The study includes a dose escalation (phase 1: 3 + 3 design; DLT evaluation over one 28-day cycle; n = 6-18) and a dose expansion (phase 2: n = 41). PLD has been reported to have a 25% PFS6. A sample size of 41 evaluable pts yields 80% power to test the null hypothesis of a PFS6 rate of ≤ 25% against the alternative hypothesis of a PFS rate of ≥ 45% at an alpha level of 0.05 (one-sided). Blood and tumor samples were also collected for assessment of correlative immunologic responses.

Results: First pt dosed: 09Aug2016. As of 05Mar2018, 40 female pts (median age: 65 [32-83] years) were enrolled in phase 2 of the study; each received at least 1 dose of study therapy (PLD 40 mg/m^2 + durva 1500 mg Q4W) and are included in the safety analyses. Most frequent (in ≥ 25% pts) treatment-emergent adverse events (AEs, all causality) were palmar-plantar erythrodysesthesia syndrome (PPES)/rash, stomatitis, fatigue, abdominal pain, nausea, pyrexia, and vomiting. Grade 3 treatment-related AEs in ≥ 2 pts included PPES/rash, stomatitis, lymphocyte count decreased, lipase increased, and anemia. As of the cutoff date, 33 pts reached the timepoint for PFS6 assessment. Twelve pts were progression-free at 6 months; PFS6 = 30% (12/40 pts). The remaining data will mature by July 2018, and further improvement in PFS6 may occur. Updated PFS6 and preliminary correlative results will be presented at the meeting.

Conclusions: The combination of durva and PLD in women with PROC appears to have a tolerable safety profile and promising efficacy. PFS6 and translational endpoints are pending additional data.

Clinical trial identification: NCT02431559. May 1st 2015.

Legal entity responsible for the study: Ludwig Institute for Cancer Research.

Funding: Ludwig Institute for Cancer Research, Cancer Research Institute with funding also from VentiRx, and Medimmune. This study was funded in part through the NIH/NCI Support Grant P30 CA008748.

Disclosure: A. Wolfer: Advisory board: AstraZeneca. J.K. Bryan: CMO Novella Clinical, a contract research organization (January 2017-present); Previously CMO VentiRx Pharmaceuticals (2013-2016), with neither equity nor patent ownership on the technology at VentiRx. B.J. Monk: Consultant and speaker: AstraZeneca; Received honoraria for services. All other authors have declared no conflicts of interest.

946P Brain metastases in primary ovarian cancer: Real-world data

E. Ratner[1], M. Bala[2], M. Louie-Gao[2], S. Hazard[3], P. Brastianos[4]

[1]Obstetrics, Gynecology and Reproductive Sciences, Yale University, New Haven, CT, USA, [2]Health Economics and Outcomes Research, Tesaro, Inc., Waltham, MA, USA, [3]Clinical Science, Tesaro, Inc., Waltham, MA, USA, [4]Hematology/Oncology, Dana-Farber Harvard Cancer Center, Harvard Medical School, Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA

Background: Brain metastasis (BM) is infrequently reported in patients (pts) with ovarian cancer (OC), with past studies reporting a rate of approximately 1%.[1] This study estimated real-world incidence of BM in OC and assessed whether *BRCA* mutation (*BRCA*mut) increased risk of BM in OC pts.

Methods: This retrospective study included 4515 pts diagnosed with OC between Jan 1, 2011 and Jan 31, 2018 from the Flatiron Health database. This is a longitudinal, demographically and geographically diverse database derived from electronic health record data from over 265 cancer clinics and over 2 million active US cancer pts. A time-to-event analysis was conducted to assess whether pts with a known *BRCA*mut were more likely to develop BM compared with *BRCA* wild type (*BRCA*wt) pts.

Results: Of 4515 OC pts, 473 were *BRCA*mut, 1679 were *BRCA*wt, and 2363 had unknown *BRCA* status. A total of 46 pts (1%) had a diagnosis of BM subsequent to OC diagnosis. Of those with *BRCA*mut, 3% (14/473) developed BM; the BM rate was 0.6% (10/1679) for *BRCA*wt. The K-M estimate for the proportion of pts with BM within 5 years of diagnosis was 5.7% in the *BRCA*mut population compared with 1.4% in *BRCA*wt. *BRCA*mut pts had a significantly higher risk of developing BM compared with *BRCA*wt (HR 4.44 [95% CI 1.97, 10.00], $P < 0.0001$). A total of 281 OC pts also had a breast cancer (BC) diagnosis (186 developed BC prior to OC, 95 developed BC after OC diagnosis). After excluding these pts from the analysis, the HR for developing BM among *BRCA*mut pts vs. *BRCA*wt pts was 3.84 (95% CI 1.60, 9.22), $P = 0.001$. Multivariate models adjusting for other pt characteristics yielded similar HRs. Among pts who developed BM, median time from OC diagnosis to BM diagnosis was 27 months in *BRCA*mut pts and 35 months in *BRCA*wt. Median survival after diagnosis of BM was 7.16 months (95% CI 3.48, 16.49). Overall survival after BM did not differ significantly by *BRCA* status.

Conclusions: OC pts with *BRCA*mut seem to have a higher risk of developing BM. Further research is needed to confirm these findings and better understand potential mechanisms and implications for management, given the poor prognosis in pts who develop BM. [1]Pectasides et al. The Oncologist 2006;11:252–260.

Editorial acknowledgement: Editorial support, funded by Tesaro, Inc. (Waltham, MA, USA) and coordinated by Michael Stillman PhD of Tesaro, Inc., was provided by Dena McWain of Ashfield Healthcare Communications (Middletown, CT, USA).

Legal entity responsible for the study: Tesaro, Inc.

Funding: Tesaro, Inc.

Disclosure: E. Ratner: Advisory board: Tesaro Inc. M. Bala, M. Louie-Gao, S. Hazard: Employment and stock and other ownership interests in Tesaro Inc. All other authors have declared no conflicts of interest.

947P Subgroup analysis of rucaparib in platinum-sensitive recurrent ovarian carcinoma: Effect of prior chemotherapy regimens in ARIEL3

D. Lorusso[1], R.L. Coleman[2], A.M. Oza[3], C. Aghajanian[4], A. Oaknin[5], A. Dean[6], N. Colombo[7], J.I. Weberpals[8], A.R. Clamp[9], G. Scambia[10], A. Leary[11], R.W. Holloway[12], M. Amenedo Gancedo[13], P.C. Fong[14], J.C. Goh[15], D.M. O'Malley[16], S. Banerjee[17], S. Goble[18], T. Cameron[19], J.A. Ledermann[20]

[1]Unità di Ginecologia Oncologica, Fondazione IRCCS Istituto Nazionale dei Tumori and MITO, Milan, Italy, [2]Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [4]Gynecologic Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [5]Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [6]Department of Oncology, Saint John of God Subiaco Hospital, Subiaco, Australia, [7]Gynecologic Cancer Program, European Institute of Oncology and University of Milan-Bicocca, Milan, Italy, [8]Division of Gynecologic Oncology, Ottawa Hospital Research Institute, Ottawa, ON, Canada, [9]Department of Medical Oncology, The Christie NHS Foundation Trust and University of Manchester, Manchester, UK, [10]Gynecologic Oncology, Policlinico Universitario A. Gemelli IRCCS Università Cattolica del Sacro Cuore Roma, Rome, Italy, [11]Gynecological Unit, Gustave Roussy Cancer Center, INSERM U981, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), Villejuif, France, [12]Department of Gynecologic Oncology, Florida Hospital Cancer Institute, Orlando, FL, USA, [13]Medical Oncology Department, Oncology Center of Galicia, La Coruña, Spain, [14]Medical Oncology Department, Auckland City Hospital, Auckland, New Zealand, [15]Department of Oncology, Cancer Care Services, Royal Brisbane and Women's Hospital and University of Queensland, Herston, Australia, [16]Clinical Research Gynecologic Oncology, The Ohio State University, James Cancer Center, Columbus, OH, USA, [17]Gynaecology Unit, The Royal Marsden NHS Foundation Trust, London, UK, [18]Biostatistics, Clovis Oncology, Inc., Boulder, CO, USA, [19]Clinical Science, Clovis Oncology, Inc., Boulder, CO, USA, [20]Department of Oncology, UCL Cancer Institute and UCL Hospitals, London, UK

Background: In the randomised, placebo-controlled, phase 3 study ARIEL3, patients were randomised 2:1 to oral rucaparib (600 mg BID) or placebo as maintenance treatment following response to platinum-based chemotherapy. Rucaparib significantly improved progression-free survival (PFS) vs placebo in all patient populations regardless of biomarker status (Coleman et al. *Lancet.* 2017;390:1949-61). This post hoc exploratory analysis investigated the effect of the number of prior chemotherapy regimens on the primary and secondary endpoints of investigator-assessed and blinded independent central review (BICR)-assessed PFS in ARIEL3.

Methods: In ARIEL3, all patients received ≥2 prior platinum-based regimens in accordance with the protocol. PFS was explored in subgroups of patients who received 2 or ≥ 3 prior chemotherapy regimens. These subgroup analyses were presented for the following predefined cohorts: *BRCA* mutant; *BRCA* mutant or *BRCA* wild type/high loss of heterozygosity (LOH); and intent-to-treat (ITT) population (ie, all randomised patients).

Results: The visit cutoff dates for efficacy and safety were 15 April 2017 and 15 August 2017, respectively. In each predefined cohort, rucaparib significantly improved PFS compared to placebo irrespective of the number of prior chemotherapy regimens (ie, 2 or ≥ 3) (Table). Rucaparib's safety profile was consistent between patients who received 2 or ≥ 3 prior chemotherapy regimens as assessed by the rate of all grade (100% and 100%) and grade ≥3 (59% and 59%) treatment-emergent adverse events (TEAEs) and dose modifications (ie, treatment interruptions and/or dose reductions due to a TEAE) (70% and 74%) in each respective subgroup.

Table: 947P

Cohort	Rucaparib, n	Placebo, n	PFS (investigator review)		PFS (BICR)	
			HR* (95% CI) Rucaparib vs placebo	Median PFS, mo; *P* value† Rucaparib vs placebo	HR* (95% CI) Rucaparib vs placebo	Median PFS, mo; *P* value† Rucaparib vs placebo
Patients with 2 prior chemotherapy regimens						
BRCA mutant	73	40	0.24 (0.14–0.40)	21.9 vs 5.4; *P*<0.0001	0.24 (0.13–0.45)	26.8 vs 5.5; *P*<0.0001
BRCA mutant or *BRCA* wild type/ high LOH	136	75	0.34 (0.23–0.49)	14.1 vs 5.5; *P*<0.0001	0.33 (0.21–0.52)	26.8 vs 5.5; P < 0.0001
ITT	231	124	0.42 (0.32–0.55)	10.4 vs 5.4; *P*<0.0001	0.37 (0.27–0.50)	17.1 vs 5.4; *P*<0.0001
Patients with ≥3 prior chemotherapy regimens						
BRCA mutant	57	26	0.21 (0.11–0.40)	13.7 vs 5.4; *P*<0.0001	0.17 (0.08–0.35)	18.0 vs 5.4; *P*<0.0001
BRCA mutant or *BRCA* wild type/high LOH	100	43	0.27 (0.16–0.44)	11.1 vs 5.4; *P*<0.0001	0.30 (0.18–0.52)	13.6 vs 5.4; *P*<0.0001
ITT	144	65	0.28 (0.19–0.41)	11.1 vs 5.3; *P*<0.0001	0.36 (0.24–0.53)	13.3 vs 5.3; *P*<0.0001

*Cox proportional hazards model; *P* values for treatment-by-prior chemotherapy regimen subgroup interaction were nonsignificant for all analyses. †Stratified log-rank *P* value. CI, confidence interval; HR, hazard ratio.

Conclusions: Maintenance treatment with rucaparib improved PFS vs placebo in all 3 predefined cohorts regardless of the number of prior chemotherapy regimens received.

Clinical trial identification: NCT01968213.

Editorial acknowledgement: Writing and editorial support, funded by Clovis Oncology, Inc. (Boulder, CO, USA) was provided by Nathan Yardley, PhD, and Shannon Davis of Ashfield Healthcare Communications (Middletown, CT, USA).

Legal entity responsible for the study: Clovis Oncology, Inc.

Funding: Clovis Oncology, Inc.

Disclosure: D. Lorusso: Consulting or advisory role: AstraZeneca, Clovis Oncology, Roche, Tesaro, PharmaMar; Support for travel or accommodation: Roche, PharmaMar. R.L. Coleman: Grants: AstraZeneca, Roche/Genentech, Janssen, OncoMed, Millennium, Merck, Clovis Oncology, Esperance, AbbVie; Advisor: AstraZeneca, Roche/Genentech, Janssen, OncoMed, Millennium, Merck, Clovis Oncology, Esperance, Tesaro, GamaMabs, Pfizer, Genmab, Gradalis, Bayer, AbbVie. A.M. Oza: Steering committees: AstraZeneca, Clovis Oncology, Tesaro. C. Aghajanian: Steering committee: Mateon Therapeutics, Clovis Oncology; Advisory boards: Clovis Oncology, Cerulean Pharma, Bayer, VentiRx, Tesaro; Honorarium: Mateon Therapeutics, Clovis Oncology, Cerulean Pharma, Bayer, VentiRx, Tesaro. A. Oaknin: Advisory boards: Roche, AstraZeneca, PharmaMar, Clovis Oncology, Tesaro; Travel or accommodation: Roche, AstraZeneca, PharmaMar. A. Dean: Consulting or advisory role: Specialised Therapeutics Australia, Shire Pharmaceuticals, Precision Oncology Australia. N. Colombo: Consulting or advisory role: Roche, AstraZeneca, Tesaro, PharmaMar, Clovis Oncology, Pfizer, Advaxis. J.I. Weberpals: Research support: AbbVie and AstraZeneca; Advisory boards: AstraZeneca. A.R. Clamp: Advisory boards: AstraZeneca, Roche; Research funding: AstraZeneca; Travel and accommodation for congress attendance: AstraZeneca. G. Scambia: Consulting or advisory role: Roche, AstraZeneca, PharmaMar, Clovis Oncology, Tesaro. A. Leary: Advisory board: Clovis Oncology, Pfizer, PharmaMar; Institutional research grant support: GamaMabs, Merus; Boarding and travel expenses for congress activities: AstraZeneca. R.W. Holloway: Speakers bureau: AstraZeneca, Clovis Oncology, Tesaro; Advisory board: Clovis Oncology. P.C. Fong: Advisory boards: Clovis Oncology, AstraZeneca; Honoraria: AstraZeneca. J.C. Goh: Honoraria: Bristol-Myers Squibb, AstraZeneca; Consulting or advisory role: Bristol-Myers, Squibb, AstraZeneca, Janssen; Speakers bureau: AstraZeneca, Novartis; Support for travel or accommodation: Roche, Bristol-Myers Squibb, Astellas. D.M. O'Malley: Advisory board: Clovis Oncology, AstraZeneca, Janssen, Gynecologic Oncology Group, Myriad, Tesaro; Steering committees: Clovis Oncology, Amgen, Immunogen; Consultant to AbbVie, AstraZeneca, Tesaro, Health Analytics, Ambry; Institution received research support from Agenus, Ajinomoto, Array BioPharma, AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, Ergomed Clinical Research, Exelixis, Genentech, GlaxoSmithKline, Gynecologic Oncology Group, ImmunoGen, INC Research, inVentiv Health Clinical, Janssen Research and Development, Ludwig Institute for Cancer Research, Novartis Pharmaceuticals, PRA International, Regeneron Pharmaceuticals, Serono, Stemcentrx, Tesaro, Tracon Pharmaceuticals. S. Banerjee: Institutional research support: AstraZeneca, Janssen-Cilag; Consulting or advisory role: AstraZeneca, Roche, GamaMabs Pharma, PharmaMar, AstraZeneca/MedImmune, Tesaro, Clovis Oncology; Support for travel or accommodation: AstraZeneca, Clovis Oncology, Tesaro. S. Goble, T. Cameron: Employee of Clovis Oncology and may own stock or have stock options in that company. J.A. Ledermann: Advisory role: Clovis Oncology, AstraZeneca, Pfizer; Speakers bureau for and research grants from: AstraZeneca, Merck/MSD. All other authors have declared no conflicts of interest.

948P Intraperitoneal chemotherapy (IP CT) after cytoreductive surgery benefits survival in epithelial ovarian cancer (EOC): Results of a pooled meta-analysis including 9 randomized clinical trials (RCT)

M. Jimenez-Heredia[1], J.A. Perez Fidalgo[2], M. Morales Suarez-Varela[3], J. Sanchis[4], M. Aranda[4], A. Cervantes[2]

[1]Pharmacology, Hospital Clínico Universitario de Valencia. INCLIVA, Valencia, Spain, [2]Medical Oncology, Hospital Clinico Universitario de Valencia. INCLIVA. CIBERONC Spain, Valencia, Spain, [3]Public Health, University of Valencia. CIBERESP, Valencia, Spain, [4]Gynaecology, Hospital Clinico Universitario de Valencia. INCLIVA, Valencia, Spain

Background: IP CT after upfront cytoreductive surgery has been the standard of care in EOC. Nevertheless, results from the recent GOG252 trial showed no impact of this strategy vesus IV CT in the concurrence of bevacizumab therapy. The aim of this study was to perform a meta-analysis of the survival benefit of IP vs IV CT after cytoreductive surgery including recent evidence.

Methods: A literature search in order to identify most relevant RCT comparing IV vs IP CT after cytoreductive surgery in EOC was performed. Non comparative studies or trials with no hazard or risk ratios were excluded. Statistical analyses were done using SPSS STATISTICS V.21. Fixed-effect meta-analysis for combining data was made. Degree of heterogeneity using the I^2statistic was calculated. Endpoints meta-analysed were disease-free survival (DFS) and overall survival (OS).

Results: Initially 92 papers were identified. After exclusion criteria only nine RCT including pooled data from 3668 pts (2068 treated with IP CT and 1620 treated with IV CT) were included. In 8 RCTs IPCT was given after upfront surgery and in 1 (OV21/PETROC) after neoadjuvant CT. In all RCTs 6 CT cycles were foreseen in the IP arms. Seven RCTs including 3006 pts had DFS as endpoint. Among these, GOG252 cohorts A and B were analysed separately. IP CT showed a survival benefit over IV CT with HR = 0.86; (95% confidence interval (CI): 0.80 to 0.93). Heterogeneity was moderate (I^2=37.3) Eight RCTs including 2289 pts had OS as endpoint. IP CT showed a significant impact on OS with HR = 0.81; 95% CI: 0.73 to 0.90). Heterogeneity was low (I^2<0.01). Benefit of IP CT remained unchanged in the sensitivity analysis performed for both DFS and OS by eliminating the latest RCT of the meta-analysis.

Conclusions: IP CT benefits DFS and OS in this meta-analysis of pooled data from 9 RCTs and 3668 pts including latest negative results.

Legal entity responsible for the study: Hospital Clinico Universitario de Valencia. INCLIVA.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

949P Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), with pembrolizumab in platinum-resistant ovarian cancer (PROC): Initial results of an expansion cohort from FORWARD II, a phase Ib study

U.A. Matulonis[1], K.N. Moore[2], L.P. Martin[3], I.B. Vergote[4], C. Castro[5], L. Gilbert[6], K. Malek[7], M.J. Birrer[8], D.M. O'Malley[9]

[1]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [2]Gynecologic Oncology, Stephenson Cancer Center/University of Oklahoma, Oklahoma City, OK, USA, [3]Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [4]Gynaecology, University Hospitals Leuven, Leuven, Belgium, [5]Medical Oncology, Massachusetts General Hospital, Boston, MA, USA, [6]Obstetrics and Gynecology, McGill University Health Center, Montreal, QC, Canada, [7]Clinical Development, Immuno Gen Inc., Waltham, MA, USA, [8]Division of Hematology-Oncology, University of Alabama at Birmingham, Birmingham, MA, USA, [9]Clinical Research Gynecologic Oncology, The Ohio State University, James Cancer Center, Columbus, OH, USA

Background: Mirvetuximab soravtansine is an ADC comprised of a FRα-binding antibody linked to the tubulin-disrupting maytansinoid DM4. This agent activates monocytes and upregulates immunogenic cell death markers on ovarian tumor cells, providing a rationale for combining with immune checkpoint blockade. Mirvetuximab soravtansine is being evaluated in combination with pembrolizumab in patients with PROC.

Methods: Eligibility criteria include FRα positivity by IHC ($\geq$ 25% of cells with $\geq$ 2+ staining intensity), 2-4 prior systemic treatments, and no prior immunotherapy. Mirvetuximab soravtansine (6 mg/kg; adjusted ideal body weight) and pembrolizumab (200 mg) were administered intravenously on day 1 of a 21-day cycle. Responses were assessed with RECIST 1.1 and adverse events (AEs) by CTCAE v4.03.

Results: During dose-escalation (n = 14 patients), the mirvetuximab soravtansine-pembrolizumab combination demonstrated favorable tolerability, with primarily $\leq$ grade 2 AEs observed. Overall, the AE profile was manageable and consistent with the known profiles of each agent. In addition, promising evidence of durable antitumor activity was observed, including a confirmed objective response rate of 43%, median duration of response of 6.9 months, and median progression-free survival of 5.2 months. These findings supported enrollment of an expansion cohort to further evaluate this combination in the setting of PROC. At time of analysis, 37/46 patients were enrolled, who received a median of 3 prior regimens. Median age was 62y (range 40-77), and 92% had tumors with high grade serous histology. Initial safety, antitumor activity, and exploratory biomarker data will be presented, including for the subset of patients with medium/high FRα expression, which showed the highest degree of clinical activity during escalation.

Conclusions: Preliminary data have demonstrated a manageable safety profile and encouraging signals of clinical activity for the mirvetuximab soravtansine-pembrolizumab combination in recurrent PROC. The results of this expansion cohort will guide further development of this novel combination.

Clinical trial identification: NCT02606305.

Legal entity responsible for the study: ImmunoGen, Inc.

Funding: ImmunoGen, Inc.

Disclosure: U.A. Matulonis, K.N. Moore, L.P. Martin, M.J. Birrer, D.M. O'Malley: Advisory board: ImmunoGen, Inc. I.B. Vergote: Advisory board: ImmunoGen, Inc. K. Malek: Employee: ImmunoGen, Inc. All other authors have declared no conflicts of interest.

950P Olaparib maintenance therapy in patients (pts) with platinum-sensitive relapsed (PSR) ovarian cancer (OC) and stable disease (SD) following platinum-based chemotherapy

A.M. Oza[1], D. Cibula[2], A. Oaknin[3], C. Poole[4], R.H.J. Mathijssen[5], G.S. Sonke[6], N. Colombo[7], J. Špaček[8], P. Vuylsteke[9], H. Hirte[10], J. Pfisterer[11], M. Plante[12], L.C. Hanker[13], A. Fielding[14], V. Haddad[15], J. Chmielecki[16], M. Friedlander[17]

[1]Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, ON, Canada, [2]Department of Gynaecology and Obstetrics, General University Hospital, Prague, Czech Republic, [3]Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [4]Medical Oncology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK, [5]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [6]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [7]Gynecologic Oncology, University of Milan-Bicocca and Istituto Europeo di Oncologia, Milan, Italy, [8]Department of Obstetrics and Gynecology, University Hospital, Hradec Kralove, Czech Republic, [9]Oncologie Médicale, CHU UCL Namur, Ste Elisabeth, Namur, Belgium, [10]Department of Oncology, Juravinski Cancer Centre, Hamilton, ON, Canada, [11]AGO Study Group, Center of Gynecological Oncology, Kiel, Germany, [12]Gynecologic Oncology Division, Laval University, Quebec City, QC, Canada, [13]Department of Gynaecology and Obstetrics, University of Lübeck, Lübeck, Germany, [14]Medical Science, AstraZeneca, Cambridge, UK, [15]Statistical Science, AstraZeneca UK, Cambridge, UK, [16]Translational Science, Oncology, IMED Biotech Unit, AstraZeneca, Waltham, MA, USA, [17]Medical Oncology, University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia

Background: The PARP inhibitor olaparib (Lynparza®) is approved as maintenance therapy in pts with PSR OC who are in complete or partial response to platinum-based chemotherapy. Currently, pts with SD are observed until disease progression; the efficacy of maintenance olaparib in these pts is unknown. In a Phase II study (NCT01081951), progression-free survival (PFS) was significantly prolonged in pts with PSR OC receiving olaparib plus platinum-based chemotherapy followed by maintenance olaparib vs those receiving platinum-based chemotherapy alone (Oza et al. Lancet Oncol 2015). This post hoc analysis evaluated outcomes in pts with SD on scans at the end of chemotherapy and the efficacy of maintenance olaparib vs observation.

Methods: In this open-label, multicentre trial, pts with PSR serous OC, primary peritoneal cancer or fallopian tube cancer were randomized to olaparib capsules 200 mg twice daily (bid) on days 1–10 of each 21-day cycle plus paclitaxel and carboplatin AUC 4 on day 1 (n = 81) followed by maintenance olaparib 400 mg bid (continuously), or paclitaxel and carboplatin AUC 6 on day 1 (n = 81) without maintenance olaparib. The latest scan from randomization up to 2 weeks after the final dose of carboplatin was used to assess the best objective RECIST v1.1 response at the end of chemotherapy (blinded independent central review).

Results: At the end of chemotherapy, 24 (29.6%) pts who had also received low-dose olaparib and 21 (25.9%) pts without olaparib had SD as their best response (timing of the scan ranged from 2.10 months before to 0.49 months after the last dose of carboplatin). Median PFS, calculated from the end of chemotherapy, was 8.74 months with maintenance olaparib at standard dose vs 5.40 months without maintenance olaparib (hazard ratio 0.50; 95% CI 0.25, 1.00). Delayed responses following the end of chemotherapy occurred in four pts receiving maintenance olaparib (16.7%; two complete and two partial responses) and three pts without maintenance olaparib (14.3%; all partial responses). The number of lines of prior chemotherapy did not appear predictive of PFS benefit.

Conclusions: Maintenance olaparib may prolong PFS in OC pts with SD following platinum-based therapy.

Clinical trial identification: NCT01081951.

Editorial acknowledgement: Editorial assistance was provided by Gillian Keating, Mudskipper Business Limited, funded by AstraZeneca.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: A.M. Oza: Honoraria: Intas Pharma. D. Cibula: Fees for advisory boards: Roche, AstraZeneca. A. Oaknin: Fees for advisory boards: Roche, AstraZeneca, PharmaMar, Clovis Oncology, Tesaro; Support for travel/accommodation: Roche, AstraZeneca, PharmaMar. C. Poole: Honoraria for advisory boards: Pfizer, AstraZeneca, Genomic Health, Lilly; Honoraria for talks: Pfizer, AstraZeneca, Genomic Health; Consultancy fees: Creavo Medical Technologies. R.H.J. Mathijssen: Research funding: Astellas, Bayer, Boehringer Ingelheim, Cristal Therapeutics, Novartis, Pamgene, Pfizer, Roche, Sanofi; Consultation fees: Novartis, Servier; Travel support: Astellas, Pfizer. G.S. Sonke: Research funding: AstraZeneca, Merck, Novartis, Roche. N. Colombo: Honoraria: Genentech, AstraZeneca, PharmaMar; Fees for consulting/advisory boards: Genentech, PharmaMar, AstraZeneca, Clovis Oncology, Pfizer, MSD, Tesaro; Research funding: AstraZeneca. P. Vuylsteke: Fees for advisory boards: AstraZeneca, Roche, Eli Lilly. H. Hirte: Honoraria for advisory boards: AstraZeneca, Roche. J. Pfisterer, L.C. Hanker: Fees for advisory boards: Roche, AstraZeneca, Tesaro. M. Plante: Support for travel/accommodation: AstraZeneca. A. Fielding, V. Haddad, J. Chmielecki: Employee of AstraZeneca. M. Friedlander: Fees for advisory boards: AstraZeneca, MSD. All other authors have declared no conflicts of interest.

951P A phase Ib study of navicixizumab & weekly paclitaxel in heavily pre-treated platinum resistant ovarian, primary peritoneal or fallopian tube cancer

S. Fu[1], B. Corr[2], E. Hamilton[3], R.A. Burger[4], R. Wenham[5], R.W. Naumann[6], R. Stagg[7], K.N. Moore[8]

[1]Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA, [2]Gynecologic Oncology, University of Colorado Denver, Aurora, CO, USA, [3]Gynecologic Oncology, Sarah Cannon at Tennessee Oncology, Nashville, TN, USA, [4]Gynecologic Oncology, University of Pennsylvania Medical Center, Philadelphia, PA, USA, [5]Gynecologic Oncology, Moffitt Cancer Center, Tampa, FL, USA, [6]Gynecologic Oncology, Levine Cancer Institute, Charolette, NC, USA, [7]Clinical Research, Oncomed Pharmaceuticals, Redwood City, CA, USA, [8]Gynecologic Oncology, Stephenson Cancer Center/University of Oklahoma, Oklahoma City, OK, USA

Background: Anti-VEGF & anti-DLL4 have both demonstrated single agent activity in ovarian cancer. Navicixizumab is an anti-DLL4/VEGF IgG2 bispecific monoclonal antibody that had a response rate of 25% (3/12) in heavily pretreated ovarian cancer pts who were treated in an earlier single agent phase Ia trial.

Methods: This is an ongoing Phase 1b study of paclitaxel & navicixizumab in platinum resistant ovarian cancer pts who have failed > 2 prior therapies &/or bevacizumab. Paclitaxel 80 mg/m2 is given on Days 1, 8 and 15 & navicixizumab is given on Days 1 & 15 of every 28 day cycle. This study was designed as a dose escalation trial testing navicixizumab doses of 3 or 4 mg/kg followed by an expansion cohort to enroll a total of 30 patients. The expansion cohort was undertaken with 3 mg/kg of navicixizumab as higher doses did not show increased activity, but did result in more pronounced chronic toxicity in the Phase 1a study. A standardized treatment algorithm for hypertension is being employed.

Results: Eighteen pts were treated; 5 are still ongoing. The median number of prior therapies was 4 (range 2-8), all 18 pts had received prior paclitaxel & 13 had received bevacizumab. Eight pts (44%) had a PR, 6 (33%) had SD, 2 (11%) had PD & 2 (11%) were NE. The clinical benefit rate was 78%. Ten of 14 (71%) pts with an elevated CA-125 had a GCIG-defined response. The related AEs (all grades) that occurred in > 15% of the pts were: hypertension (67%), fatigue (44%), diarrhea (44%), headache (22%), neutropenia (17%), GERD (17%) & decrease appetite (17%). Other related AEs of significance were an infusion reaction (6%), Gr2 pulmonary hypertension (6%), Gr 4 thrombocytopenia (6%) & Gr4 GI perforation (6%). Anti-drug antibody occurred in 3 of 16 pts who have been evaluated; drug exposure was impacted in 1 pt.

Conclusions: The efficacy data in these heavily pre-treated platinum resistant ovarian cancer pts are encouraging & enrollment is ongoing. The safety profile appears to be manageable with hypertension being the most common adverse event related to navicixizumab.

Clinical trial identification: NCT03030287 January 25, 2017.

Legal entity responsible for the study: OncoMed Pharmaceuticals.

Funding: OncoMed Pharmaceuticals.

Disclosure: All authors have declared no conflicts of interest.

952P Long-term tolerability of olaparib tablets as maintenance therapy for platinum-sensitive relapsed ovarian cancer (PSR OC): Phase III SOLO2 trial

J. Korach[1], G. Freyer[2], S. Banerjee[3], R. Asher[4], J. Cosin[5], A.M. Oza[6], A.M. Poveda[7], M. Di Napoli[8], C. Scott[9], M. Lapresa[10], F. Heitz[11], K. Takehara[12], G.S. Sonke[13], S. Tjulandin[14], J-W. Kim[15], R. Hegg[16], I.B. Vergote[17], S. Turner[18], E. Pujade-Lauraine[19]

[1]Gynecologic Oncology, Chaim Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel, [2]Medical Oncology, Lyon University Hospital Cancer Institute, Lyon, France, [3]Gynaecology Unit, The Royal Marsden NHS Foundation Trust, London, UK, [4]NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia, [5]Gynecologic Oncology, Hartford Healthcare Cancer Institute, New Britain, CT, USA, [6]Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, ON, Canada, [7]Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [8]IRCCS Fondazione Pascale, Istituto Nazionale Tumori, Naples, Italy, [9]Walter and Eliza Hall Institute of Medical Research, Peter MacCallum Cancer Centre, Melbourne, Australia, [10]Division of Gynaecology, Istituto Europeo di Oncologia, Milan, Italy, [11]Gynaecological Oncology, Kliniken Essen-Mitte, Essen, Germany, [12]Gynecologic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [13]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [14]Department of Clinical Pharmacology and Chemotherapy, NN Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [15]Gynecologic Oncology, Seoul National University College of Medicine, Seoul, Republic of Korea, [16]Oncology Research Center, Pérola Byington Hospital, São Paulo, Brazil, [17]Gynecology, University of Leuven, Leuven Cancer Institute, Leuven, Belgium, [18]Global Medicines Development, AstraZeneca, Cambridge, UK, [19]Medical Oncology, Université Paris Descartes, AP-HP, Paris, France

Background: The PARP inhibitor olaparib (Lynparza®) has shown significant efficacy as maintenance therapy for patients (pts) with PSR OC, especially pts with BRCA mutations, as capsules (Ledermann et al Lancet Oncol 2014) and tablets (Pujade-Lauraine et al Lancet Oncol 2017). Olaparib capsules have shown long-term benefit, with pts staying on treatment for ≥5 years (yrs; Gourley et al ASCO 2017). We analysed the long-

term tolerability of olaparib tablets in the SOLO2 trial (ENGOT-Ov21; NCT01874353).

Methods: In SOLO2, pts with BRCA-mutated PSR OC in response to platinum received maintenance olaparib tablets (300 mg bid) or placebo until disease progression. Adverse events (AEs) were graded by CTCAE v4.0.

Results: At the primary data cut-off (DCO; 19 Sep 2016), of 195 pts treated with olaparib, 62 (32%) had received olaparib for ≥1–<2 yrs (Group 1) and 59 (30%) for ≥2 yrs (Group 2), vs 12/99 (12%) and 9/99 (9%), respectively, who received placebo. Most AEs that began after ≥1 yr (Group 1) or ≥ 2 yrs (Group 2) were grade 1–2, with few serious AEs (Table). The most common AEs with onset during the second yr of olaparib treatment were anaemia (19%), nausea (18%), and vomiting (15%). The most common AEs with onset after ≥2 yrs were diarrhoea (8%), abdominal pain (5%), and upper abdominal pain (5%). Four pts in Group 1 discontinued olaparib because of AEs (acute myeloid leukaemia, decreased neutrophil count, muscular weakness, disturbance in attention and depression; all n = 1) vs no pts in Group 2.

Table: 952P Long-term AE data for olaparib tablets as maintenance therapy

	Group 1 (n = 62) AEs with onset reported during the second yr (≥1–<2 yrs) of olaparib treatment	Group 2 (n = 59) AEs with onset reported after ≥2 yrs of olaparib treatment
AE (any grade), n (%)	54 (87)	23 (39)
AE (grade ≥3), n (%)	11 (18)	1 (2)
Serious AE, n (%)	7 (11)	1 (2)
Dose interruption caused by AE, n (%)	14 (23)	4 (7)
Dose reduction caused by AE, n (%)	4 (6)	0
Treatment discontinuation caused by AE, n (%)	4 (6)	0

Conclusions: AEs reported during long-term olaparib maintenance therapy were mostly low grade, non-serious and associated with a low rate of treatment discontinuation. Common AEs were consistent with the known safety profile. Olaparib tablets are suitable for long-term maintenance therapy for PSR OC pts, without cumulative toxicity and with few late-onset AEs.

Clinical trial identification: NCT01874353, January 2017.

Editorial acknowledgement: Editorial assistance was provided by Rachel Patel, Mudskipper Business Limited, funded by AstraZeneca.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: J. Korach: Advisory board member: AstraZeneca Israel. G. Freyer: Board and speaker fees: AstraZeneca, Pfizer, Lilly, Novartis, Biogaran, Clovis, Amgen; Speaker fees: Roche; Research funding: AstraZeneca, BMS, Amgen; Consultant honoraria: Amgen. S. Banerjee: Honoraria: AstraZeneca, Tesaro, Clovis, PharmaMar, and Gamamabs; Research funding to institution: AstraZeneca. J. Cosin: Consultant for Medtronic. A.M. Oza: Steering committees (non-compensated) for trials: AstraZeneca, Clovis, Tesaro; Honoraria: Intas Pharma. A.M. Poveda: Advisor: AstraZeneca, Roche, Tesaro, Clovis, PharmaMar. C. Scott: Personal fees and non-financial support: AstraZeneca; Grants, personal fees, non-financial support, and others: Clovis Oncology, Roche; Others: Eisai Australia, Beigene. M. Lapresa: Fees: AstraZeneca, PharmaMar. G.S. Sonke: Institutional research support: AstraZeneca, Merck, Novartis, Roche. S. Tjulandin: Honoraria: AstraZeneca, Pfizer, Eli Lilly, MSD, Hoffmann La Roche. I.B. Vergote: Advisory board fees: Roche, Genmab, Advaxis, Morphotek, Hoffmann La Roche, Cerulean Pharma, Novocure, AstraZeneca, Mateon Therapeutics, Immunogen, Eli Lilly Benelux, Amgen, Theradex Europe, Pfizer, Debiopharma International, Vifor Pharma, Novartis, MSD, Janssen-Cilag, Bayer, Clovis Oncology, Takeda, PharmaMar, Oncoinvent; Research grants: Amgen, Roche; Accommodation and travel expenses: Tesaro, Clovis Oncology, Takeda, PharmaMar, Roche, Genmab, Oncoinvent; Institutional research grants: Morphotek. S. Turner: Employee of AstraZeneca and owns stock. E. Pujade-Lauraine: Honoraria, advisory board member: AstraZeneca, Roche, Tesaro, Clovis, Pfizer. All other authors have declared no conflicts of interest.

953P The impact of lymph node dissection on high risk versus low risk endometrial cancer

C. Zhang, A. Soochit, J.H. Liu

Gynecologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: The aim of this study is to determine the benefits of lymph node dissection (LND) and the pattern of recurrence in low and high risk endometrial cancer (EC) patients.

Methods: EC patients who underwent surgery as primary treatment between April 2003 to March 2012 was identified and stratified into low-risk and high-risk groups for lymph node metastasis (LNM) according to these criteria: poor differentiation, non-endometrioid histology, deep myometrial invasion, cervical stromal involvement, adnexal involvement, tumor diameter ≥ 3cm, suspicious node in imaging. Univariate survival analysis followed by Cox-regression model for multivariate analysis was used to find prognostic factors for survival. The χ^2 and Fisher's exact test were used to compare categorical valuables.

Results: A total of 847 patients were included, among whom 524 received LND. After stratification 579 patients were assigned to high-risk group while 268 patients were assigned to low-risk group. LND was performed in 451 high-risk patients and in 73 low-risk patients with a rate of positive nodes of 14.1% (n = 64) and 2.7% (n = 2), respectively. Poor differentiation, non-endometrioid histology, deep myometrial invasion and adnexal involvement were independent prognostic factors. Whereas LNM was an independent prognostic factor for overall survival (OS, p = 0.03) but not for progression-free survival (PFS, p = 0.07). LND did not improve PFS (p = 0.56) or OS (p = 0.47) in the low-risk group and was not associated with OS (p = 0.17) in high-risk group. In 89 patients who had recurrence, 73 (13.9%) occurred in those with LND and 16 (5.0%) in those without LND. In high-risk group no significant difference was noted in recurrence rate (LND 16.0% vs without LND 8.6%, p = 0.06). Distant organs (lung, liver, bone, spleen and brain) and distant lymph nodes were the most common site of recurrence in both patients who underwent (5.9%, n = 31) LND and those who did not undergo (3.4%, n = 11) LND (p = 0.14).

Conclusions: According to our findings LND seemed not to have survival benefit for both high-risk and low-risk patients based on the above criteria, and it could not decrease risk of distance recurrence. A more reliable stratification model should be considered to determine the benefit of LND in EC.

Legal entity responsible for the study: Sun Yet-sen University Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

954P HOXA9 methylation in circulating tumor DNA as a prognostic biomarker in BRCA-mutated ovarian cancer patients treated with PARP inhibitor

M. Rusan[1], R. Fredslund Andersen[2], A. Jakobsen[1], K.D. Steffensen[3]

[1]Dept. of Oncology, Vejle Hospital Sygehus Lillebaelt, Vejle Sygehus, Vejle, Denmark, [2]Dept. of Biochemistry, Vejle Hospital, Vejle, Denmark, [3]Department of Clinical Oncology, Vejle Hospital Sygehus Lillebaelt, Vejle Sygehus, Vejle, Denmark

Background: Quantification of circulating tumour DNA methylation is a promising novel approach for predicting and monitoring treatment efficacy in cancer. The currently frequently employed biomarker CA-125, has been recently shown to not be prognostic for overall survival in platinum-resistant patients, making it further relevant for identifying novel biomarkers. HOXA9 promoter methylation has been observed in a large proportion of patients with high grade serous ovarian carcinoma (OC), and hypermethylation of HOXA9 is associated with worse progression-free survival and overall survival. The aim of the current study was to investigate whether HOXA9 methylation at baseline and during treatment, could predict treatment efficacy in BRCA-mutated ovarian cancer patients treated with the PARP inhibitor, Veliparib.

Methods: Plasma from OC patients was retrieved at baseline before initiation of daily oral single agent Veliparib, as well as following each treatment cycle, as part of a phase II investigator initiated trial (NCT01472783). DNA was purified from 4 ml of plasma, bisulfite converted and analysed by droplet digital PCR with a HOXA9 methylation-specific assay. Beta-2-microglobulin alleles/mL were used for normalization, and the fractional abundance of methylated HOXA9 was calculated.

Results: 32 patients were enrolled in a phase II trial, of which 24 had methylated HOXA9 at baseline. There was no significant different in overall survival based on HOXA9 methylation at baseline (p = 0.4), however patients with HOXA9 methylation following three treatment cycles had a significantly worse overall survival compared to patients with non-methylated HOXA9 (median overall survival was 8 months vs. 19 months for patients with methylated vs. non-methylated HOXA9, respectively, p = 0.0001). A similar trend was noted for progression free survival.

Conclusions: Methylation of HOXA9 detected in circulating tumor DNA may serve as a prognostic and treatment efficacy biomarker in BRCA-mutated ovarian cancer patients undergoing treatment with PARP inhibitors.

Clinical trial identification: NCT01472783.

Legal entity responsible for the study: Vejle Hospital, Vejle, Denmark.

Funding: Vejle Hospital, Abbvie.

Disclosure: All authors have declared no conflicts of interest.

955P Prevalence and clinical implications of mismatch repair (MMR) deficiency in unselected endometrial cancer (EC) patients

C.M.A. Orbegoso Aguilar[1], K. Vroobel[2], S. Lalondrelle[1], A. Taylor[3], M. Nobbenhuis[3], A. Attygalle[2], S. Banerjee[3], A. George[1]

[1]Gynae-Oncology Unit, Royal Marsden Hospital NHS Foundation Trust, London, UK, [2]Histopathology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [3]Gynaecology, Royal Marsden Hospital NHS Foundation Trust, London, UK

Background: Endometrial cancer (EC) is the most common gynaecological malignancy worldwide. The TCGA data suggested up to 30% of EC pts have a MMR deficient (MMRd) tumours, however the exact concordance of this with the presence of a germline mutation (Lynch syndrome) in an unselected population is unclear. Lynch-associated tumours appear to have a better prognosis, however the implications for prognosis and survival in all MMRd tumours are less known.

Methods: 396 pts with primary endometrial cancer, treated at RMH were evaluated for MMR proteins by immunohistochemistry (IHC). Tumours with loss of at least one protein were considered MMRd, those with intact expression were MMR proficient (MMRp). Clinico-pathological characteristics and survival data was collected from electronic records. Progression free survival (PFS) and overall survival (OS) were assessed using Kaplan Meier and log-rank tests.

Results: Of 396 samples tested to date, 29% (114 pts) were MMRd. Frequencies of IHC MMR loss of expression were: MLH1/PMS2 loss: 80, MSH2/MSH6 loss: 10, MSH6 loss: 12, PMS2 loss: 9, other patterns: 3. Germline testing has been completed in 37% (42 pts) thus far; 14pts had a concordant germline mutation: MLH1 (2/25), MSH2 (3/7), MSH6 (7/8), PMS2 (2/2) respectively. Mean age varied significantly, at 66 yrs (MMRd), 65yrs (MMRp) and 58 yrs (Lynch mutation carriers, LS) $p = 0.022$: as did mean BMI: 33 (MMRd), 26 (LS) and 36 (MMRp), $p = 0.023$. Stage at diagnosis did not differ significantly between the groups but MMRd and LS patients were significantly more likely to have LVSI than MMRp ($p = 0.01$), and to be high EORTC risk ($p = 0.006$). OS for the entire cohort was 160mths (75-244.9) and PFS was 51.6mths (32.4-70.7). MMRd pts had a shorter OS (96.4mths, 95%CI 65.7 – 127) than MMRp (160mo, 54.9 – 265) and a shorter PFS median PFS 41.4mo (IC 95% 18.9– 64) vs 51.6mo (IC 95% 30- 72), p.021].

Conclusions: Almost one in three EC tumours are MMRd, with concordance between IHC loss and presence of a germline mutation varying by gene. Those with somatically derived MLH1/PMS2 loss may have a poorer prognosis, and as a group may potentially benefit from checkpoint inhibitors. Further exploration of the clinical correlations and outcome with MMR status is warranted.

Legal entity responsible for the study: The Royal Marsden NHS Foundation Trust.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

956P A phase Ib and randomised phase II trial of pazopanib with or without fosbretabulin in advanced recurrent ovarian cancer

R.D. Morgan[1], G.C. Jayson[1], S. Banerjee[2], A.R. Clamp[1], A.R. Lyon[3], W.D. Ryder[4], R. Hutson[5], N. Mescallado[1], C. Orbegoso Aguilar[6], S. Taylor[7], J. Tugwood[7], M. Hall[8], C. Dive[9], G.J.S. Rustin[8]

[1]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [2]Gynaecology, The Royal Marsden NHS Foundation Trust in Chelsea, London, UK, [3]Cardiology, Royal Brompton Hospital and Imperial College, London, London, UK, [4]MAHSC-CTU, The Christie NHS Foundation Trust, Manchester, UK, [5]CTU, The Christie NHS Foundation Trust, Manchester, UK, [6]Medical Oncology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [7]Clinical & Experimental Pharmacology Group, Cancer Research UK Manchester Institute, Macclesfield, UK, [8]Medical Oncology, Mount Vernon Cancer Centre, Northwood, Middlesex, UK, [9]Clinical & Experimental Pharmacology, Cancer Research UK Manchester Institute, Manchester, UK

Background: Prospective trials have validated angiogenesis as a treatment target in ovarian cancer although improvements in PFS have been modest. One potential strategy to improve efficacy is to combine anti-vascular agents. Fosbretabulin (F) is an intravenous vascular disrupting agent and pazopanib (P) is an oral VEGFR tyrosine kinase inhibitor.

Methods: A multi-centre Phase 1b(P1b)/randomised phase 2 (RP2) trial that recruited women with recurrent epithelial ovarian cancer and a platinum-free interval of 3-12 months. Any Bevacizumab had been received $\geq$6 months prior to recruitment. Phase 1b dose levels ranged from $F = 54mg/m^2$ d1,8,15q28d + $P = 600mg/day$ (F54+P600) up to $F = 60mg/m^2$ d1,8,15q28d + $P = 800mg/day$. In RP2 participants received either RP2D or $P = 800mg/day$ (P800). Primary outcome in P1b was safety plus RP2D and in RP2 was RECIST PFS.

Results: 12 and 21 patients were recruited to P1b & RP2 respectively. The RP2D was F54+P600. In the RP2 median PFS was 7.6 months (95%CI 4.1-not estimated) in F54+P600 group vs. 3.7 months (95%CI 1.0-8.1) in P800 group (HR 0.30, 95%CI 0.08-1.03, $P = 0.06$). Four patients who received F+P (2 in P1b and 2 in RP2) developed acute hypertension plus reversible secondary cardiac toxicity. The occurrence of cardiac toxicity resulted in premature discontinuation of the trial. Data on circulating biomarkers of angiogenesis collected in in P1b & RP2 will also be presented.

Conclusions: F54+P600 appeared effective but was associated with reversible secondary cardiac toxicity that with better hypertension control might have been avoided.

Clinical trial identification: EudraCT: 2013-005471-40.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: Novartis & Mateon Therapeutics.

Disclosure: G.J.S. Rustin: Advisory board: Mateon, Roche, AstraZeneca in past 3 years, only Roche in past year. All other authors have declared no conflicts of interest.

957P Genomic profiling of the residual disease of advanced high-grade serous ovarian cancer after neoadjuvant chemotherapy

J-Y. Lee[1], S. Paik[2]

[1]Gynecologic Cancer Center, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea, [2]Genomics, Yonsei University, Seoul, Republic of Korea

Background: Tumor response to NAC predicts survival and can be considered a surrogate prognostic marker. Three tiered chemotherapy response score (CRS) of omental tissue sections showed a significant association with survival. In patients with CRS 1 or 2, NAC selects a subpopulation of chemotherapy resistant tumor cells. Residual tumors remaining after neoadjuvant chemotherapy contain cell population intrinsically resistant to chemotherapy. However, the standard of care for patients who have residual disease after NAC is the same regimen, as therapies that would be effective in reducing recurrences are unknown. We hypothesize that comprehensive molecular analyses of residual disease after NAC measured by targeted sequencing and Immunohistochemistry would be helpful to find out innovate new therapeutic targets.

Methods: During the study period between 2006 and 2018, Pre- and post NAC tumor tissue samples were collected from patients with advanced HGSC. Combined NGS and IHC was performed to identify actionable target and pathway activation in chemo-resistant tumor cells. We examined whether profiling residual HGSC after NAC identifies targetable molecular lesions in the chemotherapy-resistant component of tumor.

Results: Alteration in TP53 were identified in 76 of 104 post-NAC samples (72.1%). HRR gene alteration were found in 30 of 104 post-NAC samples (28.8%). Patients with DNA repair alterations (BRCA1, BRCA2, ATM mutations) were found in 30% of HGSC and they had better chemotherapy sensitivity and survival outcomes than those with intact DNA repair system. Otherwise, rare individual actionable targets (less than 5%) were found in most of patients.

Conclusions: We showed the genomic landscape of drug-resistant tumor cells remaining in advanced HGSC after NAC.

Clinical trial identification: NCT03491033.

Legal entity responsible for the study: Jung-Yun Lee.

Funding: NRF.

Disclosure: All authors have declared no conflicts of interest.

958P Cemiplimab, a human PD-1 monoclonal antibody, in patients (pts) with recurrent or metastatic cervical cancer: Interim data from phase I cohorts

D. Rischin[1], M. Gil-Martin[2], A. González-Martín[3], I. Brana[4], J.Y. Hou[5], D. Cho[6], G.S. Falchook[7], S. Formenti[8], S. Jabbour[9], K. Moore[10], A. Naing[11], K.P. Papadopoulos[12], J. Baranda[13], A. Weise[14], M.G. Fury[15], M. Feng[16], J. Li[17], I. Lowy[15], M. Mathias[15]

[1]Department of Medical Oncology, Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, Australia, [2]L'Hospitalet de Llobregat, Institut Català d'Oncologia, Barcelona, Spain, [3]Clinica Universidad de Navarra, Formerly of MD Anderson International España, Madrid, Spain, [4]Department of Medical Oncology, Vall D'Hebron Institute of Oncology, Barcelona, Spain, [5]Division of Gynecologic Oncology, Columbia University Medical Center, New York, NY, USA, [6]Langone Medical Center, New York University, New York, NY, USA, [7]Drug Development, Sarah Cannon Research Institute at HealthONE, Denver, CO, USA, [8]Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, USA, [9]Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA, [10]Stephenson Cancer Center at the University of Oklahoma Health Sciences Center, Sarah Cannon Research Institute, Oklahoma City, OK, USA, [11]Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [12]Clinical Research, START, San Antonio, TX, USA, [13]University of Kansas Cancer Center, Early Phase Program Clinical Research Center, Fairway, KS, USA, [14]Department of Medical Oncology, Karmanos Cancer Institute, Detroit, MI, USA, [15]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [16]Clinical Sciences, Oncology, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA, [17]Biostatistics & Data Management, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA

Background: For pts who progress after first–line platinum based therapy for recurrent/metastatic cervical cancer, there are no therapies available that have been demonstrated to improve survival or quality of life. Cemiplimab (REGN2810), a human monoclonal antibody to PD-1, exhibited encouraging efficacy and acceptable tolerability in a phase 1 dose escalation study. The present report focuses on interim data from the phase 1 cervical cancer expansion cohorts (ECs) of cemiplimab as a monotherapy

(EC 23) or in combination with hypofractionated radiotherapy (hfRT) (EC 24) (NCT02383212).

Methods: Pts with recurrent or metastatic cervical cancer resistant to or intolerant of platinum and taxane doublet therapy received cemiplimab 3 mg/kg Q2W for up to 48 weeks, in ECs 23 and 24, and hfRT (9 Gy x 3 times/week given 1 week after first dose of cemiplimab) in EC 24. The co-primary objectives were to evaluate the safety, tolerability, and efficacy of cemiplimab monotherapy or in combination with hfRT. Tumour response assessments (in non-irradiated target lesions) were performed by RECIST 1.1 Q8W.

Results: As of 1 Sept, 2017, these ECs were fully enrolled with 20 pts (EC 23, n = 10, EC 24, n = 10). Median (range) age was 55.0 (31–76) years (EC 23) and 51.5 (29–65) years (EC 24). ECOG performance status 1 vs. 0 was 60% vs. 40% and 80% vs. 20%, respectively, for EC 23 and EC 24. Investigator-assessed overall response rate (ORR; complete response [CR] + partial response [PR]) was 10.0% (0 CR and 1 PR) in each of EC 23 and EC 24. At the time of data cut-off, both responses were ongoing with durations of 3.7+ months. The most common treatment-emergent adverse events (TEAEs) of any grade were diarrhoea (40.0%), fatigue, hypokalaemia and pain in extremity (each 30.0%) in EC 23, and diarrhoea and urinary tract infection (each 30.0%) in EC 24. There was no grade ≥3 TEAE reported in > 1 patient in either cohort.

Conclusions: Cemiplimab as monotherapy and in combination with hfRT demonstrated antitumour activity with an acceptable safety profile in pts with metastatic or recurrent cervical cancer. Cemiplimab monotherapy vs. chemotherapy in ≥ 2nd line cervical cancer is currently being evaluated in a global randomised phase 3 study (NCT03257267).

Clinical trial identification: NCT02383212.

Editorial acknowledgement: Medical writing support under the direction of the authors was provided by Emmanuel Ogunnowo, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc. and Sanofi.

Legal entity responsible for the study: Regeneron Pharmaceutical, Inc. and Sanofi.

Funding: Regeneron Pharmaceutical, Inc. and Sanofi.

Disclosure: D. Rischin: Research funding: Genentech/Roche, Merck, Amgen, Regeneron, Bristol-Myers Squibb. A. González-Martín: Consulting, Advisory, Speakers' bureau and Travel accommodation expenses: AstraZeneca, Tesaro, Roche, Pharmamar. J.Y. Hou: Consultant and receives fees: Foundation Medicine, Massive Bio, Inc. D. Cho: Consulting fees: Pfizer, BMS, Exelixis, Genentech, Prometheus. G.S. Falchook: Funding: Regeneron Pharmaceuticals for trial for submitted work. S. Jabbour: Research funding grants: Merck, Nestle outside of the submitted work. K. Moore: Institutional consultancy (honorarium and ad board) fees: Tesaro, Genentech Roche, Clovis, AstraZeneca (for agents not involved in the SOLO-1 study), Immunogen, VBL Therapeutics, Janssen. M.G. Fury: Employee of and shareholder: Regeneron Pharmaceuticals, Inc.; Patents, royalties, other intellectual property: Regeneron Pharmaceuticals, Inc. M. Feng: Employee and shareholder: Regeneron Pharmaceuticals, Inc., Bayer. J. Li: Employee and shareholder: Regeneron Pharmaceuticals, Inc., Novartis. I. Lowy: Employee of, shareholder of, and fees for travel and accommodation expenses as well as leadership: Regeneron Pharmaceuticals, Inc. M. Mathias: Employee and shareholder: Regeneron Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

959P Molecular profiles as a function of treatment response/progression free survival in a prospective cervical cancer study (RAIDs)

S. Scholl[1], L. De Koning[2], M. Popovic[3], D.L.R. Anne[4], A. Floquet[5], E. Berns[6], G. Kenter[7], A. Kereszt[8], E. Girard[9], H. von der Leyen[10], S. Dureau[11], V. Fourchotte[12], R. Rouzier[12], M. Kamal[1], R. Consortium[1]

[1]Department of Drug Development and Innovation, Institut Curie, Paris, France, [2]Translational Department, Institut Curie, Paris, France, [3]Surgery, Institut of Oncology of Vojvodina, Novisad, Serbia, [4]Radiotherapy, Institut Curie, Paris, France, [5]Oncologie Médicale, Institute Bergonié, Bordeaux, France, [6]Biology, Erasmus, Rotterdam, Netherlands, [7]Gynaecology, NKI, Amsterdam, Netherlands, [8]SeqOmics, Moraholem, Hungary, [9]Bioinformatics, Institut Curie, Paris, France, [10]HCTC, Hanover, Germany, [11]Biometry, Institut Curie, Paris, France, [12]Surgery, Institut Curie, Paris, France

Background: BioRAIDs is a supervised longitudinal collection of tumor and blood together with clinical outcome data in 419 primary cervical cancer patients from 7 European countries (NCT02428842).

Methods: Molecular analysis [Next Generation Sequencing (NGS) at SeqOmics (Hungary) & Reverse Phase Protein array (RPPA) at Institut Curie] was performed on quality-controlled primary tumor samples in 295 patients (70%) who subsequently had received primary radio chemotherapy (RCT). Integrative bioinformatics analyses were performed to identify pathway activations suggesting the need for additional/different therapies.

Results: NGS demonstrated driver Tyrosine Kinase Receptor/ PI3 kinase (TKR/PI3K) pathway mutations in 27%; TKR/PI3K + epigenetic pathway alterations (MLL2, MLL3) in 32 % and epigenetic alterations alone in 13% of patients. At a median follow up of 19 months [2-38], tumors for which no mutations in relevant genes from the TKR/PI3K pathways nor alterations in genes involved in epigenetic signaling appeared to be associated with a significantly better prognostic profile: HR = 2.4 [95% CI: 1.1 – 5.2]. RPPA analysis was carried out separating patients in 3 subgroups according to signaling pathway activation [EMT (epithelial mesenchymal transition), DNA damage and MAPK/PI3K], none of which was associated with bad prognosis.

Conclusions: The high frequency of epigenetic alterations with or without TKR/PI3K pathway mutations, suggests that epigenetically acting drugs (Vorinostat[R]) may be relevant for patients whose tumors have genetic mutations of significance in epigenetically acting enzymes. Relevance of copy number alterations and of other frequently mutated genes (CSMD3, SYNE1), needs to be integrated and cross validated in a larger complementary dataset.

Clinical trial identification: NCT02428842.

Legal entity responsible for the study: Institut Curie.

Funding: This project has received founding from the European Union's Seventh Program for research, technological development and demonstration under grant agreement No 304810.

Disclosure: All authors have declared no conflicts of interest.

960P Phase I study of BVAC-C in HPV type 16 or 18 positive recurrent cervical carcinoma: Safety, clinical activity and immunologic correlates

C.H. Choi[1], H.J. Choi[2], J-W. Lee[2], E-S. Kang[2], D. Cho[2], Y-M. Kim[3], D. Kim[3], H. Seo[4], M. Park[4], W. Kim[5], T. Oh[5], C-Y. Kang[4], B-G. Kim[2]

[1]Obstetrics and Gynecology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Obstetrics and Gynecology, Samsung Medical Center, Seoul, Republic of Korea, [3]Obstetrics and Gynecology, Asan Medical Center, Seoul, Republic of Korea, [4]Molecular Medicine and Biopharmaceutical Sciences, Seoul National University, Seoul, Republic of Korea, [5]Cellid Inc., Seoul, Republic of Korea

Background: BVAC-C is a B cell- and monocyte-based immunotherapeutic vaccine transfected with recombinant HPV E6/E7 gene and loaded with alpha-galactosyl ceramide, a natural killer T cell ligand. It may have activity against HPV positive cancer. This phase I study was performed to determine the safety and tolerability of BVAC-C in patients with HPV type 16 or 18 positive recurrent cervical carcinoma and to preliminarily assess antitumor activity and immunologic correlates.

Methods: Ten patients who had experienced recurrence after at least one prior platinum-based combination chemotherapy, received three intravenous infusion of BVAC-C every 4 weeks in dose-escalating three-patient cohorts at $1x10^7$, $4x10^7$, or $1x10^8$ cells/dose.

Results: BVAC-C was well tolerated: grade 1 fever or myalgia were the most frequently observed without any grade 3 or 4 toxicity. One patient expired 3 weeks following 3rd dose for clinical disease progression. Of the 8 evaluable cases, one partial responses (12.5 %), and four stable diseases (50%) were seen. Three patients are surviving more than a year. Adenocarcinoma and bulky tumor burden were associated with poor response to the therapy. Immunologic response analysis showed that BVAC-C induced activation of natural killer T cells, natural killer cells, and HPV E6/E7 specific CD4 and CD8 T cells upon vaccinations in all patients evaluated. More follow-up results will be presented.

Conclusions: BVAC-C is well tolerated and associated with evidence of antitumor activity in HPV 16 or 18 positive cervical carcinoma. We are now planning further phase 2 efficacy trial.

Clinical trial identification: NCT02866006.

Legal entity responsible for the study: Cellid Inc.

Funding: Cellid Inc.

Disclosure: All authors have declared no conflicts of interest.

961P Risk of secondary hematological malignancies and hematological toxicities in recurrent ovarian cancer patients treated with poly adenosine diphosphate ribose polymerase (PARP) inhibitors maintenance

K.Z. Thein[1], A. Sultan[1], M.H. Zaw[2], M.M. Han[3], R. Yendala[1], M.M. Zin[4], S. Awasthi[1], N. D'Cunha[1], F. Hardwicke[1], C. Jones[1]

[1]Hematology Oncology, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [2]Internal Medicine, The Brooklyn Hospital Center, Brooklyn, NY, USA, [3]Oncologic Emergency, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]Internal Medicine, Kingsbrook Jewish Medical Center, Brooklyn, NY, USA

Background: Most patients with advanced ovarian cancer, the eighth most common cause of cancer death in women worldwide, recur after they receive initial platinum-based chemotherapy. PARP inhibitors showed a synthetic lethality in cancer cells via specific DNA repair defects. Yet, the risk of secondary hematological malignancies (SHM) and hematological toxicities, remains substantial. We undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of SHM and hematological toxicities.

Methods: MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018 were queried. Phase III RCTs that mention any hematological malignancies and toxicities as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) and absolute risk difference (RD) with 95% confidence interval (CI). Fixed effects model was applied.

Results: Three phase III RCTs with 1401 patients were eligible. The study arms used olaparib or niraparib or rucaparib while the control arms utilized placebo. The I^2 statistic for heterogeneity was 16.86, and the heterogeneity X^2 (Cochran's Q) was 2 ($P = 0.30$), suggesting homogeneity. The SHM incidence was 12 (1.28%) in PARP inhibitors group vs 5 (1.07%) in control group. The RR for SHM was 1.14 (95% CI: 0.42 – 3.08, $P = 0.79$) and RD was 0.002 (95% CI: - 0.01 – 0.014, $P = 0.72$). The RR of all-grade side effects were as follows: anemia, 6.57 (95% CI: 4.64 – 9.30, $p < 0.001$); thrombocytopenia, 9.80 (95% CI: 6.19 – 15.50, $p < 0.001$); and neutropenia, 4.13 (95% CI: 2.79 – 6.12, $p < 0.001$). The RR of high-grade adverse effects were as follows: anemia, 28.85 (95% CI: 10.06 – 82.72, $p < 0.001$); thrombocytopenia, 28.74 (95% CI: 8.24 – 100.24, $p < 0.001$); and neutropenia, 5.90 (95% CI: 3.01 – 11.57, $p < 0.001$).

Conclusions: Patients on PARP inhibitors experienced a notable increase in the risk of all grades of hematological toxicities. However, there was no significant increase in the risk of secondary hematological malignancies in PARP inhibitors group. Long-term follow-up of these patients is required to determine the actual relation.

Legal entity responsible for the study: Kyaw Zin Thein/ Texas Tech University Health Sciences Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

963P A phase IIa study of tisotumab vedotin in patients with previously treated recurrent or metastatic cervical cancer: Updated analysis of full cervical expansion cohort

N. Concin[1], I.B. Vergote[1], U.N. Lassen[2], Y. Drew[3], J-P. Machiels[4], H-T. Arkenau[5], M.D. Forster[6], R. Jones[7], M.L. Johnson[8], B.M. Slomovitz[9], J. Spicer[10], N. Cornez[11], C. Gennigens[12], R.L. Coleman[13], K. Windfeld[14], S. Ghatta[15], R.A. Rangwala[15], D.S. Hong[13]

[1]BGOG and University of Leuven, Leuven Cancer Institute, Leuven, Belgium, [2]Department of Oncology, Rigshospitalet, Copenhagen, Denmark, [3]Newcastle University, Northern Institute for Cancer Research, Newcastle-upon-Tyne, UK, [4]Department of Medical Oncology and Early Drug Development, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [5]Sarah Cannon Research Institute, SCRI, London, UK, [6]University College London Cancer Institute, UCLH, London, UK, [7]Velindre Cancer Centre, Cardiff University, Cardiff, UK, [8]Sarah Cannon Research Institute, SCRI, Nashville, TN, USA, [9]Gynecologic Oncology, University of Miami Health System, Miami, FL, USA, [10]Medical Oncology, King's College London, London, UK, [11]Oncology, Centre Hospitalier Universitaire et Psychiatrique de Mons-Borinage, Mons, Belgium, [12]Centre Hospitalier Universitaire, Chu-Sart-Tilman, Liege, Belgium, [13]The University of Texas, MD Anderson Cancer Center, Houston, TX, USA, [14]Genmab, A/S, Copenhagen, Denmark, [15]Genmab, US, Inc., Princeton, NJ, USA

Background: Treatment options for recurrent or metastatic cervical cancer are limited, with no standard of care beyond 1L treatment and 2L response rates of ~13%. Tisotumab vedotin (TV) is an antibody-drug conjugate comprised of a fully human monoclonal antibody specific for tissue factor (TF) conjugated to the microtubule disrupting-agent monomethyl auristatin E (MMAE) via a protease cleavable linker. TV is being evaluated in GEN701 (innovaTV 201), a Phase I/IIa dose-escalation and expansion study in patients (pts) with previously treated recurrent locally advanced or metastatic solid tumours. A previous report of the preliminary expansion cohort for cervical cancer (n = 34) showed an investigator (INV)-assessed response rate of 32% (26% confirmed) (Vergote et al., ESMO 2017 abstract #931O). INV response for the full cervical expansion cohort (N = 55) and response by independent imaging review (IIR) (n = 34) are presented here.

Methods: Key eligibility criteria included recurrent or metastatic cervical cancer that progressed on standard therapy, adequate organ function and ECOG 0-1. TV 2 mg/kg Q3W was given until progression, toxicity or withdrawal. Activity and safety were assessed by RECIST 1.1 and CTCAE 4.03, respectively. Enrollment started in November 2015 and continued through May 2018.

Results: The full cohort has 55 pts (median age was 47 y [21-74]). Updated efficacy by INV review, safety data, and response by TF expression will be presented. Median age in the first 34 pts was 44 y (21-74) and pts received a median of 2 prior lines for recurrent or metastatic disease. ORR by IIR of 41% (95% CI: 25%-59%), including 1 CR and 13 PR. 8 (1 CR, 7 PRs) were confirmed (24%; 95% CI: 11%-41%). Confirmed response rate was concordant between INV and IIR (26% and 24%). Median duration of response was 4.9 months and median PFS was 4.2 months by IIR.

Conclusions: These data demonstrate that TV has encouraging activity in previously treated recurrent or metastatic cervical cancer, an underserved population with a high unmet need, and that responses observed with TV are numerically higher than those achieved by historical controls. These data support the continued investigation of TV in this population.

Clinical trial identification: NCT02001623.

Editorial acknowledgement: Medical writing and editorial support provided by Ogilvy CommonHealth, during the development of this abstract, under the guidance of the primary author Dr. Nicole Concin, and funded by Genmab A/S and Seattle Genetics, Inc.

Legal entity responsible for the study: Genmab A/S and Seattle Genetics, Inc.

Funding: Genmab A/S and Seattle Genetics, Inc.

Disclosure: I.B. Vergote: Consulting/Advisory board: Roche NV, Genmab A/S, Advaxis Inc, Morphotek Inc, F. Hoffmann-La Roche Ltd, Cerulean Pharma Inc, Novocure GMBH, AstraZeneca, Mateon Therapeutics Inc, Immunogen Inc, Eli Lilly Benelux NV, Amgen Inc, Theradex Europe Limited, Pfizer Inc, Debiopharma International SA, Vifor Pharma Belgi€e NV, Novartis Pharma AG, MSD Belgium BVBA, Janssen-Cilag, Bayer Pharma AG, Clovis Oncology, Takeda, PharmaMar, Oncoinvent; Contracted research: Morphotek; Grants/corporate sponsored research: Amgen, Roche; Accommodations/travel expenses: Tesaro, Clovis Oncology, Takeda, PharmaMar, Roche, Genmab, Oncoinvent. M.L. Johnson: Research funding: BerGenBio, Lilly, EMD Serono, Janssen, Mirati Therapeutics, Genmab, Pfizer, AstraZeneca, Genentech/Roche, Stemcentrix, Novartis, Checkpoint Therapeutics, Array BioPharma, Regeneron, Apexigen, Abbvie, Tarveda, Adaptimmune, Syndax, Neovia, Boehringer Ingelheim, Sanofi, Hengrui Therapeutics, INC, Merck, Daiichi-Sankyo, Lycera, G1 Therapeutics, Dynavax; Consulting/advisory: Genentech/Roche, Celgene, Boehringer Ingelheim, Sanofi, Mirati, LOXO; Contract lobbyist: Astellas, Otsuka Pharmaceuticals. R.L. Coleman: Grant funding and Scientific Steering Committee roles: Janssen, AstraZeneca, Clovis, Merck, Abbvie, Gamamab, Genmab, Samumed, Roche/Genentech. K. Windfeld: Employee of Genmab; Stock ownership Genmab. S. Ghatta, R.A. Rangwala: Employee of Genmab. D.S. Hong: Research/Grant funding: Adapitmmune, Abbvie, Amgen, AstraZeneca, Bayer, BMS, Daiichi-Sanko, Eisai, Genentech, Genmab, Ignyta, Infinity, Kite Kyowa, Lilly, LOXO, Mirati, Merck, Medimmune, Molecular Template, Novartis, Pfizer, Takeda; Travel, Accommodations, Expenses: Loxo, MiRNA; Consulting or Advisory role: Baxter, Bayer, Guidepoint Global, Janssen; Other ownership interests: Molecular Match (Advisor), Oncoresponse (founder). All other authors have declared no conflicts of interest.

964P Preoperative c-reactive protein and thrombocyte count as potential markers for longterm survival in ovarian cancer

E.I. Braicu[1], J. Sehouli[2], R. Richter[2], I.B. Vergote[3], N. Concin[3], E. van Nieuwenhuysen[3], P. Achimas[4], A. Berger[5], B. Fetica[4], S. Mahner[6], J. Glajzer[2], A. Papadia[7], L. Woelber[8], M.L. Gasparri[7], A. Vanderstichele[9], P. Benedetti Panici[10], M. Mueller[7], I. Ruscito[2], J. Zimmer[2], H. Woopen[1]

[1]Department for Gynecology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Department for Gynecology, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [3]Department of Gynecology, University Hospitals Leuven, Leuven, Belgium, [4]Gynecological Oncology, Oncological Institute Ion Chiricuta, Cluj-Napoca, Romania, [5]Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria, [6]Gynaecology, AGO Study Group & University Medical Center Hamburg-Eppendorf and University of Munich; University of Munich, Munich, Germany, [7]Department of Obstetrics and Gynecology, University of Bern and Inselspital University Hospital of Bern, Bern, Switzerland, [8]Department for Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [9]Gynaecological Oncology, University Hospitals Leuven, Leuven, Belgium, [10]Department of Gynecology and Obsetrics, Università La Sapienza, Rome, Italy

Background: Aim of this study was to evaluate the predictive role for C-reactive protein (CRP) and thrombocyte count as surrogate markers for the interleukin-6 pathway for longterm survival with ovarian cancer.

Methods: Patients and methods: Within the tumorbank ovarian cancer (TOC) preoperative CRP values and thrombocyte counts were collected for longterm survivors (survival of $\geq$ 8 years after initial diagnosis) from seven gynecologic-oncology centers as well as classical ovarian cancer patients diagnosed in the same timeframe (survival < 5 years after initial diagnosis). Receiver operating characteristics (ROC) curves and logistic regression analyses were conducted to evaluate differences between cohorts.

Results: In this study 336 longterm survivors (LTS) and 172 control patients could be included. There was no difference in preoperative thrombocyte count with a median of 326/nl in LTS (n = 136) vs. 325/nl in control patients (n = 151), $p = 0.59$. Regarding preoperative CRP values at initial diagnosis there was a significant difference in both univariate and multivariate analyses: Median CRP was 9.2 mg/l in LTS (n = 56) compared to 18.4 mg/l in control patients (n = 85), $p = 0.002$. ROC-curves showed an area under the curve of 0.66 (95% CI 0.56-0.75), $p = 0.002$. After adjusting for age, FIGO stage, grading and histology there was still a significant difference between the two cohorts ($p = 0.002$). Patients with CRP <1.3 mg/l had a 15-fold higher chance to survive longer than eight years compared to patients with a CRP >40 mg/l at initial diagnosis ($p = 0.001$, 95% CI 3.3-70.5).

Conclusions: Preoperative C-reactive protein was significantly lower in longterm survivors compared to classical ovarian cancer patients indicating the potential role of CRP as prognostic marker for longterm survival. Further studies are highly warranted in order to gain more insight in this unique and sparcely known patient cohort.

Legal entity responsible for the study: Charité Medizinische Universitaet.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

965P Prognostic factors in patients with uterine leiomyosarcoma: A multiinstitutional retrospective study from the Japanese gynecologic oncology group

K. Takehara[1], N. Yamashita[2], T. Motohashi[3], K. Harano[4], T. Nakanishi[5], H. Tokunaga[6], N. Susumu[7], Y. Ueda[8], Y. Yokoyama[9], Y. Watanabe[5], R. Watanabe[10], N. Teramoto[11], H. Tsuda[12], T. Saito[13]

[1]Gynecologic Oncology, Shikoku Cancer Center, Matusyama, Japan, [2]Clinical Research Center, Shikoku Cancer Center, Matsuyama, Japan, [3]Obstetrics and Gynecology, Kuwana City Hospital, Kuwana, Japan, [4]Breast Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [5]Obstetrics and Gynecology, Tohoku Medical and Pharmaceutical University, Sendai, Japan, [6]Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan, [7]Obstetrics and Gynecology, International University of Health and Welfare, Narita, Japan, [8]Obstetrics and Gynecology, Osaka University, Osaka, Japan, [9]Obstetrics and Gynecology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, [10]Pathology, National Cancer Center Hospital, Tokyo, Japan, [11]Pathology, Shikoku Cancer Center, Matusyama, Japan, [12]Basic Pathology, National Defense Medical College Hospital, Tokorozawa, Japan, [13]Gynecology Service, National Kyushu Cancer Center, Fukuoka, Japan

Background: Uterine leiomyosarcomas (uLMSs) are rare and aggressive tumours. Despite complete tumour resection, uLMSs are destined to relapse, and its prognosis is poor. The prognostic factors are not sufficiently known.

Methods: We performed a multi-institutional, retrospective study of women with stage I–IV uLMS, who were diagnosed between 2000 and 2012. For all cases, the histopathological slides of primary lesions were submitted to the central pathological review. Data obtained from medical records included clinicopathological factors, treatment and outcome information.

Results: In total of 259 patients (median age 54 years) were confirmed to have uLMS of which 159 (61%) were stage I, 19 (7%) were stage II, 21 (8%) were stage III, 58 (22%) were stage IV and 2 (1%) were unknown. The median disease-free survival (DFS) period was 18.2 months [95% confidence interval (CI) 13.6–24.1], and the median overall survival (OS) period was 44.2 months [95% CI 32.7–66.2]. Overall, 161 (62%) patients received adjuvant treatment; 155 (60%) received chemotherapy and 8 received radiotherapy. With regard to chemotherapy regimens, 65 (42%) were given docetaxel and gemcitabine; 32 (21%) were given Ifosfamide, doxorubicin and cisplatin; 10 (6%) were administered taxane and carboplatin; 39 (25%) were given other regimens and 9 (6%) were unknown. In a multivariate analysis, stage III–IV disease, high serum lactate dehydrogenase (LDH) level and no adjuvant treatment were significantly associated with shorter median DFS and OS periods. Even in stage I of the disease, high LDH level and no adjuvant treatment were significantly associated with shorter median DFS and OS.

Conclusions: Advanced stage, high LDH level and no adjuvant treatment were associated with poor prognoses. In stage I of the disease, when the tumour was confined to the corpus uteri, postoperative adjuvant chemotherapy was associated with improved survival.

Editorial acknowledgement: Enago for English language review.

Legal entity responsible for the study: Japanese Gynecologic Oncology Group.

Funding: Eisai, Ono Pharmaceutical Co., Kaken Pharmaceutical Co., Kyowa Hakko Kirin Co., Sanofi K. K., Sawai Pharmaceutical Co., Shionogi & Co., Zeria Pharmaceutical Co., Taiho Pharmaceutical Co., Daiichi Sankyo Company, Chugai Pharmaceutical Co., Nihon Kayaku Co., Bristol-Myers Squibb Company, Yakuly Honsha Co., Janssen Pharmaceutical K.K., Roche Diagnostics K.K., Fuji Pharma Co., Astra Zeneca, ASKA Pharmaceutical Co.

Disclosure: All authors have declared no conflicts of interest.

966P Screening for inherited cancer syndromes in Chinese patients with endometrial cancer

H. Wang[1], W. Tian[1], R. Bi[2], Y. Ren[1], H. He[3], S. Shi[4], B. Shan[1], Q. Wang[5]

[1]Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, Shanghai, China, [2]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China, [3]Medical Affairs, Shanghai Topgen Bio-Pharm Co, Ltd., Shanghai, China, [4]Research and Development, Shanghai Topgen Bio-Pharm Co, Ltd., Shanghai, China, [5]Plateforme de Génomique des Cancers, Centre Léon Bérard, Lyon, France

Background: Endometrial cancer (EC) is a component of several cancer syndromes especially the Lynch syndrome, caused by the germline mutations in corresponding cancer predisposition genes. This study aims to outline the mutation prevalence, clinical and biological characteristics of the cancer susceptibility genes in Chinese EC patients, and to establish a screening criterion for identifying affected individuals.

Methods: The pathologic diagnosed EC patients meeting at least one of the following criteria were involved: (1) diagnosed before 50 years, (2) personal or (3) family history of Lynch related cancers, (4) loss of any MMR protein expression by immunohistochemistry (IHC). Next generation sequencing (NGS) was used for the germline mutation screening in 29 genes (APC, ATM, AXIN2, BLM, BMPR1A, BRCA1, BRCA2, BUB1B, CDH1, CDKN2A, CHEK2, EPCAM, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, PALB2, PMS1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11 and TP53). Multiplex ligation-dependent probe amplification (MLPA) method were used for quantitative detection of genomic deletions and duplications.

Results: Of the 199 patients recruited, 71 (35.7%) were diagnosed before 50 years, 26 (13.1%) had a second LS related cancer, 50 (25.1%) had a family history and 157 (78.9%) performed dMMR by IHC. We identified 43 (21.6%) deleterious mutations, of which, 41 located in LS associated genes (10 MLH1, 17 MSH2, 11 MSH6 and 3 PMS2) and 2 located in non-LS genes (1 BRCA1 and 1 PALB2). 58 uncertain significance variations were also identified in 53 patients (26.6%) while 20 (34.5%) of them were located in LS genes. Two suspected genomic deletion in MSH2 were detected and were still under further verification. 18 (72%) deleterious mutations were detected in the 25 patients meeting 3 or 4 inclusion criteria and 12 (25%) were detected in 48 patients meeting 2 criteria.

Conclusions: To our knowledge, this is the first NGS based study focus on inherited EC in Asian population. The high frequency of positive results indicated that multi-gene panel testing could be recommended to the patients with high risk of hereditary EC. The selection criterion used in current study is feasible and at a high sensitivity for screening the suspected inherited individuals.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

967P Clinical relevance of circulating MACC1 and S100A4 transcripts in serum of ovarian cancer patients

P. Wimberger[1], T. Link[1], P. Herrmann[2], D. Kobelt[2], Y. Vassileva[1], F. Kerstin[3], J.D. Kuhlmann[1], U. Stein[2]

[1]Department of Gynecology and Obstetrics, Technische Universität Dresden, Dresden, Germany, [2]Dept. Translational Oncology of Solid Tumors, Charité - Universitätsmedizin Berlin, Berlin, Germany, [3]DRK-Blood Donor Service, ITM Plauen, Dresden, Germany

Background: Metastasis-associated in colon cancer 1 (MACC1) and S100 calcium binding protein A4 (S100A4) promote metastasis. Their overexpression in the tumor was proposed as a prognostic and/or predictive biomarker for a variety of solid malignancies, including ovarian cancer. However, clinical relevance of circulating MACC1 and S100A4 transcripts as blood-based biomarkers for ovarian cancer is unknown. Therefore, the objective of our study was to systematically track serum levels of both transcripts in the course of surgery and adjuvant therapy and to analyze their clinical relevance for ovarian cancer.

Methods: The levels of MACC1 and S100A4 transcripts were analyzed in a total of 318 serum samples from 79 ovarian cancer patients (thereof 80% FIGO III or IV), including samples at primary diagnosis and at 4 follow-up time points in the course of treatment. MACC1 was relatively quantified by RT-qPCR and S100A4 was absolutely quantified by digital droplet PCR.

Results: MACC1 and S100A4 transcripts were significantly elevated in serum of ovarian cancer patients, compared to healthy controls ($p = 0.024$;$p<0.001$) and showed a highly concordant (CA125 independent) dynamic in the course of treatment. Higher levels of MACC1 and S100A4 at primary diagnosis paralleled advanced disease ($p = 0.023$;$p=0.004$) and predicted ineffective primary debulking surgery with no achievement of a macroscopically complete tumor resection ($p = 0.011$;$p=0.006$). Moreover, higher levels of MACC1 and S100A4 at primary diagnosis indicated poor DFS ($p = 0.0035$; $p = 0.0019$) and OS ($p < 0.001$;$p=0.001$).

Conclusions: This is the first liquid biopsy approach, systematically analyzing MACC1 and S100A4 transcripts in ovarian cancer and proposing their prognostic capacity at primary diagnosis.

Legal entity responsible for the study: TU Dresden.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

968P Outcomes of ovarian clear cell carcinoma (OCCC) of the Vall d'Hebron Hospital/Vall d'Hebron Institute of Oncology (VHIO)

F. Amair Pinedo[1], L. Fariñas-Madrid[1], V. Rodriguez Freixinos[1], F.J. Ros Montañá[1], G. Villacampa[2], R. Dienstmann[2], A. Oaknin[1]

[1]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [2]Oncology Data Science, Vall d'Hebron University Hospital, Barcelona, Spain

Background: OCCC is a rare entity linked to good prognosis at early stages but chemoresistance and poor survival in advanced setting. Molecular heterogeneity is common in OCCC, with PI3K/mTOR pathway alterations as most common drivers.

Methods: Consecutive series of 75 patients (pts) with OCCC treated in VHH/VHIO from 2000 to 2016. Objective: to study outcomes with standard therapy (progression-free survival [PFS], overall survival [OS]) and treatment selection in a chemotherapy (ChT) resistant setting based on molecular profiling performed in house (targeted NGS panel).

Results: Median age was 55 years (y), FIGO (2014) stage I 51%, II 11%, III 33%, IV 5%. Primary surgery was performed in 92% achieving optimal cytoreduction in 86%. All pts received first-line of platinum (Pt)-based ChT. With a median follow-up of 9.5 y,

50.6% pts relapsed (I 34.2%, II 62.5%, III 68%, IV 50%), median OS was 11.2 y (CI95%: 6-NR). Factors significantly associated with relapse and death in univariate Cox models were ECOG performance status and stage at diagnosis ($p < 0.001$). At 1st and 2nd relapse, 58 and 50% remained Pt-sensitive, respectively. Median PFS with therapies after 1st relapse in a Pt-sensitive setting (91% Pt combos) was 12.6 months (m) (CI95% 9.5-25.4) and in Pt-resistant setting (69% non-platinum ChT) 3 m (2.5-NA). In total, 18 pts (24%) had genomic profiling (7 PIK3CA mut, 1 BRCA1 mut, 1 MSH6 mut), and 16 pts (21%) received experimental agents after 1st relapse (8 antiangiogenic, 4 targeted or immunotherapy unmatched, 4 targeted matched [3 PI3K inh and 1 PARP inh]). Median PFS was 4.8, 5.6 and 9.6 m respectively. When compared to non-Pt ChT in a Pt-resistant setting increased PFS was found with matched targeted agents (HR = 0.26, CI95% 0.1-1).

Conclusions: As reported in the literature, in our cohort, OCCC are more frequent diagnosed at early stages having a better prognosis. In the relapse setting Pt sensibility and Pt-based ChT imply better outcomes. However, in the Pt-resistant setting targeted therapies result in better PFS compared to ChT. Molecular profiling allows to select matched agents which may improve outcomes in this poor prognosis population. Further research in molecular characterization and matched targeted therapy is an unmet need.

Legal entity responsible for the study: Vall d'Hebron Institute of Oncology (VHIO).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

969P A systematic review and meta- analysis of randomized controlled trials to evaluate the risk of gastrointestinal and hepatic toxicities in patients with recurrent ovarian cancer treated with poly adenosine diphosphate ribose polymerase inhibitors maintenance

K.Z. Thein[1], A. Sultan[1], M.H. Zaw[2], M.M. Han[3], A.M. Hein[4], H.H. Aung[5], S. Awasthi[1], C. Jones[1], F. Hardwicke[1], N. D'Cunha[1]

[1]Hematology Oncology, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [2]Internal Medicine, The Brooklyn Hospital Center, Brooklyn, NY, USA, [3]Oncologic Emergency, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]Internal Medicine, Nassau University Medical Center, New York, NY, USA, [5]Internal Medicine, Kingsbrook Jewish Medical Center, New York, NY, USA

Background: Inhibition of poly adenosine diphosphate ribose polymerase (PARP) enzymes resulted in synthetic lethality in ovarian cancer cells by terminating an alternative DNA repair pathway in homologous recombination deficient tumors. Many PARP inhibitors have shown to improve survival with noteworthy safety concerns. We undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of gastrointestinal (GI) and hepatic toxicities.

Methods: We conducted a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018. Phase III RCTs that mention GI toxicities and elevation of liver function tests (LFT) either aspartate or alanine aminotransferase as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Fixed effects model was applied.

Results: Three phase III RCTs with 1401 patients were eligible. The study arms used olaparib or niraparib or rucaparib while the control arms utilized placebo. The randomization ratio was 2:1 in all studies. The RR of all-grade side effects were as follows: diarrhea, 1.29 (95% CI: 1.05 – 1.58, P = 0.015); dyspepsia, 1.73 (95% CI: 1.20 – 2.49, P = 0.003); nausea, 2.11 (95% CI: 1.86 – 2.40, P < 0.001); vomiting, 2.20 (95% CI: 1.76 – 2.75, P < 0.001); dysgeusia, 4.38 (95% CI: 3.00 – 6.41, P < 0.001); and elevated LFT, 4.74 (95% CI: 2.82 – 7.95, P < 0.001). The RR of high-grade side effects were as follows: diarrhea, 1.225 (95% CI: 0.992 – 1.512, P = 0.060); nausea, 4.35 (95% CI: 1.45 – 13.06, P = 0.009); vomiting, 3.39 (95% CI: 1.19 – 9.63, P = 0.02); and elevated LFT, 10.19 (95% CI: 2.47 – 42.06, P = 0.001).

Conclusions: Our meta-analysis demonstrated that PARP inhibitors increased the risk of all grades of GI and hepatic toxicities with a relative risk of 10.19 for grade 3 and 4 elevated LFT. These toxicities have significant impact on patients' quality of life and may ultimately affect patients' compliance. Timely intervention with proper supportive care is necessary.

Legal entity responsible for the study: Kyaw Zin Thein/ Texas Tech University Health Sciences Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

970P Evaluation of chemotherapy response score and lymphocytic infiltration as prognostic markers in ovarian cancer patients treated with neoadjuvant chemotherapy

M. Liontos[1], M. Sotiropoulou[2], M. Kaparelou[1], K. Tzannis[1], G. Tsironis[1], A. Kyriazoglou[1], A. Tsiara[1], R. Zakopoulou[1], K. Koutsoukos[1], F. Zagouri[1], D. Vlachos[3], N. Thomakos[3], D. Haidopoulos[3], A. Rodolakis[3], M.A.C. Dimopoulos[1], A. Bamias[1]

[1]Oncology Unit, Department of Clinical Therapeutics, Alexandra Hospital, Athens, Greece, [2]Pathology Department, Alexandra Hospital, Athens, Greece, [3]Obstetrics and Gynecology Department, Alexandra Hospital, Athens, Greece

Background: Neoadjuvant Chemotherapy (NACT) followed by Interval Debulking Surgery (IDS) is an alternative frontline treatment in patients with advanced Epithelial Ovarian Cancer (EOC). Histopathologic assessment of tumor post NACT is an ideal mean of response to treatment. The present study aims to characterize the pathological response and to examine its prognostic significance in these patients.

Methods: Medical records of women with EOC treated at Alexandra Hospital from 2011 to 2016 were retrospectively identified. Clinicopathological data, treatment and survival data were analyzed. IDS specimens were reviewed by study pathologist and Chemotherapy Response Score (CRS), lymphocytic infiltration, necrosis and mitosis were assessed. Survival differences were estimated using the long-rank test.

Results: 55 patients with EOC treated with NACT were identified, 48 had complete clinical and pathological data. Median age was 63 years. All patients had high grade disease and 45 of them had serous carcinoma. At baseline 38 patients had stage IIIc disease and 10 stage IV. All patients received Paclitaxel-Carboplatin combination for 3 cycles. 20 patients had complete debulking (no macroscopic residual disease), 18 had optimal (macroscopic disease <1cm) and 7 suboptimal. 22 patients received also bevacizumab as part of their treatment post IDS. CRS assessed at omentum predicted PFS when adjusted for age, stage, debulking status (complete, optimal, suboptimal) and post IDS bevacizumab administration (mPFS CRS 1vs2vs3: 11.9-14-19.5 months 95% CI [7.4-18.3], [12.2-20.7], [13.5-31.3]). Lymphocytic invasion was associated with improved OS (log-rank test p = 0.022). Presence of necrosis and mitosis per HPF did not predict either PFS or OS. BRCA status was known for 19 patients and presence of BRCA1/2 mutations was strongly correlated with lymphocytic infiltration (P = 0.011) but not CRS (p = 0.801).

Conclusions: Our study confirms the predictive value of CRS in EOC patients treated with NACT and IDS, but also demonstrates the prognostic significance of lymphocytic infiltration in IDS specimens. The later was associated with presence of BRCA mutations with obvious therapeutic implications.

Legal entity responsible for the study: Michalis Liontos.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

971P Embryonic protein nodal as a novel marker of progression and drug resistance in ovarian cancer

O. Bilyk[1], L. Lee[1], N. Le[2], L. Cook[3], M. Koebel[4], L. Postovit[1]

[1]Oncology, University of Alberta, Edmonton, AB, Canada, [2]Cancer Control Research, British Columbia Cancer Research Center, Vancouver, BC, Canada, [3]Internal Medicine, University of New Mexico, New Mexico, NM, USA, [4]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada

Background: Cancer cells can exploit normally dormant embryonic stem cell pathways to promote cancer progression. Studying embryonic signaling pathways in aggressive cancers has led to the discovery of the re-expression of the embryonic protein Nodal. It maintains pluripotency and cell plasticity of human embryonic stem cells. In many cancers Nodal signalling promotes tumor growth and metastasis. The objective of this study is to investigate the role of Nodal as a potential biomarker of ovarian cancer (OC) progression and resistance to chemotherapy.

Methods: We applied bioinformatics approach and RNA sequencing to investigate the impact of Nodal on biological processes in OC cells and disease outcome in OC patients (TCGA data). In vitro assays designed to assess cancer stem cell phenotypes and chemoresistance in OC cells wherein Nodal was overexpressed, or knocked out with CRISP/Cas9 genome editing were conducted. We performed IHC staining of Nodal in tissue microarrays of high-grade serous OCs (HGSOC) to evaluate prognostic significance of Nodal. HGSOC samples were obtained from Ovarian Cancer in Alberta and British Columbia study (OVAL-BC) cohort of OC patients (563 HGSOC samples).

Results: RNA seq data showed that Nodal induces transcriptional reprogramming in OC cells via altering immune response, metabolism and drug resistance gene expression. In vitro, we showed that Nodal is a stress response gene which expression and protein increased in OC cells after treatment with cisplatin/carboplatin and retained for 96h after drug withdrawal. OC cells overexpressing Nodal characterized by increased resistance to cytostatic drugs, tumorigenicity and cell plasticity (partial EMT and stem cell-like phenotype). Analysis of TCGA microarray data and IHC staining of tissue microarrays of HGSOCs determined that Nodal predicts poor overall and progression-free survival in HGSOC patients.

Conclusions: Nodal predicts poor survival in HGSOC patients and likely drives tumorigenic potential and resistance to platinum in OC cells by promoting cancer stem cell plasticity and upregulating target genes involved in immune response, drug

resistance and metabolism, and may hold promise as a therapeutic target to prevent disease recurrence following chemotherapy.

Legal entity responsible for the study: Lynne Postovit.

Funding: CIHR.

Disclosure: All authors have declared no conflicts of interest.

972P Bcl-2 proteins expression and response to navitoclax in platinum resistant/refractory recurrent ovarian cancer (PROC)

P.E. Brachet[1,2,3], F. Joly Lobbedez[1,2], M. Fabbro[4], A. Leary[3,5,6,7], J. Medioni[8], P. Follana[9], A.F. Lesoin[10], J-S. Frenel[11], S. Abadie Lacourtoisie[12], A. Floquet[13], L. Gladieff[14], B. You[3,15], C. Gavoille[16], E. Kalbacher[17], M. Briand[2], P.A. Just[2,18], C. Blanc-Fournier[2,19], F. Giffard[2], B. Clarisse[1], L. Poulain[2]

[1]Clinical Research, UNICANCER Centre Francois Baclesse, [2]INSERM U1086 "ANTICIPE" (Interdisciplinary Research Unit for Cancers Prevention and Treatment, Axis BioTICLA "Biology and Innovative Therapeutics for Ovarian Cancers"), [3]GINEGEPS, GINECO Group on Early Phase Studies, [4]Oncology Department, UNICANCER ICM Regional Cancer Institute of Montpellier, Montpellier, France, [5]Gynecological Unit, UNICANCER Gustave Roussy Cancer Center, Villejuif, France, [6]INSERM U981, [7]Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), [8]Medical Oncology Department, AP-HP Hôpital Européen Georges Pompidou, Paris, France, [9]Medical Oncology, UNICANCER Centre Anticancer Antoine Lacassagne, Nice, France, [10]Oncology Department, UNICANCER Centre Oscar Lambret, Lille, France, [11]Oncology Department, UNICANCER ICO Institut de Cancerologie de l'Ouest René Gaudducheau, Saint-Herblain, France, [12]Oncology Department, UNICANCER Institut de Cancérologie de l'Ouest, Site Angers, Angers, France, [13]Oncologie Médicale, UNICANCER Institute Bergonié, Bordeaux, France, [14]Oncology Department, UNICANCER, Institut Claudius Regaud- IUCT-Oncopole, Toulouse, France, [15]Oncology Department, Centre Hospitalier Lyon Sud, Paris, Pierre Bénite, France, [16]Oncology Department, UNICANCER Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandoeuvre les Nancy, France, [17]Oncology Department, CHU Besançon, Hôpital Jean Minjoz, Besançon, France, [18]Anatomo-pathology, AP-HP Hôpital Cochin and GINEGEPS, Paris, France, [19]Anatomo-pathology, UNICANCER, Centre François Baclesse, Caen, France

Background: Here is no convincing active treatment for patients with PROC. Anti-apoptotic bcl-2 proteins have been implicated in chemotherapy (CT) resistance. In pre-clinical studies, we demonstrated promising activity of Navitoclax, an anti-apoptotic inhibitor of Bcl-2 family, in ROC tumors, suggesting a potential action in platinum resistant pts. We conducted a multicentric phase II trial of Navitoclax monotherapy and reported modest efficacy (ESMO 2017, abstract #2269). Here we aimed to describe the relationship between Bcl-2 protein expression and response to Navitoclax; we also reported response to subsequent line of CT.

Methods: Pts (N = 46) with high grade serous PROC received oral Navitoclax (150 mg daily for 7 days followed by 250 mg daily) until disease progression or toxicity. All pts had a biopsy of relapsed disease before navitoclax initiation to assess the expression level of Bcl-2 proteins by histoimmunochemistry (IHC), as low, medium or high. We first evaluated the efficacy of Navitoclax for pts with high BIM level, then with high BIM expression combined with low Mcl-1 and/or phospho-ERK. Response to subsequent CT was also described.

Results: 44 pts (with median of 4 prior lines) were assessable for efficacy: PFS was 50 days [6-234] with 1 partial response (PR), 15 stable diseases (SD). IHC data were available for 35 pts. BIM was highly expressed in 9 pts, 4 of them with PR/SD ($p = 0.68$). Among them, 7 had a low expression of Mcl-1 and/or phospho-ERK, of whom 4 with PR/SD, showing no evidence of relation with clinical response. After Navitoclax, 32 pts were retreated with CT: 4PR and 9SD were noted, including 11 pts with long response (6-13 months). Median delay from previous platinum-based treatment to subsequent CT was 9 months [2-23] for PR/SD pts. Especially, 12 pts received platinum after Navitoclax with high response rate (3PR/4SD, 58%), median delay from previous platinum-CT was 18 months.

Conclusions: BIM expression, alone or combined with Mcl-1 and/or pERK, is not predictive of Navitoclax benefit. High proportion of PROC pts response to platinum rechallenge; the potential implication of Navitoclax needs further explorations. Other Bcl-2 family proteins (activator BH3-only BID and PUMA) expression may be more relevant. This trial is granted by the French Cancer Research Hospital Program in 2011 and the Mariapia Bressan award in GINEGEPS 2014.

Clinical trial identification: Eudract: 2015-000193-35.

Legal entity responsible for the study: Centre François Baclesse.

Funding: Abbvie.

Disclosure: All authors have declared no conflicts of interest.

973P Expression of CD4, CD8 and Foxp3 and its clinical significance in neoadjuvant chemotherapy for locally advanced cervical cancer

X. Yin

Obstetrics and Gynecolgoy, Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Cervical cancer ranks first among gynecologic malignancies. Neoadjuvant chemotherapy combined with surgery is currently a recommended treatment for locally advanced cervical cancer, however the patient's prognosis is still poor and easy to recur even if the chemotherapy works significantly. We need more effective assessment method for local advanced cervical cancer. Therefore, we evaluated relationship between chemotherapeutic effect and prognosis on the expression of immunological biomarkers including CD4+, CD8+ and Foxp3 pre- and post-neoadjuvant chemotherapy for locally advanced cervical cancer.

Methods: CD4+, CD8+ and Foxp3 expression by IHC in 45 cases of locally advanced (IB2-IIB) cervical cancer pre- and post-neoadjuvant chemotherapy, computer software was used to quantitatively analyzed. The relationship between IHC results and clinicopathological characteristics, chemotherapy efficacy, PFS and OS was analyzed by SPSS software.

Results: The expression of CD4, CD8 and Foxp3 in locally advanced cervical cancer before and after neoadjuvant chemotherapy was not related to patients' age and size of tumor ($P > 0.05$), which was related to FIGO staging and histological grade. The expression of CD4 and CD8 increased significantly after chemotherapy ($P = 0.016$, $P = 0.009$), while the expression of FoxP3 decreased significantly ($P = 0.002$). There was a significant correlation between the expression of CD8 ($P = 0.005$), Foxp3 ($P = 0.041$) and PFS in locally advanced cervical cancer, while CD4 had no significant correlation ($P = 0.581$). However, there is no significant correlation between OS and CD4 ($P = 0.686$), CD8 ($P = 0.858$) and Foxp3 ($P = 0.689$).

Conclusions: CD4, CD8 and Foxp3 are associated with tumor staging and pathological grading in neoadjuvant chemotherapy for locally advanced cervical cancer, and the expression change of CD8 and Foxp3 before and after chemotherapy can be used as an independent prognostic indicator.

Legal entity responsible for the study: Wen Di.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

974P Clinical study on the efficacy of apatinib treatment for advanced ovarian cancer after second-line chemotherapy failure

S. Sun, D. Zhai, C. Yu

Gynecologic Department of Traditional Chinese Medicine, Changhai Hospital of Shanghai, Shanghai, China

Background: Ovarian carcinoma has the highest mortality rate among gynecologic malignancies. Primary drug resistance and multi-drug resistance are major clinical obstacles to treatment and is the main reason for the dismal 5-year survival rate of patients. Apatinib is independently developed in China as an effective small-molecule tyrosine kinase inhibitor. It mainly functions by competitively blocking the binding of VEGF with VEGFR-2 and auto-phosphorylation of VEGFR-2, thereby inhibiting the function of VEGF in stimulating endothelial cell proliferation and migration and reducing microvascular density to elicit its anti-tumor effects.

Methods: This study is a prospective, open label, single-arm clinical trial aimed to evaluate the efficacy and safety of apatinib mesylate as treatment after failure of second-line chemotherapy in patients with advanced epithelial ovarian cancer. The study enrolled 20 patients, and 17 were evaluated. Patients received an oral dosage of apatinib (500 mg or 250 mg) once daily for 28 days as an observation cycle. The efficacy of the treatment was evaluated after three treatment cycles. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and adverse events (AEs) were assessed.

Results: After 3 cycles of treatment, 6 (35.3%) and 2 (11.8%) patients achieved partial response (PR) and stable disease (SD), respectively. The ORR and DCR were 35.3% and 47.1%, respectively. The efficacy of apatinib was not significantly different between patients with initial dosages of 500 mg (ORR, 30%; DCR, 30%) and 250 mg (ORR, 42.8%; DCR, 71.4%). The median PFS was 2.2 months (95% confidence interval (CI), 1.0m-8.9m) and the median OS was 6.3months (95% CI, 1.5m-12.8m). The most common AEs were hypertension (70.6%), hand-foot syndrome (52.9%), and oral mucosa damage (35.3%).

Conclusions: In conclusion, oral apatinib treatment was efficacious, safe, and had no serious adverse effects in patients with advanced EOC who failed second-line chemotherapy.

Clinical trial identification: ChiCTR-OOC-16008034. Registration time: 2016-03-01.

Legal entity responsible for the study: Gynecologic Department of Traditional Chinese Medicine, Changhai Hospital.

Funding: CSCO-Hengrui Cancer Research Fund (No. Y-HR2015-244).

Disclosure: All authors have declared no conflicts of interest.

975P Clear cell ovarian cancer (CCOC): Predicting risk of relapse (ROR)

M-J. Devlin[1], J.A. Ledermann[2], M. Lockley[1], N. Wilkinson[3], J. McDermott[4], R.S. Kristeleit[5], R. Miller[1]

[1]Medical Oncology, University College London Hospital UCLH NHS Foundation Trust, London, UK, [2]Cancer Trials Centre, University College London Cancer Institute, London, London, UK, [3]Pathology, University College London Hospital UCLH NHS Foundation Trust, London, UK, [4]Academic Pathology, University College London Hospital UCLH NHS Foundation Trust, London, UK, [5]Academic Department of Oncology, UCL Cancer Institute, London, UK

Background: Patients (pts) with advanced CCOC have a significantly poorer prognosis than other Epithelial ovarian cancer (EOC) subtypes. Being able to predict which pts are more likely to relapse could assist with treatment and monitoring decisions. The system inflammatory score (SIS) aims to predict postsurgical prognosis for CCOC by stratifying pts into 3 groups (gps). The Risk of OVarian cAncer Relpase (ROVAR) score aims to predict ROR for EOC following first line treatment and stratifies pts into low/intermediate (int)/high gps. We attempted to validate both scores in a non-trial population.

Methods: We reviewed the medical records for pts with CCOC treated at two UK gynaecological cancer centres between 2002 and 2017. Data comprising pt and tumor characteristics, treatment and outcome. Analysis was performed using Mantel Cox and Fisher Exact Tests.

Results: 119 pts; stage I (65), II (19), III (22), IV (10) and unknown (3). ROVAR was calculated for 90 (75%) pts; 24 (20%) had incomplete data, 6 (5%) excluded for other. Pts classified into low (20%), int (44%) and high (36%) gps. ROR for low or int gps vs high $p = 0.0001$; ROR for low vs int gps $p = 1$. Compared to low/int, pts in high-risk gp were younger 53.87yrs (34-72) vs 57.81yrs (35-74), had smaller tumours 106mm (45-240) vs 136mm (50-230), with increase in both hypercalcaemia (21% vs 5%; $p = 0.306$) and thromboembolic events (37.5% vs 10%; $p = 0.0047$). SIS was calculated for 67 pts (56%); 39 (33%) had insufficient data, 13 (11%) excluded for other. Pts classified into gp 0 (34.3%), 1 (37.3%) and 2 (28.3%) with no statistical difference in PFS ($p = 0.9118$) or OS ($p = 0.849$) between gps.

Conclusions: ROVAR significantly predicts ROR in CCOC in pts with high vs low/int risk disease. Our data suggests that the features that promote treatment-resistance are linked to paraneoplastic phenomenon and emerge early in tumour development, resulting in diagnosis at a smaller size in younger women. Another possibility is that these are two pathologically similar, but ultimately distinct, disease entities from the outset. Patients with high risk disease may benefit from more intensive follow-up and, given the chemo-resistant phenotype of the disease, early enrolment in clinical trials.

Legal entity responsible for the study: Michael-John Devlin.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

976P Comparison of PARPi with angiogenesis inhibitors and chemotherapy for maintenance in ovarian cancer: A network meta-analysis

Y.L. Feng, J.H. Liu, H. Huang, C. Zhang, T. Wan, C.J. Tong, T. Deng, H. Tu, Y.W. Huang, G. Liu, Q.D. Huang, Z.M. Liu

Gynecologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Recent targeted therapies such as poly-ADP ribose polymerase inhibitors (PARPi) and angiogenesis inhibitors (AI) are known to ease burden and recurrence of ovarian cancer. This network meta-analysis conducted an indirect treatment comparison between PARPi, AI and chemotherapeutic agents (CTA) in terms of clinical efficacy and safety as maintenance therapy in ovarian cancer patients irrespective of BRCA status.

Methods: We searched relevant sources (PubMed, EMBASE) to identify randomized controlled trials in ovarian cancer patients undergoing maintenance therapy. Studies assessing efficacy and safety of PARPi ($n = 4$), AIs ($n = 12$), CTA ($n = 8$) with placebo were analyzed. Primary outcome included progression free survival (PFS), safety and tolerability were secondary outcomes. A network meta-analysis to compare 3 drug classes was performed using statistical software R.

Results: PARPi [Hazard Ratio (HR) =0.64; 95% Credible Intervals (CrI) =0.55-0.73] and AI (HR = 0.87; 95% CrI=0.81-0.93) showed significant improvement in PFS compared to placebo but not CTA (HR = 1.00; 95% CrI=0.86-1.15, Table). PARPi showed significant improvement in PFS compared to AI (HR = 0.73; 95% CrI=0.63-0.86) and CTA (HR = 0.64; 95% CrI=0.52-0.78). Adverse events (AEs) leading to treatment discontinuation and dose reduction were lower in PARPi [Incidence Rate Ratio (IRR) =1.64; CrI=0.84-3.19, IRR=0.73, 95% CrI=0.50-1.06 respectively] compared to AI, but not significant.

Table: 976P Comparison of PFS data across different therapies

Treatment	AI	CTA	PARPi	Placebo
AI	-	1.14 (0.98, 1.35)	0.73 (0.63, 0.86)	1.15 (1.07, 1.24)
CTA	0.87 (0.74, 1.02)	-	0.64 (0.52, 0.78)	1.00 (0.87, 1.16)
PARPi	1.37 (1.16, 1.6)	1.57 (1.28, 1.92)	-	1.57 (1.36, 1.81)
Placebo	0.87 (0.81, 0.93)	1.00 (0.86, 1.15)	0.64 (0.55, 0.73)	-

AI angiogenesis inhibitors; CTA chemotherapeutic agents; PARPi poly ADP ribose polymerase inhibitors.

Conclusions: PARPi as maintenance treatment improved PFS in ovarian cancer and was relatively safer in terms of AEs caused implications when compared to other therapies. This network meta-analysis provides valuable evidence and significant insights in treatment of ovarian cancer.

Legal entity responsible for the study: Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou.

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.

977P The role of bevacizumab plus front-line chemotherapy in patients with malignant ascites of ovarian cancer

M. Nikolaou[1], N. Ziras[2], I. Athanasiadis[3], A. Ardavanis[4], M. Vaslamatzis[5], N. Kentepozidis[6], P. Makrantonakis[7], A.N. Christopoulou[8], V. Michalaki[9], A. Polizos[10], C. Emmanouilidis[11], V. Georgoulias[12]

[1]Oncology Unit, General and Maternity Hospital Helena Venizelou, Athens, Greece, [2]Oncology Department, Metaxa, Athens, Greece, [3]Oncology Department, Hygeia Hospital, Athens, Greece, [4]Oncology Department, Agios Savvas Regional Cancer Hospital, Athens, Greece, [5]Oncology Department, Evangelismos General Hospital of Athens, Athens, Greece, [6]Oncology Unit, 251 Hellenic Airforce General Hospital, Athens, Greece, [7]Oncology Department, Theagenion Cancer Hospital, Thessaloniki, Greece, [8]Oncology Unit, Hospital AG. Andreas, Patras, Greece, [9]Oncology Department, Areteion Hospital, University of Athens, Athens, Greece, [10]Oncology Unit, Laiko, Athens, Greece, [11]Oncology Department, Balkan Medical Centre, Thessaloniki, Greece, [12]Oncology Department, University Hospital of Heraklion, Heraklion, Greece

Background: Epithelial Ovarian Cancer (EOC) is a group of different types of cancer and is the most common cause of death among women. The time at diagnosis 75% of them have stage III - IV disease. The standard of care is the combination of a taxane plus a platinum (TC) compound whereas, the addition of bevacizumab (bev) as a part of first-line treatment (TC-bev) was evaluated in many trials and has been shown to improve the PFS but OS only in retrospective subgroup analysis. Patients with ascites appear to have more aggressive disease and less overall survival. We aimed to evaluate the role of TC-bev in EOC patients suffering from ascites. Ferris et al. proved that, ascites may predict the population of women more likely to derive long-term benefit from bevacizumab.

Methods: A multi-center observational, Phase IV study, which enrolled patients with stage III/IV EOC was conducted (11.2011-06.2014) in Greece. 314 patients were treated with front-line TC-bev ($n = 205$ pts) or TC ($n = 109$ pts) according to the physician's choice. There were two independent cohorts of patients with similar characteristics. 83 (40.5%) and 40 (36.7%) in the TC-bev and TC groups presented with ascites. The data were collected from the patients' records; the study has been approved by the institutional review board (IRB) of the participating centers.

Results: Patients treated with TC-bev experienced a better overall response rate (ORR) (68.7% Vs 55%) and less progression disease (PD) compared to patients received TC (13.2% Vs 30.8%). It is worth mentioning that the Complete Response (CR) was 20.5% and 10% in the TC-bev and TC respectively and Partial Response (PR) was 48.2% and 45% respectively. Both of arms showed the expected toxicity and Bev-TC was well tolerated. The median PFS was 18.1mo and 10.3mo in the TC-bev and TC group respectively ($p < 0.001$). OS is not mature (mOS has not reached in the TC-bev group and it is 22.5m in the TC group) ($p = 0.023$). The 3 year survival rate was 55.3% and 30% in the TC-bev and TC respectively.

Conclusions: Patients with advanced or metastatic ovarian cancer and ascites are in high risk group and have worse OS and PFS. The addition of Bevacizumab to TC offer survival benefit in patients with stage III/IV EOC and ascites. We need largest studies to confirm these observations.

Clinical trial identification: NCT01982500.

Legal entity responsible for the study: The authors.

Funding: Roche.

Disclosure: All authors have declared no conflicts of interest.

978P Quality of life in newly diagnosed patients with cervical cancer in Brazil: Results of EVITA study (EVA/LACOG 0215)

A. Nogueira-Rodrigues[1], A.C. de Melo[2], A.F.D.C. Calabrich[3], E. Cronenberger[4], K.L. Torres[5], F. Damian[6], R. Cossetti[7], C.R.A.S. De Azevedo[8], A.J. da Fonseca[9], Y. Nerón[10], J.S. Nunes[11], A. Lopes[12], F. Thomé[13], R. Leal[14], G. Borges[15], P.R.S. Nunes Filho[16], F. Zaffaroni Caorsi[17], R.D.S. Freitas[18], G. Werutsky[19], F.C. Maluf[20]

[1]Medical School, Federal University of Minas Gerais, Belo Horizonte, Brazil, [2]Clinical Research Department, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [3]Medical Oncology, Assistencia Multidisciplinar em Oncologia Clinic, Salvador, Brazil, [4]Medical Oncology, Centro Regional Integrado de Oncologia, Fortaleza, Brazil, [5]Medical Oncology, Fundação Centro de Controle de Oncologia do Estado do Amazonas, Manaus, Brazil, [6]Centro de Pesquisa em Oncologia, Hospital São Lucas, Porto Alegre, Brazil, [7]Medical Oncology, Hospital Aldenora Bello, Sao Luis, Brazil, [8]Medical Oncology, Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil, [9]Medical Oncology, Hospital Geral de Roraima, Boa Vista, Brazil, [10]Medical Oncology, Centro de Pesquisas Oncológicas, Florianópolis, Brazil, [11]Medical Oncology, Hospital Erasto Gaertner, Curitiba, Brazil, [12]Medical Oncology, Instituto Brasileiro de Controle do Câncer, São Paulo, Brazil, [13]Medical Oncology, Hospital São Vicente de Paulo, Passo Fundo, Brazil, [14]Medical Oncology, Hospital Universitário Walter Cantídio, Fortaleza, Brazil, [15]Medical Oncology, Clínica Neoplasias Litoral, Itajaí, Brazil, [16]Latin American Cooperative Oncology Group, Porto Alegre, Brazil, [17]Clinical Research, Latin American Oncology Group, Porto Alegre, Brazil, [18]Oncology, Latin American Cooperative Oncology Group, Porto Alegre, Brazil, [19]Clinical Research, Latin American Cooperative Oncology Group, Porto Alegre, Brazil, [20]Medical Oncology, Hospital Beneficencia Portuguesa of São Paulo, São Paulo, Brazil

Background: Cervical cancer (CC) is the fourth most common malignancy worldwide and 85% of new cases are diagnosed in low and middle-income countries. CC impact women health quality of life (HQoL) although the association between socioeconomic factors and HQoL is not well described in the literature. We aim to evaluate HQoL in patients newly diagnosed with CC in Brazil.

Methods: This is a prospective, observational cohort study (EVITA) that included patients from 16 institutions in Brazil. Main eligibility criteria were age $\geq$18 years-old, newly diagnosed stage I to IV invasive CC. Data were collected during a medical visit and from medical charts. HQoL was assessed at baseline using EORTC QLQ-C30 and CX24 questionnaires. Educational level and household income were assessed as a continuous variable and categorized for this analysis as $<$ 8y or $>=$9y and $<$1 or $>=$1 minimum wage, respectively. Student t test was used for comparisons between early (stages I and II) and advanced (stages III and IV) disease.

Results: A total of 631 patients were included from January 2016 to November 2017. Mean age at diagnosis was 49.3y ($\pm$13.9). Most patients had $<$8 years of formal education (69.5%), household income £ one minimum wage (20.9%) and were treated in the public health system (95.7%). Regarding stage at diagnosis, patients with early stage disease (I and II) displayed better physical functioning (88 vs 80; $P < 0.001$) and role functioning (72 vs 61; $P = 0.0115$) scores, while patients with advanced disease had worse fatigue (27 vs 39; $P = 0.0114$), pain (26 vs 43; $P < 0.001$), constipation (23 vs 35; $P = 0.0072$), sexual activity (90 vs 95; $P = 0.008$), symptom experience (18 vs 24; $P = 0.0083$) and sexual worry (24 vs 33; $P = 0.0489$) scores. Sexual worry was worse in patients with $>=$9 years of education (21 vs 32; $P = 0.0022$). Other quality of life measures were not different among educational level and household income subgroups.

Conclusions: This is the most comprehensive evaluation of HQoL in cervical cancer in Brazil. Our study found that patients with advanced stage at diagnosis had worse quality of life. In patients newly diagnosed CC socioeconomic factors were of limited association with HQoL.

Clinical trial identification: NCT02671071.

Legal entity responsible for the study: Latin American Cooperative Oncology Group.

Funding: Roche.

Disclosure: All authors have declared no conflicts of interest.

979P Oregovomab (orego) and nivolumab (nivo) as a combinatorial immunotherapy strategy for recurrent epithelial ovarian cancer (rEOC): ORION-01 phase Ib cohort

J.J. Chan[1], S.H. Tan[2], T.W. Lim[2], T.J.Y. Tan[1], W.Y. Chay[1], E.H. Lim[1], L.T. Soh[1], S.L. Lim[3], J.W.K. Chia[4]

[1]Division of Medical Oncology, National Cancer Centre Singapore, Singapore, [2]Division of Clinical Trials & Epidemiological Sciences, National Cancer Centre Singapore, Singapore, [3]Department of Gynaecological Oncology, KK Women and Children's Hospital, Singapore, [4]OncoCare Cancer Centre, Singapore

Background: Orego is an anti-CA 125 cancer vaccine whereas nivo is a programmed death-1 inhibitor. Both agents are clinically active in advanced EOC. We hypothesize that their combination will elicit a systemic CA 125-specific T cell response which is synergistic, safe and clinically efficacious in rEOC patients (pts).

Methods: Pts with rEOC, fallopian tube or primary peritoneal carcinoma who have received $\geq$2 prior chemotherapy lines were recruited in this phase Ib/IIa study. Study objectives were to characterize the safety and tolerability of orego + nivo, and determine the recommended dose for expansion (RDE)/recommended phase II dose (RP2D) of this combination. Using a modified 3 + 3 design, pts were treated starting at orego 2mg Q4W (dose level 1) + nivo 240mg Q2W. 2 lower doses of orego were specified in case of dose-limiting toxicities (DLT). A minimum of 6 and maximum of 18 pts would be accrued for dose finding. Additional 14 pts will be treated at RP2D in the dose expansion cohort.

Results: 6 pts with median age 61 years (range 52.0 – 63.0) and ECOG performance status 1 were treated at dose level 1. All had EOC (4 high grade serous, 2 clear cell) and a median of 4 (range 3 – 9) treatment lines before study entry. No DLT were observed. Treatment-related adverse events (AE) included grade 1 events of arthralgia, rash, transaminitis, fatigue, and anorexia. 2/6 (33.3%) pts experienced grade 1-2 thyroid-related immune-related AE. 5 serious adverse events (SAE) were observed but they were deemed unlikely/not related to study treatment, including 2 episodes of grade 4 sepsis in 1 pt who eventually died of progressive disease (PD). Dose delay of orego and nivo occurred in 1 pt because of hospitalization for fever (SAE) followed by scheduling reasons. Dose omissions of nivo occurred in 2 pts due to grade 4 sepsis in 1 pt, and grade 1 thyroiditis in another. Analysis of exploratory immune correlate(s) is underway and will be reported at the meeting.

Conclusions: Orego 2mg Q4W with nivo 240mg Q2W was selected as the RDE/RP2D to treat rEOC. Further evaluation of safety and efficacy of this novel combination is ongoing in our dose expansion cohort.

Clinical trial identification: NCT03100006.

Legal entity responsible for the study: National Cancer Centre Singapore.

Funding: OncoQuest Inc.

Disclosure: J.J. Chan: Advisory role: Eisai, Pfizer; Travel, Accommodations, Expenses: Synthon, Novartis, Pfizer. T.J.Y. Tan: Advisory role: Novartis, Pfizer; Research funding: Bayer, Novartis; Travel, Accommodations, Expenses: Merck Sharp & Dohme, Eisai, Pfizer. J.W.K. Chia: Honoraria: AstraZeneca; Consulting or Advisory role: Tessa Therapeutics, Biomark, Aslan Pharmaceuticals, MSD, AstraZeneca, Roche; Research funding: Bayer, Bristol Myers Squibbs; Travel, Accommodations, Expenses: AstraZeneca, Bristol Myers Squibbs. All other authors have declared no conflicts of interest.

980P Genomic characterization of vulvar squamous cell carcinoma

K. Prieske[1], M. Alawi[2], S.A. Joosse[3], K. Eylmann[1], E. Burandt[4], B. Schmalfeldt[5], L. Oliveira-Ferrer[1], L. Woelber[1]

[1]Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]Bioinformatics Core, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [3]Tumorbiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4]Institute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [5]Gynaecology, AGO Study Group & Technical University of Munich - Klinikum rechts der Isar; University of Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Despite an increasing incidence, vulvar squamous cell cancer (VSCC) is still a rare disease. So far two etiological pathways have been described: A high-risk human papillomavirus (HPV)-dependent route and an HPV–independent pathway often associated with lichen sclerosus. To date, therapeutic strategies in VSCC are not influenced by molecularpathological information and therapeutic options for advanced or recurrent disease are limited.

Methods: Whole exome sequencing of DNA isolated from 34 VSCC samples and matched normal tissue for each individual was performed on an Illumina HiSeq4000. Short variant discovery was carried out using BWA and MuTect2. Variants were annotated using ANNOVAR. For the detection structural variants and copy number aberrations, Pindel, ADTEx and FREEC were employed. Presence of HPV integration sites was assessed using Bowtie2.

Results: All pts (median age 60) received surgery with (partial) vulvectomy as primary treatment. In 82% a surgical staging of the groins was performed. FIGO stages were: n = 5 IB, n = 13 II, n = 5 stage III and n = 2 IVA (n = 7 unknown). 10/34 (29.4%) samples were HPV positive (all HPV16). 17.6% pts suffered from recurrence (4 local, 2 groin, 1 pelvic) after a median of 10 months. TP53 mutations were most commonly detected, with 41% (14/34). Additionally, we observed mutations in the following genes, which were affected in at least three samples: MUC3A (7/34), FSIP2 (4/34), AKAP9 (4/34), TDRD15, PKD1L1, FCHO1, RANBP2, FBXW7, VPS13C, MDGA2, SCN9A, VEPH1, ABCA5, KIAA0368, NCAM2, GCC2, MYCBP2, PRPF39, WDR49, ZNF729, UTRN, ANKRD36, GRAMD1c, ADGRV1 in 3/34 samples. Significantly less mutations were detected in pts with a OS $>$ 48 months ($p = 0.032$). However, there was no significant difference in PFS or OS between HPV positive and negative tumors ($p = 0.78$ and 0.92). In an univariate analysis there was a significant correlation between HPV negative tumors and TP53 mutations ($p < 0.0001$). No correlation between pT status, pN status, tumor size or number of mutations and HPV status was detected.

Conclusions: The key mutation in vulvar cancer affects TP53. This first work and progress analysis of whole exome sequencing of VSCC with corresponding normal tissue has the potential to identify further key mutations and therewith new targets for the treatment of VSCC.

Legal entity responsible for the study: The authors.

Funding: Hamburger Krebsgesellschaft.

Disclosure: All authors have declared no conflicts of interest.

981P Economic and humanistic burden of cervical cancer in the United States

C. Nwankwo[1], R. Shah[2], Y. Kwon[2], S. Corman[2]

[1]MRL, Merck & Co., Inc., Kenilworth, NJ, USA, [2]HEOR, Pharmerit International, Inc, Bethesda, MD, USA

Background: An estimated 12,820 women in the United States (US) will be diagnosed with cervical cancer this year, with 4,210 deaths from the disease. The economic and humanistic burden of cervical cancer has not been adequately studied.

Methods: This was a retrospective, cross-sectional analysis of Medical Expenditure Panel Survey (MEPS) data from 2006-2015. Cervical cancer cases were identified using ICD-9 CM code 180 or clinical classification software code 26. The control group consisted of women without a diagnosis of cancer. Study outcomes included healthcare resource use (institutional inpatient and outpatient, ER, and physician office visits), healthcare costs, activities of daily living (physical, cognitive, social, and activity limitations), quality of life measures (general health, SF-12v2 physical component score [PCS], mental component score [MCS], EQ-5D and SF-6D health utility, and PHQ-2 depression severity). Multivariate generalized linear models (GLMs) which controlled for key socio-demographic and clinical covariates were conducted to compare study outcomes in cervical cancer cases to non-cancer controls.

Results: The analytic cohort consisted of 275,246 cervical cancer cases and 146,061,609 non-cancer controls. Cervical cancer cases were significantly older (mean age: 42.03 vs 36.98 years), and had a higher comorbidity burden (mean Charlson comorbidity index: 1.06 vs 0.46) as compared to non-cancer controls (all $p < 0.05$). Results from the GLMs suggested that cervical cancer cases had significantly higher institutional outpatient costs ($1,610 vs $502), physician visit costs ($2,422 vs $1,321), and total healthcare costs ($10,031 vs $4,913) (all $P < 0.05$) compared to controls. Cervical cancer patients were 1.99 (odds ratio [OR]: 1.991; 95% CI: 1.23 to 3.22) and 2.56 (OR: 2.562; 95% CI: 1.78 to 3.68) times as likely to report activity limitations and poor general health as compared to non-cancer controls. Cervical cancer patients had a significantly lower PCS, MCS, EQ-5D health utility, and higher PHQ-2 depression severity (all $P < 0.01$).

Conclusions: Cervical cancer is associated with significant economic burden, activity limitations, and quality of life impairment among ambulatory women in the US.

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA.

Funding: Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosure: C. Nwankwo: Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own/hold stock/stock options in the company. R. Shah, Y. Kwon, S. Corman: Consultant for Merck & Co., Inc., Kenilworth, NJ, USA for this work.

982P Risk of fatigue and neuropathy in patients with advanced cancer treated with olaparib: A meta-analysis of randomized controlled trials

V.C. Ruiz-Schutz[1], L.M. Gomes[2], C.Z. Oliveira[2], R.C. Mariano[3], D.V.P. Almeida[3], J.M. Pimenta[2], G.Z. Dal Molin[4], F.R. Kater[3], R. Yamamura[3], F.C. Maluf[3], F.A. Schutz[3]

[1]Internal Medicine, Universidade de São Paulo, São Paulo, Brazil, [2]Oncology, Hospital Beneficência Portuguesa de São Paulo, São Paulo, Brazil, [3]Medical Oncology, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil, [4]Oncology, MD Anderson Cancer Center, Houston, TX, USA

Background: Poly ADP ribose polymerase (PARP) inhibitors are a new class of drugs that are currently being studied in several malignancies. Olaparib is FDA-approved for patients with advanced breast cancer and advanced ovarian cancer. Fatigue is the most common symptom associated with advanced cancer and treatment. Neuropathy is also a treatment related adverse event associated commonly with platinum and taxanes. We did a systematic and up to date review of the literature and a meta-analysis of randomized controlled trials (RCT) to characterize the risk of fatigue and neuropathy associated with olaparib use.

Methods: PubMed databases were searched for articles published till February 2018. The search was restricted to randomized controlled trials (RCTs) with olaparib and were selected according PRISMA. Safety profile from each selected study was evaluated for all-grade and high-grade fatigue and neuropathy events in control/placebo and olaparib arms. Summary incidences and the relative risk (RR), with 95% confidence intervals, of all-grade and high-grade events were calculated using random-effects or fixed-effects model based on the heterogeneity of selected studies.

Results: A total of 7 trials were selected, and included a total of 1750 patients with advanced ovarian, gastric or breast cancer. 746 patients received placebo/control treatments and 1004 received olaparib alone or in association with control. All-grade fatigue was increased by 21% (HR 1.21; 95% CI 1.07-1.37) while all-grade neuropathy was increased by 55% (HR 1.55; 95% CI 1.14-2.09). High-grade fatigue analysis showed a HR of 1.64 (95% CI 0.98-2.77) and high-grade neuropathy a HR of 3.61 (95% CI 0.60-21.85).

Conclusions: Our findings suggest that the olaparib treatment is associated with an increased risk of fatigue and neuropathy adverse events. Since fatigue and neuropathy are very common treatment related adverse events, and both can impair the quality of life of patients, it is important to identify it early and manage it accordingly in order to optimize the overall treatment.

Legal entity responsible for the study: BP - A Beneficencia Portuguesa de São Paulo.

Funding: BP - A Beneficencia Portuguesa de São Paulo.

Disclosure: All authors have declared no conflicts of interest.

983P Risk of cancer associated death in younger vs older patients with FIGO stage I endometrial cancer

J. Ko[1], B. Lester[2], G. Bowering[1], C. Rugayan[2], I. Ghement[3], K. Aalok[4]

[1]Medical Oncology, BC Cancer - Abbotsford, Abbotsford, BC, Canada, [2]Radiation Oncology, BC Cancer - Abbotsford, Abbotsford, BC, Canada, [3]Biostatistics, Ghement Statistics, Vancouver, BC, Canada, [4]Medical Oncology, BC Cancer - Surrey, Surrey, BC, Canada

Background: Although age is considered a traditional risk factor for relapse in stage I endometrial cancer, whether it impacts endometrial cancer-related death is unclear. We aimed to assess disease risk factors, overall survival (OS), disease-free survival (DFS), and cancer-specific survival, in patients $>=70$ (OP) vs. <70 (YP) years of age with or without adjuvant therapy.

Methods: We reviewed medical records of all patients who underwent surgery for stage I endometrial cancer between 2000 and 2013 in British Columbia, Canada. Descriptive, logistic regression, multivariate Cox regression and competing risks analyses were used to evaluate patient outcomes.

Results: 365 OP and 1063 YP were included ($n = 1428$). No significant differences were found between OP and YP with regards to disease risk factors such as stage IB disease and lymphovascular invasion (LVI). However, OP had higher odds of non-endometrioid histology (OR 1.88, $p < 0.001$). 22 (6%) OP and 78 (7.3%) YP received adjuvant chemotherapy (CT); 120 (32.9%) OP and 290 (27.3%) YP received adjuvant radiotherapy (RT). When adjusted for histology, LVI and grade, YP were more likely to receive CT (OR 2.10, $p = 0.009$); no significant difference in odds of receiving RT was found between YP and OP (OR 0.86, $p = 0.33$). OP experienced higher odds of relapse (OR 1.95, $p = 0.001$) and worse OS (HR 4.12, $p < 0.001$) and DFS (HR 2.18, $p < 0.001$) than YP after adjusting for risk factors. 10-year OS (endometrioid: 61.9 vs 89.2%; non-endometrioid: 46.1 vs 85.8%, $p < 0.001$) and DFS (endometrioid: 86.7 vs 91.9%; non-endometrioid: 69.6 vs 84.5%, $p < 0.001$) were worse for OP. Controlling for risk factors, OP experienced a higher incidence of endometrial cancer-related death than YP ($HR = 2.09$, $p < 0.001$).

Conclusions: In patients with stage I endometrial cancer, patients $>=70$ years had higher odds of having non-endometrioid histology as well as relapse and death due to endometrial cancer, yet were less likely to receive adjuvant CT. Appropriate adjuvant therapy should be considered regardless of age, as recurrent disease is still a significant cause of mortality in older patients with stage I endometrial cancer.

Legal entity responsible for the study: BC Cancer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

984P Clinical outcomes according to age and comorbidities in the OSCAR UK observational study of front-line bevacizumab (BEV)-containing therapy for advanced ovarian cancer (aOC)

M. Hall[1], G. Bertelli[2], L. Li[3], C. Green[4], S. Chan[5], C.C. Yeoh[6], J. Hasan[7], A. Ograbek[8], T.J. Perren[9]

[1]Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, Middlesex, UK, [2]Sussex Cancer Centre, Brighton & Sussex University Hospitals NHS Trust, Brighton, UK, [3]Department of Oncology and Radiotherapy, James Cook University Hospital, Middlesbrough, UK, [4]Oncology Department, Southampton University NHS Trust, Southampton, UK, [5]Department of Oncology and Radiotherapy, Nottingham University Hospital NHS Trust (City Hospital Campus), Nottingham, UK, [6]Oncology Department, Queen Alexandra Hospital Portsmouth, Portsmouth, UK, [7]Department of Medical Oncology, The Christie Hospital, Manchester, UK, [8]Medical Affairs, Roche Products Ltd, Welwyn Garden City, UK, [9]Leeds Institute of Cancer and Pathology, St James's University Hospital, Leeds, UK

Background: The efficacy and safety of front-line BEV with carboplatin and paclitaxel (CP) for aOC were demonstrated in two randomised phase III trials (GOG-0218 and ICON7). OSCAR (NCT01863693; funded by Roche Products Ltd) evaluated front-line BEV-containing therapy in routine oncology practice in 29 UK centres.

Methods: Eligible patients received BEV (7.5 or 15 mg/kg q3w, typically for up to 12 months, per UK clinical practice) during and after front-line chemotherapy (physician's choice) for high-risk stage IIIB–IV ovarian cancer. Co-primary endpoints were progression-free survival (PFS) and safety (NCI CTCAE v4.0). Patients were evaluated according to standard practice/physician's discretion during BEV treatment, with an end-of-study assessment 12 months after the last BEV dose. We report post hoc subgroup analyses in populations defined by age and comorbidities.

Results: Of 299 patients starting treatment between May 2013 and Mar 2015, 80 were aged $\geq$70 years, of whom 9 were $\geq$80 years. Almost all patients (91%) had comorbidities (pre-existing medical condition at BEV initiation), most commonly hypertension/essential hypertension (27%), constipation (22%) or fatigue (22%). Most (93%) received BEV 7.5 mg/kg with CP; 22% had primary debulking surgery, 40% interval debulking surgery and 38% no surgery. Patient characteristics, treatment exposure,

PFS and safety are summarised below. In multivariable Cox regression analysis, neither age nor number of comorbidities was prognostic for PFS.

Conclusions: Older patients were more likely to receive single-agent chemotherapy, have ongoing comorbidities and have worse surgical outcome than their younger counterparts. However, median BEV exposure, incidence of grade 3/4 AEs and median PFS were similar in younger and older patients. Grade ≥3 AEs were more common in patients with ≥3 than <3 comorbidities but PFS was similar.

Clinical trial identification: NCT01863693.

Editorial acknowledgement: Medical writing assistance was provided by Jennifer Kelly, MA (Medi-Kelsey Ltd, Ashbourne, UK), funded by Roche Products Ltd.

Legal entity responsible for the study: Roche Products Ltd.

Funding: Roche Products Ltd.

Disclosure: M. Hall: Advisory boards: Roche, Tesaro, Clovis Oncology, AstraZeneca. G. Bertelli: Advisory boards: Roche, Novartis, Genomic Health. J. Hasan: Advisory boards: Roche, AstraZeneca, Tesaro. A. Ograbek: Employee: Roche. T.J. Perren: Advisory boards: Roche, Novartis, Merck Sharp & Dohme Limited; Travel/accommodation: IGEA Medical. All other authors have declared no conflicts of interest.

985P Prolonged survival (SV) associated with pulmonary metastasectomy (PM) for carcinomas of the cervix (CC)

J.F. Corona-Cruz[1], A. Castillo-Castañon[1], C.Z. Deneken[2], L.A. Ramirez-Tirado[1], A. Gonzalez-Enciso[3], D. Gallardo-Rincon[3], E. Jimenez-Fuentes[1], O. Arrieta[4]

[1]Thoracic Oncology Clinic, Instituto Nacional de Cancerologia - Mexico, Mexico City, Mexico, [2]Centro de Cancer ABC, Centro Medico ABC, Mexico City, Mexico, [3]Gynecology Oncology Clinic, Instituto Nacional de Cancerologia - Mexico, Mexico City, Mexico, [4]Thoracic Oncology Clinic, Instituto Nacional de Cancerologia, Mexico City, Mexico

Background: CC is a public health problem in developing countries. Dissemination is typically lymphogenous but can develop hematogenous metastases. Chemotherapy alone is associated with a median SV of 13 months on metastatic disease. In selected cases with Isolated lung metastases (LM), PM is associated with prolonged SV.

Methods: Observational, retrospective cohort. Patients (ptes) with CC who underwent PM at the National Cancer Institute (INCan) Mexico from January 2005 to December 2017. Primary end-points were Overall Survival (OS) and Disease-Free Survival (DFS) Secondary end-points were morbidity and mortality of PM.

Results: A total of 29 ptes were identified. Squamous carcinoma was primary histology in 21 (72.4%). Most presented with advanced tumors at initial diagnosis, 11 (37.9%) stage II, 5 (17.2%) stage III and 7 (24.1%) stage IV. Unilateral nodules were seen in 27 (93.1%) and a single nodule was present in 24 (82.4%). Nodules were diagnosed as metachronous (after 6 months of diagnosis) in 21 (72.4%). Surgery was the initial treatment in 25 (86.2%) and only 4 (13.8%) received pre-operative chemotherapy. A wedge resection was performed in 16 (55.2%), interestingly, a lobectomy was needed in 12 cases (41.4%) and 1 case required a pneumonectomy. One case developed hemothorax requiring exploration for a 90-day morbity of 3.4% and 90-day mortality was 0%. An R0 resection was achieved in 26 (89.7%) On pathological analysis, only in 20 ptes (69%) LM were confirmed, in the other ptes a benign condition was diagnosed. Postoperative chemotherapy was indicated in 12 cases. Median follow up was 101.5 months (6 – 260). For SV analysis only ptes with proved LM were included. Median OS has not been reached, 5-year OS 35%. Median DFS 100 months (6.4 -193.5) Only R2 resection (p 0.05), no postoperative chemotherapy (p 0.025) and disease relapse (p 0.007) were statistically significantly associated with a worst SV.

Conclusions: In our cohort, PM is associated with better OS than chemotherapy alone. Although some ptes required a lobectomy, a very low morbidity and zero mortality in our cases is very encouraging. PM should be considered as fundamental part of multidisciplinary treatment in cases of CC with isolated LM.

Legal entity responsible for the study: Jose Francisco Corona-Cruz.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

986P Real world occurrence of top three clinical-trial reported adverse events of PARP inhibitor niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, a national retrospective observational study of a 200 mg/day starting-dose cohort

J.R. Gallagher[1], K.J. Heap[2], S. Carroll[3]

[1]Department of Analytics, Clarity Pharma Research, LLC, Spartanburg, SC, USA, [2]Research Management, Clarity Pharma Research, LLC, Spartanburg, SC, USA, [3]Clarity Pharma Research, LLC, Spartanburg, SC, USA

Background: Niraparib (Zejula®) is an oral poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) 1/2 inhibitor that has demonstrated efficacy in patients with platinum-sensitive, recurrent ovarian cancer. Nausea, thrombocytopenia, and fatigue were commonly occurring adverse events (AEs) in the phase 3 clinical trial in which patients were started at 300 mg daily dose of niraparib. After dose adjustments in this trial, a daily dose of 200 mg was the most commonly administered dose. This analysis provides a description of AEs among patients receiving an initial dose of 200 mg niraparib.

Methods: In a retrospective observational patient study, 53 randomly selected study-qualified physicians from a national database (61% of qualified physicians screened) extracted requested anonymous information from the medical charts of 153 qualified patients. Qualified patients had received a starting dose of 200 mg/day niraparib for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer and were in complete or partial response to platinum-based chemotherapy.

Table: 984P

Characteristic, n (%)		Age, years		No. of comorbidities	
		<70 (n = 219)	≥70 (n = 80)	<3 (n = 109)	≥3 (n = 190)
Age, years	<65 ≥65	160 (73) 59 (27)	0 80 (100)	68 (62) 41 (38)	92 (48) 98 (52)
High risk[a]		200 (91)	70 (88)	99 (91)	171 (90)
No microscopic residual disease		11 (5)	1 (1)	6 (6)	6 (3)
ECOG PS	0 1 2 Missing	56 (26) 58 (26) 11 (5) 94 (43)	13 (16) 27 (34) 6 (8) 34 (43)	35 (32) 33 (30) 5 (5) 36 (33)	46 (24) 66 (35) 15 (8) 63 (33)
Pre-existing hypertension[b]		49 (22)	33 (41)	13 (12)	69 (36)
Pre-existing proteinuria[c]		11 (5)	10 (13)	4 (4)	17 (9)
Pre-existing diabetes		13 (6)	9 (11)	2 (2)	20 (11)
Selected chemotherapy	CP Carboplatin alone Other	214 (98) 2 (1) 3 (1)	71 (89) 9 (11) 0	104 (95) 3 (3) 2 (2)	181 (95) 8 (4) 1 (1)
AE leading to BEV discontinuation		21 (10)	12 (15)	11 (10)	22 (12)
Median BEV duration, months (range)		10.6 (<1–29.7)	10.4 (≤1–41.4)	10.9 (<1–29.7)	10.3 (<1–41.4)
Grade 3/4 AEs, n (%)		118 (54)	42 (53)	50 (46)	110 (58)
Grade 5 AEs, n (%)		5 (2)[d]	2 (3)[e]	1 (1)	6 (3)
Median PFS, months (95% CI)		16.1 (14.5–18.5)	14.8 (12.2–16.1)	16.5 (14.7–18.0)	14.9 (13.4–16.1)

[a]Stage III with ≥1 cm residuum, any stage IV, or no surgery.
[b]Includes essential hypertension.
[c]Includes high protein level in urine.
[d]Gastrointestinal perforation, febrile neutropenia, cardiac arrest, pneumonia, metastases to meninges.
[e]Abdominal pain, pneumonia aspiration. AE=adverse event.

Results: Of the 153 patients, 56 (37%) experienced at least one of the three AEs evaluated within the first three months after niraparib initiation, and 49 (32%) experienced only grades 1/2 AEs. Among the 153 patients, fatigue was reported for 24% (36/153) (CI 17.4% - 31.0%); nausea for 16% (25/153) (CI 10.5% - 22.2%) and thrombocytopenia for 14% (21/153) (CI 8.3% - 19.2%). Of the 21 patients with thrombocytopenia, 3 were grade 3/4 severity (2% of overall). Among the patients, 4% (6/153) had a dose interruption, 11% reduced their dose (17/153), and 2% discontinued niraparib altogether (3/153) due to AEs.

Conclusions: While over 60% of patients in the phase 3 clinical trial reported experiencing the three AEs observed in the study, only 37% reported such in real-world usage. This difference may be due to the higher dosing in the trial study (initial dose of 300 mg/day vs. 200 in the observational study). Additional real-world research is needed to understand the effects of niraparib dosing on AEs.

Legal entity responsible for the study: Clarity Pharma Research, LLC.

Funding: Tesaro, Inc.

Disclosure: All authors have declared no conflicts of interest.

987P Trabectedin plus pegylated liposomal doxorubicin (PLD) in patients with platinum-sensitive recurrent ovarian cancer (PSROC) regardless of prior use of antiangiogenics: First results of an observational, prospective study

S. Pignata[1], G. Scambia[2], T. Mazzei[3], M. Arruti Barbia[4], E. Naglieri[5], L.M. de Sande[6]

[1]Urology and Gynecology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [2]Medical Oncology, Policlinico Universitario A. Gemelli, Rome, Italy, [3]Medical Oncology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy, [4]Medical Oncology, Hospital de Galdakao, Galdakao, Spain, [5]Medical Oncology, Istituto Oncologico Giovanni Paolo II, Bari, Italy, [6]Medical Oncology, Hospital de León, Leon, Spain

Background: The non-interventional NIMES-ROC phase IV trial (NCT02825420) aimed to evaluate trabectedin (1.1 mg/m^2)+PLD (30 mg/m^2) in real-life clinical practice and given in accordance with the marketing authorization to women with PSROC regardless of previous anti-angiogenic treatment.

Methods: Eligible patients were adults with PSROC who have received ≥1 cycle of trabectedin+PLD before inclusion. The primary endpoint was to assess the PFS according to investigator criteria.

Results:

Table: 987P

NIMES-ROC*	PRIOR USE OF ANTIANGIOGENICS		
	Yes (n = 96)	No (n = 62)	Total (n = 158)
Median age (range)	62 (39-81)	61 (39-86)	62 (39-86)
ECOG PS, n (%)			
0	41 (42.7)	26 (41.9)	67 (42.4)
1	25 (26.0)	8 (12.9)	33 (20.9)
2	2 (2.1)	3 (4.8)	5 (3.2)
Missing	28 (29.2)	25 (40.3)	53 (33.5)
Papillary/serous cancer	75 (78.1)	40 (64.5)	115 (72.8)
Platinum sensitivity			
Partially platinum sensitive ROC (PFI 6-12 m)	66 (68.8)	34 (54.8)	100 (63.3)
Fully platinum sensitive ROC (PFI >12 m)	50 (52.1)	40 (64.5)	90 (57.0)
Missing	3 (3.1)	4 (6.5)	7 (4.4)
Prior surgery, n (%)	88 (91.7)	56 (90.3)	144 (91.1)
Prior chemotherapy, n (%)	95 (99.0)	61 (98.4)	156 (98.7)
Prior platinum-based therapy, n (%)	96 (100)	60 (96.8)	156 (98.7)
Prior bevacizumab, n (%)	81 (84.4)	0	81 (51.3)
Number of T+PLD cycles, median (range)	6.0 (1-34)	6.5 (2-16)	6.0 (1-34)
In-patients only	24 (25.0)	15 (24.2)	39 (24.7)
Out-patients only	58 (60.4)	41 (66.1)	99 (62.7)
Both	8 (8.3)	6 (9.7)	14 (8.9)
Missing	6 (6.3)	0	6 (3.8)
Progression-free survival (PFS), months (95% CI)	10.0 (7.3-12)	14.3 (11.4-nr)	11.4 (10-14)
PFS at 6 months, months (95% CI)	70.9 (60-79)	84.3 (72-92)	76.3 (68-83)
PFS at 12 months, months (95% CI)	39.1 (27-51)	60.9 (44-74)	47.7 (37-57)
Overall survival (OS), months (95% CI)	17.7 (13.2-nr)	nr (16.8-nr)	nr (16.8-nr)
Compete response (CR)	6 (6.3)	9 (14.5)	15 (9.5)
Partial response (PR)	25 (26.0)	20 (32.3)	45 (28.5)
Stable disease (SD)	25 (26.0)	20 (32.3)	45 (28.5)
Progressive disease (PD)	25 (26.0)	7 (11.3)	32 (20.3)
Not evaluable / Missing	15 (15.6)	6 (9.7)	21 (13.3)

∗Patients may be represented in multiple categories. CI, confidence interval; nr, not reached; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PS, performance status; ROC, recurrent ovarian cancer; T, trabectedin.

158 patients from 50 sites across Europe were evaluated. Median number of trabectedin+PLD cycles received per patient was 6, with 95 patients (50.6%) receiving ≥6 cycles and up 34 cycles. Median treatment duration was 22.2 weeks (range: 3-124), with no statistical difference concerning prior use of antiangiogenics, and mostly on an outpatient basis (≥63% of patients). Bevacizumab was the most used antiangiogenic in 84% of patients. With 73 PFS events and 32 deaths recorded, median PFS (11.4 months; 95% CI: 10-14) and OS (see Table) was significantly larger in patients not pretreated with antiangiogenics (PFS: $p < 0.009$; OS: $p < 0.018$). Non-antiangiogenic pretreated patients also obtained better overall response rate (ORR, 47% vs 32%) and disease control rate (ORR + SD: 79% vs 58%). A total of 108 trabectedin-emergent adverse reactions (TEAR) occurred. Most common grade 3/4 TEARs were neutropenia (25%) and asthenia (4%). The toxicity profile between subgroups was not different from that of the overall population.

Conclusions: Our results confirm that trabectedin+PLD is active in patients with PSROC with an acceptable and manageable safety profile. Overall our data favorably compare with those of the pivotal OVA-301 trial (NCT00113607) and suggest major benefits in patients non-pretreated with antiangiogenics who obtained significantly longer PFS.

Clinical trial identification: NCT02825420; ET-D-031-14.

Editorial acknowledgement: The authors would like to acknowledge Adnan Tanović (PharmaMar) for providing writing assistance for the manuscript.

Legal entity responsible for the study: PharmaMar, S.A.

Funding: PharmaMar, S.A.

Disclosure: All authors have declared no conflicts of interest.

988P Benefit from subsequent conventional cytotoxic chemotherapy (CTx) to immunotherapy (IT) in patients (pts) with gynaecological malignancies (GM)

F.J. Ros Montañá[1], V. Rodriguez Freixinos[1], L. Fariñas Madrid[2], F. Amair Pinedo[1], F. Ruiz-Pace[3], E. Garralda[4], R. Dienstmann[5], A. Oaknin[1]

[1]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [2]Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [3]Oncology Data Science Group (ODysSey), Vall dHebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [4]Early Drug Development Unit, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [5]Oncology Data Science, Vall d'Hebron University Hospital, Barcelona, Spain

Background: IT has been a breakthrough for the treatment of many tumour types, nevertheless it's use in GM remains an area of ongoing clinical research. Early evidence suggests that IT treatment may sensitize to subsequent CTx. Our aim was to investigate the efficacy of pre-and post-IT CTx in a cohort of GM.

Methods: From 2014 to 2017, 60 GM pts were treated with IT in phase I/II trials at Vall dHebron Hospital. Data was retrospectively collected from those pts who received Ctx pre- and post-IT. Endpoints: Progression free survival (PFS), clinical benefit rate (CBR) at 6 months (m) and overall response rate (ORR).

Results: A total of 28 (47%) pts (18 ovarian cancer [OC], 8 cervical cancer [CC] and 2 endometrial cancer [EC]) with median age of 53 (31-77), ECOG 0-1 (95%) and 2 median (1-5) pre-IT CTx lines were identified. IT was single agent PD1/L1 inhibitor in 46% of cases, the remaining receiving a combination of IT drugs. Median PFS on IT was 3.0m (2.0-5.3), CBR was 36% and ORR 10%. Platinum-based CTx was given to 83% of the patients pre-IT and 50% post-IT. The table summarizes clinical endpoints stratified by tumor type. Of note, 2 OC pts had longer PFS with platinum-based Ctx post-IT compared to pre-IT (15.9 vs 5.4 m and 21.4 vs 16.5 m). Such pattern was not observed in any pt with CC or EC. There was no association between benefit on IT and pattern of response to post-IT CTx.

Conclusions: A significant proportion of heavily pretreated GM pts are still treated with CTx after failure of IT. Although limited by sample size, our study did not show signals of improved sensitivity to CTx post-IT. GM pts retained the potential to respond to subsequent CTx. Further studies are needed to define the optimal timing of IT and to define potential predictors of improved CTx benefit.

Legal entity responsible for the study: Vall dHebron Institute of Oncology (VHIO).

Funding: Has not received any funding.

Disclosure: E. Garralda: Advisory role: Roche, NeoMed Therapeutics, Ellypses Pharma. A. Oaknin: Advisory boards: Roche, AstraZeneca, PharmaMar, Clovis Oncology, Tesaro; Support for travel or accommodation: Roche, AstraZeneca, PharmaMar. All other authors have declared no conflicts of interest.

989P Identification research and application for protein phosphorylation modification sites in human ovarian carcinoma

X. Zhan[1], N. Li[2]

[1]Key Laboratory of Cancer Proteomics of Chinese Ministry of Health, Xiangya Hospital, Central South University, Changsha, China, [2]Key Laboratory of Cancer Proteomics of Chinese Ministry of Health, Xiangya Hospital, Changsha, China

Background: Phosphorylation modification, as one kind of protein post-translational modification (PTM), increases the diverse protein functions, such as cell signaling, protein folding, enzymatic activity, protein degradation, and their subcellular location. However, the subcellular phophoproteomic of ovarian carcinoma mitochondrial proteins has not been elucidated.

Methods: Here, an 8-plex isobaric tag for relative and absolute quantification (iTRAQ) proteomics was used to identify mitochondrial expressed proteins (mtEPs) and phosphorylation modification sites of ovarian carcinomas relative to controls, followed by bioinformatics analysis.

Results: The iTRAQ-based proteomics identified 5115 proteins and 99 phosphorylated proteins with quantitative information from purified mitochondrial samples, and 262 proteins were significantly related to overall survival in ovarian cancer patients. Interestingly, the results demonstrated that cancer cells exhibit an increased dependence on lipid metabolism, such as biosynthesis of unsaturated fatty acids, butanoate metabolism, fatty acid degradation, fatty acid metabolism, which might play an important role in ovarian carcinoma invasion and metastasis. Moreover 33 proteins related to lipid metabolism as potential markers for the development of ovarian carcinoma were identified.Additionally, 3 drug-associated phosphorylation proteins and 3 phosphorylation proteins as tumor markers in the plasma were obtained. The 99 phosphorylated proteins and TCGA data were integarated, thus obtained 9 important proteins. Among those, HSP60 were highly related with lipid metabolism. In cells with increased Hsp60 levels both the amounts of total mitochondrial short-chain acyl-CoA dehydrogenase (ACADS) proteins and folded ACADS were increased, which may influence mitochondrial protein folding and lipid metabolism.

Conclusions: The current study provides a large-scale mitochondrial proteomic profiling and mitochondrion phosphoproteome with quantitative information, a certain number of proteins with the potential biomarkers, drug targets and a novel vision in the lipid metabolism bio-mechanism of human ovarian carcinoma.

Legal entity responsible for the study: Hunan Engineering Laboratory for Structural Biology and Drug Design, Xiangya Hospital, Central South University.

Funding: Xiangya Hospital Funds for Talent Introduction (to XZ), the grants from China "863" Plan Project (Grant No. 2014AA020610-1 to XZ), the National Natural Science Foundation of China (Grant No. 81272798 and 81572278 to XZ), and the Hunan Provincial Natural Science Foundation of China (Grant No. 14JJ7008 to XZ).

Disclosure: All authors have declared no conflicts of interest.

990P Enhancing prognosis prediction using nodal SUVmax and HPV status in cervical squamous cell carcinoma

S.Y. Jeong[1], G.O. Chong[2], C.M. Hong[1]

[1]Nuclear Medicine, Kyungpook National University School of Medicine, Daegu, Republic of Korea, [2]Obstetrics and Gynecology, Kyungpook National University School of Medicine, Daegu, Republic of Korea

Background: A risk stratification model using metabolic variables on PET/CT combined with other known prognostic factors has not been proposed. To evaluate the prognostic classification model for predicting tumor recurrence using metabolic parameters on F-18-FDG PET/CT, status of human papillomavirus (HPV) infection and known prognostic variables in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy (CCRT).

Methods: A total of 129 patients with cervical squamous cell carcinoma who underwent initial CCRT were eligible for this study. The clinical, pathological parameters, HPV status and metabolic parameters of pre-operative F-18 FDG PET/CT were used for analysis. Univariate and multivariate analysis for disease-free survival (DFS) were performed using traditional prognostic factors, metabolic parameters and HPV infection. Classification and regression decision tree (CART) was used to establish new classification.

Results: Among 129 patients, 29 patients (22.5%) had recurrence after a median follow-up of 60 months (range, 3–125 months). In univariate analysis, FIGO stage, tumor size, status of para-aortic lymph node metastasis, Nodal SUVmax, HPV positive were statistically significant in DFS. Multivariate analysis revealed that tumor size, paraaortic lymph node metastasis, nodal SUVmax and HPV infection status were independent prognostic factors. CART analysis classified the patients into three groups. First node was nodal SUVmax and HPV status was second node for patients with nodal SUVmax$\leq$7.49 ($p < 0.001$); Group A (nodal SUVmax$\leq$7.49 and HPV positive), group B (nodal SUVmax$\leq$7.49 and HPV negative) and group C (nodal SUVmax>7.49). There was significant difference of DFS among 3 groups ($p = 0.0012$).

Conclusions: The present study revealed that the nodal SUVmax on F-18 FDG PET/CT and HPV infection status before CCRT are powerful an independent prognostic factor for the prediction of disease free survival in patients with cervical squamous cell carcinoma who underwent initial CCRT. Furthermore, simple prognostic classification model using nodal SUVmax and HPV infection status can provide classification of recurrence.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 988P Clinical endpoints for Ctx before and after IT

	OC (n = 18)			CC (n = 8)			EC (n = 2)		
	CTx pre	IT	CTx post	CTx pre	IT	CTx post	CTx pre	IT	CTx post
Median PFS (95% CI) months	9.62 (7.8-11.4)	3.43 (1.9-12.4)	8.2 (2.97-NA)	8.75 (6-NA)	3 (2.07-NA)	1.47 (1.03-NA)	11.33 (6.93-NA)	4.67 (2.63-NA)	2.42 (1.13-NA)
ORR (%)	61%	11%	39%	75%	13%	13%	50%	0%	0%
CBR (%)	72%	44%	44%	75%	13%	25%	100%	50%	0%

991P Clinical characteristics of ovarian cancer relapse in BRCA1/2 germ-line mutation carriers and non-carriers

A.P. Sokolenko, T.V. Gorodnova, A.O. Ivantsov, I.V. Berlev, E.N. Imyanitov

Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, St. Petersburg, Russian Federation

Background: Approximately 15% of ovarian cancer (OC) incidence is attributed to germ-line mutations in BRCA1 or BRCA2 genes. Being a distinct biological subset of OC disease, BRCA1/2-driven cancers are usually characterized by good response to chemotherapy. However, even if OC patient undergoes complete surgical cytoreduction and potentially effective systemic therapy, the probability of the tumor relapse is high. This study aimed to compare some essential clinical features of OC relapses in hereditary vs. sporadic OC.

Methods: We identified 212 women with relapsed high-grade serous OC, who were treated in the N.N. Petrov Institute of Oncology within years 2000-2014, underwent complete primary (n = 113) or interval (n = 99) surgical debulking, and had available clinical data for analysis. 66 women were BRCA1/2 germ-line mutation carriers and 146 were mutation negative. Recurrences were classified according to anatomical location (local, regional, distant, marker), type (systemic or discrete) and pattern of spread.

Results: As expected, median PFI (platinum-free interval) in BRCA1/2 carriers was longer as compared to sporadic cases (13.2 months vs. 8.0 months) [$p < 0.001$]. The proportion of OC cases with PFI > 12 months was significantly higher among BRCA1/2 carriers [38/66 (58%) vs. 51/146 (35%), $p = 0.003$]. There was no statistical difference in the frequency of distant relapses between these groups [10/66 (15%) vs. 31/146 (21%), $p = 0.4$]. Systemic recurrences (i.e., multiple lesions) occurred significantly more frequently in sporadic cases as compared to patients with BRCA1/2 mutation [98/144 (68%) vs. 30/60 (50%), $p = 0.02$] and were associated with shorter duration of PFI [$p = 0.003$]. The proportion of patients who could be subjected to the local treatment (locoregional discrete recurrence with lymphatic/transcoelomic spread) was higher among BRCA1/2 mutation carriers than non-carriers [29/66 (44%) vs. 45/146 (31%), $p = 0.045$].

Conclusions: BRCA1/2-driven OC are characterized by more favorable mode of relapse than sporadic high-grade serous ovarian cancers.

Legal entity responsible for the study: N.N. Petrov Institute of Oncology.

Funding: Russian Science Foundation [grant number 14-25-00111].

Disclosure: All authors have declared no conflicts of interest.

992P Phase Ib study of metformin in combination with carboplatin/paclitaxel chemotherapy in patients with advanced epithelial ovarian cancer

K.E. Broekman[1], A.K.L. Reyners[1], D.J. Touw[2], M.A.J. Hof[2], M. Jalving[1]

[1]Medical Oncology, University Hospital Groningen (UMCG), Groningen, Netherlands, [2]Clinical Pharmacy and Pharmacology, University Medical Centre Groningen (UMCG), Groningen, Netherlands

Background: Metformin is associated with reduced cancer risk in epidemiological studies and has preclinical anti-cancer activity in ovarian cancer models, likely through inhibition of the mTOR pathway. The primary study objective was to determine the recommended phase II dose (RP2D) of metformin in combination with carboplatin/paclitaxel in ovarian cancer patients. Secondary objectives were to describe safety and pharmacokinetics.

Methods: In this phase Ib single-centre trial the RP2D of metformin in combination with carboplatin/paclitaxel chemotherapy in patients with advanced epithelial ovarian cancer was determined using a 3 + 3 escalation rule at 3 fixed dose levels: 500 mg tds, 850 mg tds and 1000 mg tds. Chemotherapy consisted of carboplatin AUC6 and paclitaxel 175 mg/m^2 q3w. Metformin was started on day 3 of the first cycle and continued until three weeks after the last chemotherapy administration. The RP2D was defined as the dose level at which 0 of 3 or $\leq$ 1 of 6 evaluable subjects experienced a metformin-related dose-limiting toxicity (DLT) during chemotherapy cycle 1 or 2. Safety was assessed according to CTCAE v4.0. Pharmacokinetic samples were collected during treatment cycles 1 and 2.

Results: Fifteen patients undergoing neo-adjuvant (n = 5) or palliative (n = 10) treatment were included. No DLTs were observed. Three patients discontinued study treatment during cycle 1 for other reasons than DLT. Six patients were treated at the RP2D of metformin 1000 mg tds. Preliminary safety data showed that most common low-grade toxicities were anemia and hypomagnesaemia. Grade 3 AE's occurred in ten patients, most commonly leukopenia (n = 4), thrombocytopenia (n = 3) and increased GGT (n = 3). There were no grade 4 AE's. Pharmacokinetic analysis showed a metformin induced increase in AUC of carboplatin (Δ24%, $p = 0.028$). All metformin trough levels were <4 mg/L.

Conclusions: The RP2D of metformin in combination with carboplatin and paclitaxel in advanced ovarian cancer is 1000mg tds. This is higher than the metformin RP2D in combination with targeted agents. The clinical relevance of the metformin-induced increase in carboplatin AUC remains to be elucidated.

Clinical trial identification: NCT02312661.

Legal entity responsible for the study: University Medical Centre Groningen (UMCG).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

993P Individual and familial phenotype in hereditary ovarian cancer

M.B.D.O. Mira[1], I. Miguel[2], S. Fragoso[3], A. Opinião[2], A.C. Luís[2], A. Clara[2], S. Bento[2], P. Machado[3], S. Santos[3], P. Rodrigues[2], J. Parreira[2], F. Vaz[2]

[1]Medical Oncology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E. (IPOLFG EPE), Lisbon, Portugal, [2]Family Risk Clinic, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E. (IPOLFG EPE), Lisbon, Portugal, [3]Molecular Pathology Investigational Center, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E. (IPOLFG EPE), Lisbon, Portugal

Background: Germline mutations impacting homologous recombination repair (HCR) have been associated with predisposition to breast (BC) and ovarian cancer (OC), and more than 1/5 of OC have hereditary susceptibility (HOC). Other genes than BRCA have been associated with HOC.

Methods: All index, consecutive, non-mucinous OC patients (pts) counselled between September 2016-December 2017 were tested upfront for a panel testing (PT) including BRCA1, BRCA2, RAD50, RAD51C, RAD51D and BRIP1 (BRCA Hereditary Cancer MASTER Plus methodology). We analyze the molecular results, their clinical characteristics and family history (FH).

Results: One hundred and one female pts with OC diagnosis consented to PT. Pathogenic variants (PV) were found in 19 pts (18.8%): BRCA2 – 8 (42%), BRCA1 – 5 (26%), RAD51C – 3 (16%), RAD51D – 2 (11%), RAD50 – 1 (5%). The majority of these OC had been previously classified as high-grade serous (HGS) (n = 13 - 68%).We identified 2 pts with low-grade serous carcinoma (LGSC) with pathogenic variants (1 BRCA2; 1 RAD51C). Although median age of diagnosis (MAD) was lower for BRCA2 (55 years) and BRCA1 (58 years) than "non-hereditary" and RAD50/RAD51C/RAD51D pts (both groups with MAD of 63 years), difference was non significant ($p = 0.21$). As for FH (defined as: other OC and/or BC < 50 years and/or male BC), only 54% of BRCA1/2 pts and none of RAD50/RAD51C/RAD51D had a positive FH. Eighteen percent of "non-hereditary" OC pts had positive FH. With a median follow up of 5 yrs, 63% of pts harboring PV and 50% of those with no PV relapsed, with 2 pts having central nervous system relapses (1 - RAD51D and 1 - RAD50). All but 7 pts were alive at analysis time, only one with a germline mutation impacting HCR (RAD50 mutation).

Conclusions: Family history was not associated with the detection of germline pathogenic variants and should not be a criteria for selection of OC for genetic testing. While the inclusion of other genes in our panel may increase our detection rate, excluding LGSC (not included in some guidelines as candidates for testing) would not detect an undetermined number of pts, since the association between LGSC and HOC is not clarified. Longer follow up may help clarify if there is a genotype/phenotype correlation regarding patterns of relapse in hereditary ovarian cancer.

Legal entity responsible for the study: Family Risk Clinic - Instituto Português de Oncologia de Lisboa Francisco Gentil EPE.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

994P Role of FGFR2 amplification in prognosis of patients with ovarian cancer

A. Tyulyandina[1], I. Demidova[2], M. Gikalo[2], S. Tjulandin[1], I. Tsimafeyeu[3]

[1]Department of Clinical Pharmacology and Chemotherapy, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [2]Laboratory of Molecular Genetics, Moscow City Oncology Hospital No. 62, Moscow, Russian Federation, [3]Head Office, Russian Society of Clinical Oncology, Moscow, Russian Federation

Background: Fibroblast growth factor receptor (FGFR) signaling has been implicated to play a role in tumorigenesis. Aim of this study was to evaluate rate of FGFR2 amplification and preliminary role in patients (pts) with ovarian cancer (OC).

Methods: Material from each patient with advanced OC included 3 paraffin-embedded samples: primary ovarian tumor, primary metastatic lesion, and relapse lesion. Samples were analyzed by fluorescence in situ hybridization (FISH) to identify FGFR2 amplification and level of polysomy. Scoring for amplification and polysomy level was adopted from previous studies for gastric cancer [Su et al. BJC 2014]. The analysis was performed in all three samples regardless of the presence of FGFR2 amplification or heterogeneity in primary tumor.

Results: 166 samples from 67 pts with advanced ovarian cancer (OC) stage Ic-IV were analysed. Amplification was detected in 11 of 67 pts (16.4%) and high-level polysomy in 31 of 67 (46.3%). All three tumour samples were analyzed in 43 pts. FGFR2 amplification, high-level polysomy were detected in 9 (20.9%) and 19 (44.2%), respectively. Analysis of survival differences revealed no statistically significant difference between

the pts with polysomy and non-amplified pts (HR 2.12; 95% CI 0.17-0.21, p = 0.32). Median progressive free survival (PFS) after first line platinum based chemotherapy was 12.6 months in pts with amplification in comparison with 23.1 months in non-amplified (p = 0,012). Pts with amplification in primary tumour (ovary) had statistically poor prognosis than non-amplified pts: median PFS was 12.0 and 22.6 months respectively (p = 0.003). Pts with FGFR2 amplification in primary metastatic lesions and relapsed tumour had tendency to poor prognosis: PFS was 10.3 and 19.6 months in primary metastasis lesions (p = 0.09), and 10.3 vs 22.6 months in relapsed lesions (p = 0.07).

Conclusions: We described FGFR2 amplification in 16.4% of pts with advanced OC. Preliminary data demonstrate a negative impact of the FGFR2 amplification in primary tumour (ovary) on long-term outcomes.

Legal entity responsible for the study: Alexandra Tyulyandina.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

995P MONITOR VII: Treatment strategies of low grade ovarian carcinomas – A German survey of the Charité – Berlin and Kliniken Essen Mitte with support of the study groups NOGGO and AGO

S. Alavi[1], P. Harter[2], R. Richter[3], M. Keller[4], G. Oskay-Özcelik[1], A. Mustea[5], B. Schmalfeldt[6], P. Wimberger[7], F. Trillsch[8], S. Mahner[8], M. Klar[9], U. Wagner[10], R. Chekerov[1], A. du Bois[2], J. Sehouli[1]

[1]Department of Gynecology and Center for Oncological Surgery and European Competence Center for Ovarian Cancer, Charité Medical University, Berlin, Germany, [2]Gynecology & Gynecologic Oncology, Kliniken Essen Mitte Evang. Huyssens-Stiftung, Essen, Germany, [3]Department of Gynecology, European Competence Center for Ovarian Cancer, Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]NOGGO, North-Eastern German Society of Gynecological Oncology, Berlin, Germany, [5]Department of Gynecology and Obstetrics, University Medicine Greifswald, Greifswald, Germany, [6]Gynaecology, University of Medical Center Hamburg-Eppendorf, Hamburg, Germany, [7]Department of Gynecology and Obstetrics, Universitätsklinikum Dresden, Dresden, Germany, [8]Gynaecology, AGO Study Group & University of Munich, Munich, Germany, [9]Department of Obstetrics and Gynecology, University Clinics of Freiburg, Freiburg, Germany, [10]Klinik für Gynäkologie, Gyn. Endokrinologie und Onkologie, University of Gießen and Marburg GmbH Site Marburg, Marburg, Germany

Background: Low grade serous carcinomas (LGSC), accounting for approximately 10% of the ovarian tumors, are associated with a better prognosis compared to high-grade serous carcinomas (HGSC). Nevertheless, we are confronted with a challenging treatment, since the median age at diagnosis is younger (55.5 years versus 62.6 years), standard platinum-based chemotherapy is less effective and most importantly, it has still not been as well studied as HGSC. The aim of this survey was to identify the current treatment strategies in Germany.

Methods: An anonymous, digital multiple-choice questionnaire, including 38 questions, was developed and provided to gynaecologists, gynaecologic oncologists and oncologists via Internet.

Results: From December 2017 to January 2018, a total of 180 participants took part in the survey (28% head physicians; 46% senior physicians). The median age was 49 years. 53% stated to have more than 15 years of experience in the treatment of cancer patients. No significant difference was seen in the extent of surgery between HGSC and LGSC (answered by 45%). While 88% stated to perform lymphonodectomy (LNE) for diagnostic and prognostic reasons, 69% used LNE as a decision-making tool for adjuvant therapy (answered by 47%). The most important factors for the indication of chemotherapy (answered by 47%) were comorbidities (92%), residual tumor (79%) and tumor histology (77%). While 43% did not consider antihormonal therapy as a treatment option, 39% stated to indicate a therapy with PARP-inhibitors (answered by 47%).

Conclusions: The results of this study underline the uncertainty in the treatment of LGSC. The implementation of own treatment standards and a prospective register for patients with LGSC is necessary and planed.

Legal entity responsible for the study: North-Eastern German Society of Gynecological Oncology (NOGGO), Berlin, Germany.

Funding: Has not received any funding.

Disclosure: B. Schmalfeldt: Advisor: Roche, Astra Zeneca, Novartis, Tesoro Clovis; Travel support: Roche, AstraZeneca; Research support: MSD, Roche, AstraZeneca. A. du Bois: Advisory board: AstraZeneca, Roche, Pharmamar, Tesaro. All other authors have declared no conflicts of interest.

996P The ability of whole body SUVmax on F-FDG PET/CT in predicting suboptimal cytoreduction at primary debulking surgery in advanced ovarian cancer

G.O. Chong[1], S.Y. Jeong[2], S-W. Lee[2]

[1]Obstetrics and Gynecology, Kyungpook National University School of Medicine, Daegu, Republic of Korea, [2]Nuclear Medicine, Kyungpook National University School of Medicine, Daegu, Republic of Korea

Background: The role of F-18 FDG PET/CT to predict primary optimal cytoreductive surgery for advanced ovarian cancer has not been reported. The aim of this study was to evaluate the predictive value of SUVmax on FDG PET/CT to predict suboptimal cytoreduction and to make risk model for predicting suboptimal cytoreduction using metabolic parameters in advanced ovarian cancer.

Methods: From 2011-2015, 51 patient underwent primary cytoreductive surgery for advanced ovarian cancer (FIGO stage III-IV). Residual disease measuring > 1 cm in maximal diameter was considered a suboptimal surgical result. Whole body 1 SUVmax (WB1SUVmax) was defined as sum of SUVmax in nine abdominal regions (central, right upper, epigastrium, left upper, left flank, left lower, pelvis, right lower, right flank). Whole body 2 SUVmax (WB2SUVmax) was added SUVmax of 3 regional lymph nodes (pelvis, paraaortic and extra-abdominal) to WB1SUVmax. We used the multiple logistic regression analysis to determine predictive value of WBSUVmax. Furthermore, disease-free survival (DFS) and overall survival (OS) were performed using risk model.

Results: Seventeen of 51 patients (33.3%) underwent suboptimal cytoreduction. According to the univariate analysis only ECOG status was associated with suboptimal cytoreduction with marginal significance among the clinical parameters (OR, 4.091; 95% CI, 0.97-17.29; p = 0.0520). Among the PET metabolic parameters, PET central (OR, 5.250; 95% CI, 1.41-19.59; p = 0.0136), PET right upper (OR, 4.148; 95% CI, 1.13-15.19; p = 0.0317), and PET left upper (OR, 5.921; 95% CI, 1.17-30.02; p = 0.0318) were significantly associated with prediction of suboptimal cytoreduction. Moreover, WB2SUVmax was significantly associated with suboptimal cytoreduction (OR, 4.148; 95% CI, 1.13-15.19; p = 0.0317). Kaplan-Meier survival plots showed DFS and OS of high risk group were significantly worse compared to those of low risk group (p = 0.0379 for DFS; p = 0.0211 for OS).

Conclusions: WBSUVmax was significantly associated with suboptimal cytoreduction. Furthermore, hypermetabolic lesions at central and both upper had predictive value for suboptimal cytoreduction.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

997P Brain metastasis in ovarian cancer patients

A.A.B.A. da Costa[1], E.S. Dos Santos[1], L. de Brot[1], A.R.G. Ribeiro[2], D.P. Cotrim[2], N. Carvalho Pandolfi[3], M.G. Cesca[3], M.J. Chen[4], G. Baiocchi[5]

[1]Medical Oncology, A.C. Camargo Cancer Center, São Paulo, Brazil, [2]Medical Oncology, A. C. Camargo Cancer Center, São Paulo, Brazil, [3]Clinical Oncology, A. C. Camargo Cancer Center, São Paulo, Brazil, [4]Radiation Therapy, A. C. Camargo Cancer Center, São Paulo, Brazil, [5]Gynaecology Oncology, A. C. Camargo Cancer Center, São Paulo, Brazil

Background: Central nervous system (CNS) metastasis is a rare event in ovarian cancer patients and current prognostic index used for other tumors do not fit for ovarian cancer patients with brain metastasis (BM). We sought to evaluate prognostic factors for overall survival (OS) in ovarian cancer patients with BM.

Methods: We retrospectively evaluated patients with diagnosis of ovarian carcinoma and BM treated at A.C. Camargo Cancer Center from January 2007 to December 2017. Clinical data from diagnosis and at the moment of diagnosis of BM were collected. OS was defined as the time from diagnosis of BM to the moment of death by any cause. OS was calculated using Kaplan Meier curves and log rank test was used to compare OS curves. Univariate cox regression was used to evaluate prognostic factors for OS.

Results: From 560 patients 26 presented BM. Median age at diagnosis of BM was 62.9 years old, 23 patients had high grade serous carcinoma, 2 had high grade endometrial carcinoma and 1 carcinosarcoma. Recurrences in the brain were classified as platinum sensitive in 14 patients (53.8%) and platinum resistant in 11 patients (42.3%), ECOG performance status was 0 or 1 in sixteen patients. Fourteen patients (53.8%) had disease progression exclusively in the CNS. The median number of BM was 4, and medium size of the largest lesion was 3.2cm. Median time from initial diagnosis to BM was 31.7

months. Eight patients were treated with surgery, 15 with whole brain radiotherapy (RT), 5 with stereotaxic RT and 4 patients received systemic treatment at the moment of BM diagnosis. Median follow up was 18.7 months and median OS was 10.8 months. Factors associated to OS were as following: platinum sensitive recurrence (HR 0.34, CI95% 0.12-0.99; p = 0.049), higher number of previous treatment lines (HR 1.57, CI95% 1.12-2.19; p = 0.008), ECOG performance status (HR 2.52, CI95% 1.24-5.09; p = 0.010), and longer interval from initial diagnosis to BM (p = 0.025). Notably, number of brain metastasis, largest tumor size and progression outside CNS were not related to survival.

Conclusions: Factors related to sensitivity to platinum therapy and BM as early event during the course of disease seem to be more related to survival than factors usually related to survival in BM from other cancers.

Legal entity responsible for the study: A.C. Camargo Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

998TiP Pamiparib, a novel PARP 1/2 inhibitor, monotherapy for gBRCAm patients with recurrent ovarian, fallopian, and primary peritoneal cancer: An open-label, multicenter, phase II trial in China

X. Wu[1], J. Wang[2], Q. Zhou[3], T. Gu[4], K. Zhang[5], J. Liang[6], S. Mu[7], R. Ge[8], H. Yang[9], V. Huang[10], R. Brachmann[11], L. Wang[12], M. Li[4]

[1]Gynaecologic Oncology, Fudan University Shanghai Cancer Center, Shanghai, China, [2]Gynaecologic Oncology, Hunan Cancer Hospital, Changsha, China, [3]Chongqing Office for Cancer Control and Research, Chongqing Cancer Hospital, Chongqing, China, [4]Medical Oncology, BeiGene (Beijing) Co. Ltd., Beijing, China, [5]Biostatistics, BeiGene USA, Inc., Emeryville, CA, USA, [6]Clinical Biomarker, BeiGene (Beijing) Co. Ltd., Beijing, China, [7]Clinical Pharmacology, BeiGene USA, Inc., Fort Lee, NJ, USA, [8]Clinical Research, BeiGene (Beijing) Co. Ltd., Beijing, China, [9]Clinical Development, BeiGene (Shanghai) Co., Ltd., Shanghai, China, [10]Medical Oncology, BeiGene USA, Inc., San Mateo, CA, USA, [11]Clinical Development, BeiGene USA, Inc., San Mateo, CA, USA, [12]China Development, BeiGene (Beijing) Co. Ltd., Beijing, China

Background: Poly (ADP-ribose) polymerase inhibitors (PARPis) represent a class of antitumor agents that exert their cytotoxic effects by inhibiting PARP activity. PARPis are also capable of trapping PARP proteins complexes on damaged DNA, further augmenting cell death. Pamiparib is a selective PARP1/2 inhibitor with potent PARP trapping ability that can cross the blood-brain barrier and has demonstrated antitumor activity in both in vitro and in vivo nonclinical tumor models harboring BRCA gene mutations ($BRCA^{mut}$) and other homologous recombination deficiencies. In Phase 1 studies (NCT02361723; NCT03333915), single-agent pamiparib was generally well tolerated and showed antitumor activity, notably in patients with high-grade non-mucinous ovarian cancer (HGOC). Antitumor activity was observed in patients with BRCA mutant and BRCA wild type ovarian cancers, whose tumors were either sensitive or had platinum-resistant disease. Data from these Phase 1 studies support the recommended Phase 2 pamiparib monotherapy dose of 60 mg PO BID.

Trial design: In this ongoing study of pamiparib in China (NCT03333915), patients with HGOC harboring germline $BRCA^{mut}$ who have received ≥2 prior lines of therapy are being enrolled in the Phase 2 part of the study. Patients with either platinum-sensitive (progression occurring ≥6 months after last dose of platinum) or platinum-resistant (progression occurring <6 months after last dose of platinum) HGOC are eligible. Germline $BRCA^{mut}$ status is identified or confirmed by central testing before enrollment. Approximately 100 patients with HGOC (platinum-sensitive, n = 80; platinum-resistant, n = 20) will receive pamiparib 60 mg PO BID until disease progression. The primary objective is to assess overall response rate according to RECIST v1.1; secondary objectives include assessment of pamiparib's safety, tolerability, and pharmacokinetic profile. Evaluation of antitumor activity will include an estimation of overall and progression-free survival, as well as duration of clinical response.

Clinical trial identification: NCT03333915.

Editorial acknowledgement: Medical writing and editorial support was provided by Regina Switzer, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: Beigene, Ltd.

Funding: Beigene, Ltd.

Disclosure: T. Gu, K. Zhang, J. Liang, S. Mu, R. Ge, H. Yang, V. Huang, R. Brachmann, L. Wang, M. Li: Employee: BeiGene. All other authors have declared no conflicts of interest.

999TiP OVARIO: A single-arm, open-label phase II study of maintenance therapy with niraparib + bevacizumab (bev) in patients (pts) with advanced ovarian cancer (OC) after response to frontline platinum-based chemotherapy (chemo)

M. Hardesty[1], J.M. Hope[1], T. Krivak[2], J. Chen[3], M. Wainszelbaum[3], D. Gupta[4], D. Richardson[5]

[1]Obstetrics & Gynecology, Alaska Women's Cancer Care, Anchorage, AK, USA, [2]Obstetrics & Gynecology, The Western Pennsylvania Hospital, Pittsburgh, PA, USA, [3]Biostatistics, Tesaro, Inc., Waltham, MA, USA, [4]Clinical Science, Tesaro, Inc., Waltham, MA, USA, [5]Gynecologic Oncology, Oklahoma University, Health Sciences Center, Oklahoma City, OK, USA

Background: Most pts with advanced OC will experience recurrence within 2 years of initial platinum-based treatment. An unmet need exists for therapies that delay disease recurrence. Niraparib (Zejula®) is a selective poly(ADP-ribose) polymerase (PARP) 1/2 inhibitor approved for maintenance in pts with recurrent OC regardless of BRCA or homologous recombination deficiency (HRD) status. Bev is a VEGF inhibitor approved in OC for treatment and maintenance therapy. Targeted therapies + VEGF inhibition showed synergy in preclinical models. Induction of intratumoural hypoxia downregulating *BRCA* and *RAD51* may sensitize tumours to PARP inhibition and lead to apoptosis via contextual synthetic lethality. Niraparib + bev is being explored in the treatment setting in the ongoing phase 1/2 AVANOVA trial, which has shown that niraparib can be safely combined with bev. In OVARIO, niraparib + bev will be evaluated in the maintenance setting in pts with advanced OC who have recovered from primary debulking surgery and responded to frontline platinum-based chemo with bev.

Trial design: Target enrolment is 90 pts, regardless of *BRCA* or HRD status, with stage 3b and 4 epithelial ovarian, fallopian tube, or peritoneal cancer. Pts must achieve complete or partial response or no evidence of disease after frontline platinum-based chemo with bev. The starting dose of niraparib will be based on baseline body weight and/or platelet count. Pts weighing ≥77 kg with a platelet count of ≥ 150,000/μL will receive 300 mg qd. Pts weighing <77 kg or with a platelet count of < 150,000/μL will receive 200 mg qd. The bev dosage will be 15 mg/kg q3w up to 15 months. Pts will be treated continuously until disease progression or unacceptable toxicity. The primary objective for OVARIO is progression-free survival at 18 months. Secondary objectives include overall survival, time to first subsequent therapy, and safety and tolerability.

Clinical trial identification: NCT03326193.

Editorial acknowledgement: Writing and editorial support, funded by Tesaro, Inc. (Waltham, MA, USA) and coordinated by Hemant Vyas, PhD of Tesaro, Inc., was provided by Nicole Renner, PhD and Mary Kacillas of Ashfield Healthcare Communications (Middletown, CT, USA).

Legal entity responsible for the study: Tesaro, Inc.

Funding: Tesaro, Inc.

Disclosure: J.M. Hope: Stock and other ownership interests: Alaska Cyberknife Center. J. Chen, M. Wainszelbaum, D. Gupta: Employment, stock and other ownership interests: Tesaro, Inc. All other authors have declared no conflicts of interest.

1000TiP OPINION: A single-arm, open-label, phase IIIb study of olaparib maintenance monotherapy in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) and without germline BRCA mutations (non-gBRCAm)

A.M. Poveda[1], R. Davidson[2], C. Blakeley[2], A. Milner[3]

[1]Department of Gynecologic Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [2]GMA Oncology TA, AstraZeneca, Cambridge, UK, [3]Biometrics and Information Sciences, AstraZeneca, Cambridge, UK

Background: Olaparib (tablet formulation) is approved in the US for maintenance treatment of PSROC based on 2 pivotal studies (Study 19 [NCT00753545], SOLO2 [NCT01874353]), which showed a significant progression free survival (PFS) benefit. In Study 19, clinical benefit was observed in pts with or without BRCA mutations, supporting the hypothesis that platinum sensitivity is a surrogate marker for homologous recombination deficiency (HRD). This study was designed to further prospectively explore olaparib activity in non-gBRCAm pts.

Trial design: This single-arm, open-label, multicenter, phase 3b study (OPINION; NCT03402841) was designed to assess the efficacy and safety of olaparib maintenance therapy in women with non-gBRCAm, high-grade serous or endometrioid PSROC. Eligible pts (≥18 y, ECOG PS 0-1, ≥2 lines of prior platinum therapy [PT], and in response [CR/PR] to last PT) will be treated with olaparib 300 mg tablets twice daily until disease progression or unacceptable toxicity. Primary endpoint is investigator-assessed PFS (RECIST v1.1). Secondary endpoints are time to first subsequent therapy or death, time to treatment discontinuation or death, chemotherapy-free interval, PFS by tumor HRD status, and health-related quality of life (FACT-O). Safety and tolerability also will be assessed. Exploratory endpoints are overall survival, evaluating treatment impact and disease state on health state utility (EQ-5D-5L), and PFS in pts stratified by molecular subgroups (including mutations in HR repair genes, microsatellite instability status, TP53 mutation disruption status, and tumor mutation load score). Correlation between HRD status from tumor and circulating tumor DNA in matched pts also will be explored. A sample size of 250 pts was opted for adequate level of precision for PFS estimation, with mean 95% CI width at 30 mo after first pt is

estimated at 3.27 mo from 500 simulations of a piecewise exponential model with median PFS of 8.5 mo at 12 mo enrollment. Efficacy analyses will be based on all enrolled pts and safety analyses on enrolled pts receiving ≥1 olaparib dose. Enrollment is ongoing.

Clinical trial identification: NCT03402841.

Editorial acknowledgement: Editorial assistance, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Kaveri Sidhu, PhD, of Cactus Communications (Mumbai, India).

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: A.M. Poveda: Consulting or advisory role: Roche, AstraZeneca, Novartis, Immunogen, Tesaro, PharmaMar. R. Davidson, A. Milner: Employment: AstraZeneca. C. Blakeley: Employment: AstraZeneca, Worldwide Clinical Trials; Stock ownership: Pfizer.

1001TiP A phase II clinical trial of veliparib and topotecan in patients with platinum resistant ovarian cancer

A.E. Wahner Hendrickson[1], B. Costello[1], A. Jewell[2], V. Kennedy[3], G. Fleming[4], B. Corr[5], S.E. Taylor[6], J. Lea[7], J. Reid[8], E. Swisher[9], D. Satele[10], J. Allred[10], J. Lensing[1], S.P. Ivy[11], C. Erlichman[1], A.A. Adjei[1], S. Kaufmann[8]

[1]Department of Oncology, Mayo Clinic, Rochester, MN, USA, [2]Department of Obstetrics and Gynecology, University of Kansas, Kansas City, KS, USA, [3]Department of Obstetrics and Gynecology, UC Davis Medical Center, Davis, CA, USA, [4]Department of Medicine (Section of Hematology/Oncology), University of Chicago, Chicago, IL, USA, [5]Department of Gynecologic Oncology, University of Colorado Denver, Aurora, CO, USA, [6]Department of Obstetrics, Gynecology and Reproductive Services, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA, [7]Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [8]Department of Oncology Research, Mayo Clinic, Rochester, NY, USA, [9]Department of Gynecologic Oncology, University of Washington, Seattle, WA, USA, [10]Department of Biostatstics, Mayo Clinic, Rochester, NY, USA, [11]Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD, USA

Background: Preclinical observations indicate that addition of PARP inhibitors to topoisomerase I-directed agents such as topotecan results in increased antitumor efficacy in vitro and in vivo. However, when veliparib or olaparib were combined with conventional 5 day topotecan in patients, the regimens were quite myelosuppressive. In contrast, a phase I trial of veliparib in combination with weekly topotecan, a less myelosuppressive but routinely used regimen, demonstrated a manageable safety profile and early signs of activity. This was manifested by responses or disease stability for ≥ 4 months in 52% of patients, particularly in ovarian cancer patients with deleterious germline repair pathway mutations. Therefore, a phase 2 clinical trial is now underway.

Trial design: This single arm, multi-center clinical trial is open and available at Experimental Therapeutics Clinical Trials Network (ETCTN) sites in the US. The primary endpoint is response rate and the secondary endpoint is progression free survival. Correlative goals include assessing differences in toxicity and efficacy based on BRCA1/2 mutation status as well as evaluating the association between pretreatment tumor cell levels of topoisomerase 1, PARP, XRCC1 or P-glycoprotein and response. Eligible patients must have platinum resistant ovarian, primary peritoneal or fallopian tube cancer and have received 2 or fewer prior chemotherapy regimens. ECOG performance status of 0, 1, or 2 and adequate bone marrow, renal and hepatic function are also required. No prior PARP inhibitor therapy is allowed.

Clinical trial identification: NCT01012817.

Legal entity responsible for the study: NCI CTEP.

Funding: NCI/ CTEP.

Disclosure: All authors have declared no conflicts of interest.

1002TiP BAROCCO: A randomized phase II study of weekly paclitaxel vs cediranib-olaparib with continuous schedule vs cediranib-olaparib with intermittent schedule in advanced platinum resistant ovarian cancer

N. Colombo[1], O. Nicoletto[2], P. Benedetti Panici[3], G. Tognon[4], A.A. Lissoni[5], A. Bologna[6], F. Tomao[3], R. Fossati[7], F. Tettamanzi[7], E. Rulli[7], F. Galli[7], M.F. Alvisi[7], V. Torri[7], E. Biagioli[7]

[1]Gynecologic Oncology, European Institute of Oncology and University of Milan-Bicocca, Milan, Italy, [2]Oncology, IRCCS Istituo Oncologico Veneto - IOV, Padua, Italy, [3]Gynecological and Obstetrics Sciences and Urological Sciences, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome, Italy, [4]Gynecology and Obstetrics, Università degli Studi di Brescia, Brescia, Italy, [5]Gynecologic Oncology, Ospedale S. Gerardo, Monza, Italy, [6]Oncology, IRCCS Azienda Ospedaliera Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, [7]Oncology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Background: Cediranib and olaparib have shown efficacy in ovarian cancer (OC) throughout several clinical settings. A phase II study demonstrated that the combination of the two drugs increased progression free survival (PFS) in women with recurrent platinum sensitive OC with respect to olaparib (Liu et al, 2014). The greatest benefit from the combination was observed in wild-type/unknown BRCA patients, therefore suggesting a possible effect of the combination in platinum resistant OC which are mainly BRCA proficient tumors. The most frequent grade ≥ 3 AEs with the combination were hypertension, diarrhea and fatigue, suggesting an amplificatory effect caused by cediranib. The purpose of this study is to test the efficacy of olaparib/cediranib combination in platinum resistant disease, comparing this regimen with weekly paclitaxel, and to identify a more tolerable schedule for this combination treatment.

Trial design: This is a randomized multicenter phase II open label study. Patients with platinum resistant OC will be randomized in a 1:1:1 ratio in a control and two experimental arms. Control treatment consists of administration of 80 mg/m^2 weekly paclitaxel, up to a maximum of 24 weeks or to progression. Combination therapy is administered up to progression with two different schedules: i. Continuous with 600 mg olaparib (tablets) and 20 mg cediranib given every day; ii. Intermittent with 600 mg olaparib (tablets) given every day and 20 mg cediranib given 5 days/week. The study has two primary endpoints: 1) PFS, to compare the efficacy between control and experimental arms with a 80% power to detect a benefit ≥ 3.3 months and, 2) the number of evacuations/day in the first 28 days of the combination therapy as tolerability indicator. If both experimental arms show superiority - in terms of PFS - to control treatment, these will be compared for tolerability. The study is registered at clinicaltrials.gov (NCT03314740) and is currently recruiting. Eighty-seven patients out of 100 planned have already been enrolled from 6 experimental sites in Italy in 11 months.

Clinical trial identification: EudraCT: 2016-003964-38; NCT03314740.

Legal entity responsible for the study: IRCCS Istituto di Ricerche Farmacologiche Mario Negri di Milano.

Funding: AstraZeneca.

Disclosure: N. Colombo: Immediate family member has been employed by Ignyta during the past 2 years; Honoraria: F. Hoffmann-La Roche Ltd, AstraZeneca, PharmaMar, Clovis, Tesaro, Pfizer during the past 2 years; Consulting or advisory role: F. Hoffmann-La Roche Ltd, AstraZeneca, PharmaMar, Clovis, Tesaro, Pfizer during the past 2 years; Travel, accommodations and other expenses: F. Hoffmann-La Roche Ltd, PharmaMar, AstraZeneca, Tesaro during the past 2 years. A.A. Lissoni: Travel, accommodations and other expenses: F. Hoffmann-La Roche Ltd during the past 2 years. R. Fossati: Travel, accommodations and other expenses: PharmaMar during the past 2 years. All other authors have declared no conflicts of interest.

1003TiP Neoadjuvant chemotherapy and radical surgery versus chemorradiation for stage IB2, IIA2 e IIB cervical cancer: A randomized controlled trial

P.T.F. Reis Filho[1], J.M. Andrade[2], M.P. Batista[3], C.B. Sousa[2], T.H.G.F. Oliveira[2], G.V. Arruda[4], T.M.G. Oliveira[4], F. Gabrielli[3], M.L.N.D. Genta[5], A.M. Poveda[6], M.D.P. Estevez Diz[3], F.J. Candido Dos Reis[7]

[1]Medical Oncology Division, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Ribeirao Preto, Brazil, [2]Division of Gynecologic Oncology, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto, Brazil, [3]Radiology and Oncology Department, Insituto do Cancer do Estado de São Paulo/Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Division of Radiology and Radiotherapy, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto, Brazil, [5]Gynecology, Insituto do Cancer do Estado de São Paulo/Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [6]Oncogynecologic Department, Hospital Quironsalud, Valencia, Spain, [7]Gynecology and Obstetrics, Ribeirão Preto Medical School, Ribeirao Preto, Brazil

Background: Chemoradiation is the current standard of care for advanced cervical cancer, however radiation is associated with long term side effects that may impair the quality of life of survivors. Recent findings from observational and case series suggest that women with stage IB2, IIA, and IIB who respond to neoadjuvant chemotherapy might be a candidate for radical surgery as the definitive treatment. This approach can

reduce long-term complications associated with chemoradiation and improve patient quality of life.

Trial design: Eligible patients are women aged ≥ 18y diagnosed with invasive cervical cancer stages IB2, IIA or IIB. The stage will be assessed by clinical examination and confirmed by pelvic MRI, CT of upper abdomen and CT of thorax. ECOG PS 0-1 and adequate organ function are required. Two hundred and forty-four patients will be randomly assigned to one of two arms. In arm 1, patients will receive standard chemoradiation (cisplatin 40mg/m2 IV: D1, D8, D15, D29 and D36 in concomitancy with external radiation 50.4Gy fractionated in 28 sessions of 1,8Gy followed by brachytherapy in four insertions of 7 Gy). In arm 2, patients will receive intravenous neoadjuvant chemotherapy (cisplatin 75mg/m2 D1 plus paclitaxel 80mg/m2) D1, D8 e D15, each 21 days, 3 cycles. After each cycle, the patient will be evaluated to verify toxicity and tumor response. After the third cycle, the patients with a complete clinical response or substantial tumor reduction (tumor restricted to cervix ≤4 cm), confirmed by pelvic MRI will undergo Piver-Rutledge class III abdominal hysterectomy and pelvic lymphadenectomy 3-6 weeks after the last cycle. Patients with tumor progression or severe toxicity after any cycle of neoadjuvant chemotherapy, or with inoperable tumor after the third cycle of neoadjuvant chemotherapy will be treated with definitive standard chemoradiation. The primary end point will be 5-years overall survival. Secondary endpoints will include survival free of disease, the rate of operability and complete pathological response in the neoadjuvant arm. The study is ongoing; one patient has been included, and three more are under preliminary evaluation for eligibility.

Clinical trial identification: UTN: U1111-1213-5169.

Legal entity responsible for the study: Division of Gynecologic Oncology - Department of Gynecology and Obstetrics - Ribeirão Preto Medical School - University of São Paulo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii359–viii371, 2018
doi:10.1093/annonc/mdy286

HAEMATOLOGICAL MALIGNANCIES

1004O Final overall survival results of frontline bortezomib plus rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) vs R-CHOP in transplantation-ineligible patients (pts) with newly diagnosed mantle-cell lymphoma (MCL): A randomized, open-label, phase III (LYM-3002) study

F. Cavalli[1], J. Jin[2], H. Pylypenko[3], G. Verhoef[4], N. Siritanaratkul[5], J. Drach[6], M. Raderer[7], J. Mayer[8], J. Pereira[9], G. Tumyan[10], R. Okamoto[11], S. Nakahara[12], P. Hu[13], C. Appiani[14], S. Nemat[15], T. Robak[16]

[1]Oncology, IOSI - Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland, [2]University College of Medicine, The First Affiliated Hospital of Zhejiang, Zhejiang, China, [3]Department of Hematology, Cherkassy Regional Oncology Dispensary, Cherkassy, Ukraine, [4]Hematology, University Hospital Leuven, Leuven, Belgium, [5]Siriraj Hospital, Mahidol University, Bangkok, Thailand, [6]Hematology, Allgemeines Krankenhaus der Stadt Wien, Vienna, Austria, [7]Vienna General Hospital, University of Vienna, Vienna, Austria, [8]Internal Haemato-Oncology Department, Masaryk University Hospital, Brno, Czech Republic, [9]De Medicina Da USP, Hospital Das Clinicas Da Faculdade, São Paulo, Brazil, [10]Cancer Research Center, N.N. Blokhin Academy of Medical Science, Moscow, Russian Federation, [11]Chibanishi General Hospital, Tokyo Metropolitan - Komagome Hospital, Chiba, Japan, [12]Oncology, Janssen Pharmaceutical K.K., Tokyo, Japan, [13]Biostatistics, Janssen Research & Development, LLC, Raritan, NJ, USA, [14]Established Products, Janssen Research & Development, LLC, Titusville, NJ, USA, [15]Established Products, Janssen Research & Development, LLC, High Wycombe, UK, [16]Copernicus Memorial Hospital, Medical University of Lodz, Lod, Poland

1005O A revised international prognostic score system for Waldenström's macroglobulinemia

M. Gavriatopoulou[1], E. Kastritis[1], P. Morel[2], A. Duhamel[3], M.C. Kyrtsonis[4], E. Durot[3], A. Symeonidis[5], K. Laribi[6], E. Hatjiharisi[7], L. Ysebaert[8], A. Vassou[9], N. Giannakoulas[10], G. Merlini[11], P. Repousis[12], M. Varettoni[13], E. Michalis[14], B. Hivert[13], M. Michalis[15], V. Leblond[13], M.A.C. Dimopoulos[1]

[1]Oncology Department, Alexandra Hospital, Athens, Greece, [2]CHU Amiens Picardie, Service d'Hematologie Clinique Therapie Cellulaire, Amiens, France, Centre Hospitalier de Lens, Lens, France, [3]Univ. Lille, CHU Lille, EA2694 – Santé Publique: Épidémiologie et Qualité des Soins, Lille, France, [4]Hematology Department, Laikon Hospital, Athens, Greece, [5]Hematology Department, Patras General Hospital, Patras, Greece, [6]Hematology Department, Hospital Le Mans, Le Mans, France, [7]Hematology Department, Ippokrateion Hospital, Thessaloniki, Greece, [8]Hematology Department, Institut Claudius Regaud - IUCT Oncopole, Toulouse, France, [9]Hematology Department, General Ioannina Hospital, Chalandri, Greece, [10]Hematology Department, Larissa General Hospital, Larissa, Greece, [11]Hematology Department, Pavia Hospital, Pavia, Italy, [12]Hematology Department, Metaksa Hospital, Athens, Greece, [13]French Innovative Leukemia Organization, French Innovative Leukemia Organization, Lille, France, [14]Hematology Department, Genikon Kratikon Hospital, Athens, Greece, [15]Hematology Department, Leukosia General Hospital, Leukosia, Cyprus

1006O Copanlisib monotherapy activity in relapsed or refractory indolent B-cell lymphoma: Combined analysis from phase I and II studies

P.L. Zinzani[1], A. Santoro[2], L. Mollica[3], G.A. Follows[4], K. Bouabdallah[5], F. Morschhauser[6], A. Patnaik[7], L. Huang[8], F. Hiemeyer[9], A. Benson[8], I. Genvresse[10], J.E. Garcia-Vargas[11], B.H. Childs[12], M.H. Dreyling[13]

[1]Institute of Hematology "L. e A. Seragnoli", University of Bologna, Bologna, Italy, [2]Department of Oncology and Haematology, Istituto Clinico Humanitas, Rozzano, Italy, [3]Department of Haematology, Hôpital Maisonneuve-Rosemont-Montreal, Montreal, QC, Canada, [4]Department of Haematology, Cambridge University Hospitals NHS Foundation Trust Addenbrooke's Hospital, Cambridge, UK, [5]Service d'Hématologie et de Thérapie Cellulaire, University Hospital of Bordeaux, Pessac, France, [6]Department of Hematology, CHRU - Hôpital Claude Huriez, Lille, France, [7]Phase I Medical Oncology Program, South Texas Accelerated Research Therapeutics (START), San Antonio, TX, USA, [8]Clinical Statistics, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, [9]Clincial Statistics, Bayer AG, Berlin, Germany, [10]Pharmaceutical Division, Bayer AG, Berlin, Germany, [11]Clinical Development, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, [12]Clinical Development, Bayer HealthCare Pharmaceuticals, New York, NY, USA, [13]Medizinische Klinik III - Klinikum der Universität, Ludwig Maximilians University Munich, Munich, Germany

1007O **Impact of initial treatment (tx) on HRQoL and outcomes in patients (pts) with newly diagnosed multiple myeloma (NDMM) without intent for immediate transplant (SCT): Results from the Connect® MM registry**

R. Abonour[1], R.M. Rifkin[2], C. Gasparetto[3], K. Toomey[4], B.G.M. Durie[5], J.W. Hardin[6], H.R. Terebelo[7], S. Jagannath[8], M. Narang[9], S. Ailawadhi[10], S. Srinivasan[11], A. Kitali[12], A. Agarwal[12], L. Wagner[13]

[1]Hematology/Oncology, Indiana University, Indianapolis, IN, USA, [2]Medical Oncology / Hematology, Mountain Cancer Centers US Oncology, Denver, CO, USA, [3]Hematologic Malignancies and Cellular Therapy, Duke University Medical Centre, Durham, NC, USA, [4]Hematology and Medical Oncology, Steeplechase Cancer Center, Somerville, MA, USA, [5]Hematology/Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [6]Epidemiology and Biostatistics, University of South Carolina, Columbia, SC, USA, [7]Hematology, Providence Cancer Institute, Novi, MI, USA, [8]Medicine, Hematology and Medical Oncology, Mount Sinai Hospital, New York, NY, USA, [9]Hematology/Oncology, US Oncology Research, Columbia, SC, USA, [10]Hematology/Oncology, Mayo Clinic, Jacksonville, FL, USA, [11]Biostatistics, Celgene Corporation, Summit, NJ, USA, [12]Medical Affairs, Celgene Corporation, Summit, NJ, USA, [13]Social Sciences & Health Policy, Wake Forest University School of Medicine, Winston-Salem, NC, USA

1008PD **CD13 and CD33 CAR-T cells for the treatment of myeloid malignancies**

K.H. Lee[1], K. Gowrishankar[2], D. Gottlieb[1], E. Blyth[1], K. Micklethwaite[1]

[1]Haematology Department, Westmead Hospital, Westmead, Australia, [2]Haematology Department, Westmead Institute for Medical Research, Westmead, Australia

1009PD The identification of the AXL/Gas6 signalling axis as a key player of myelodysplastic syndrome (MDS) and the potential of the oral selective AXL inhibitor bemcentinib in the treatment of MDS

H. Medyouf[1], I. Tirado-Gonzalez[1], A. Mies[2], A. Nevmerzhitskaya[1], A-S. Kubasch[2], U. Platzbecker[2]

[1]Georg-Spyer-Haus, Institute for Tumor Biology and Experimental Therapy, Frankfurt am Main, Germany, [2]Medical Clinic and Polyclinic I, TU Dresden, Dresden, Germany

1010PD ALK positive anaplastic large cell lymphoma: Molecular diagnosis and minimal residual disease monitoring

M. Kalinova[1], L. Krskova[1], M. Mrhalova[2], E. Kabickova[3], P. Riha[3], R. Kodet[1]

[1]Department of Pathology and Molecular Medicine, 2nd Faculty of Medicine Motol University Hospital, Prague, Czech Republic, [2]Department of Pathology and Molecular Medicine, Motol University Hospital, Prague, Czech Republic, [3]Department of Paediatric Haematology and Oncology, 2nd Faculty of Medicine Motol University Hospital, Prague, Czech Republic

1011PD Intensified 14-day rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP14) compared to RCHOP21 in patients with newly diagnosed diffuse large B cell lymphoma (DLBCL): A systematic review and meta-analysis of randomized controlled trials

J.D. Sandoval-Sus[1], S. Dalia[2], R.S. Mhaskar[3], J.C. Chavez[4], A. Ausekar[5], K. Purnapatre[5], J. Scheiber[5], L. Sokol[4]

[1]Malignant Hematology, Moffitt Cancer Center, Pembroke Pines, FL, USA, [2]Oncology and Hematology, Mercy Clinic, Joplin, MO, USA, [3]Internal Medicine, University of South Florida, Tampa, FL, USA, [4]Malignant Hematology, Moffitt Cancer Center, Tampa, FL, USA, [5]Personome, Munich, Germany

1012PD **Evaluation of safety, tolerability and efficacy of temsirolimus in patients (pts) with relapsed or refractory mantle cell lymphoma (rel/refr MCL) in routine clinical practice**

M.H. Dreyling[1], G. Hess[2], M. Woike[3], G. Krekeler[3]

[1]Medizinische Klinik III, Ludwig Maximilians University, Grosshadern, Munich, Germany, [2]III. Medizinische Klinik, Universitätsmedizin der Johannes Gutenberg-Universität, Mainz, Germany, [3]Medical Affairs, Pfizer - Germany, Berlin, Germany

1013PD **A comparative study of 18F-FDG PET/CT with bilateral bone marrow trephine biopsy for assessment of bone marrow infiltration by lymphoma**

D. Arjunan[1], G. Prakash[1], P. Malhotra[1], N. Varma[2], S.C. Varma[1], A. Das[3], B.R. Mittal[4], R. Basher[4], D. Lad[1], S. Kumari[1], A.R. Khadwal[1], S. Vikas[1], S. Naseem[2], A. Bal[3]

[1]Internal Medicine, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, [2]Hematology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, [3]Histopathology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, [4]Nuclear Medicine, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

1014PD **Phase I/II, first in human trial with M7583, a Bruton's tyrosine kinase inhibitor (BTKi), in patients with B cell malignancies**

W. Jurczak[1], S. Rule[2], W. Townsend[3], D. Tucker[4], B. Sarholz[5], J. Scheele[6], J. Gribben[7], P.L. Zinzani[8]

[1]Department of Haematology, Jagiellonian University, Krakow, Poland, [2]Department of Haematology, Plymouth University Medical School, Plymouth, UK, [3]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK, [4]Department of Haematology, Torbay and South Devon NHS Trust, Torquay, UK, [5]R&D Global Biostatistics & Epidemiology, Merck KGaA, Darmstadt, Germany, [6]Global Clinical Development, Merck KGaA, Darmstadt, Germany, [7]Department of Haematology, Barts Cancer Institute, Queen Mary University of London, London, UK, [8]Institute of Hematology "L.e A. Seragnoli", University of Bologna, Bologna, Italy

1015PD **A prospective study of first-line Helicobacter pylori eradication therapy in treating localized extragastric mucosa-associated lymphoid tissue lymphoma**

S-H. Kuo[1], M. Yao[2], C-H. Tsai[2], C-W. Lin[3], J-M. Liou[2], W-L. Ma[1], A-L. Cheng[1]

[1]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan, [2]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [3]Department of Pathology, National Taiwan University Hospital, Taipei, Taiwan

1016PD **Bendamustine and rituximab followed by 90Y-ibritumomab tiuxetan for relapsed follicular lymphoma: A preliminary analysis of a multicenter, prospective phase II study (BRiZ2012)**

M. Kanno[1], K. Miura[2], Y. Masaki[3], H. Tsujimura[4], M. Iino[5], J. Takizawa[6], Y. Maeda[7], K. Yamamoto[8], S. Tamura[9], A. Yoshida[10], H. Yagi[11], I. Yoshida[12], K. Kitazume[13], T. Masunari[14], I. Choi[15], Y. Kakinoki[16], T. Yoshino[17], S. Nakamura[18], T. Yoshida[19]

[1]Oncology Center, Nara Medical University Hospital, Kashihara, Japan, [2]Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [3]Department of Hematology and Immunology, Kanazawa Medical University, Ishikawa, Japan, [4]Division of Hematology-Oncology, Chiba Cancer Center, Chiba, Japan, [5]Department of Medical Oncology, Yamanashi Prefectural Central Hospital, Kofu, Japan, [6]Department of Hematology, Endocrinology and Metabolism, Niigata University Faculty of Medicine, Niigata, Japan, [7]Department of Hematology and Oncology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [8]Department of Hematology, Okayama City Hospital, Okayama, Japan, [9]Department of Hematology, Kinan Hospital, Minamimure, Japan, [10]Department of Hematology, Toyama Prefectural Central Hospital, Toyama, Japan, [11]Department of Hematology, Kinki University Nara Hospital, Ikoma, Japan, [12]Hematologic Oncology, National Hospital Organization, Shikoku Cancer Center, Matsuyama, Japan, [13]Department of Hematology, Showa General Hospital, Tokyo, Japan, [14]Department of Hematology, Chugoku Central Hospital, Fukuyama, Japan, [15]Department of Hematology, National Hospital Organization, Kyushu Cancer Center, Fukuoka, Japan, [16]Department of Hematology, Asahikawa City Hospital, Asahikawa, Japan, [17]Department of Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [18]Department of Pathology and Biological Response, Nagoya University Graduate School of Medicine, Nagoya, Japan, [19]Member,Society of Lymphoma Treatment in Japan, Kanazawa, Japan

1017P **Estimating the incidence of cryptogenic organising pneumonia in chronic lymphocytic leukaemia patients: A real-world cohort study**

I. Faghmous[1], H. Ramroth[1], C. Aguilar[2], A. Van Troostenburg[2], P. Badyal[1]

[1]Epidemiology, Gilead Sciences, Uxbridge, UK, [2]PVE, Gilead Sciences, Uxbridge, UK

Background: Cryptogenic Organising Pneumonia (COP) is an understudied lung disease characterised by presence of granulation tissue within the alveolar ducts and alveoli. While prognosis of patients with COP is generally positive there remains a paucity of information on the condition in the academic literature. This abstract presents the largest real-world study of COP in Chronic lymphocytic Leukaemia (CLL) patients to date.

Methods: A retrospective cohort study utilising the IMS Pharmetrics Plus database. A CLL patient cohort was identified using ICD9/10 codes; patients with previous history of COP prior to CLL diagnosis were excluded from the analysis. As a comparator, a random 5% sample of all patients with no history of CLL was taken. Crude Incidence rates (CR) of COP were estimated in both groups. A Poisson regression model (PRM) was

fitted to estimate the age and sex adjusted incidence rate ratio (IRR) of experiencing COP in CLL patients versus those with no history of CLL. Tests for trend were conducted for age and sex.

Results: A total of 64,773 CLL and 3,201,48 non-CLL patients were included in the study. The CLL cohort comprised of 59% males with a total of 436 patients experiencing COP. The non-CLL cohort comprised of 47% males with 1,971 patients experiencing COP. The CR of COP in the CLL cohort was 2.4 (95% CI 2.2- 2.61) per 1,000 person years (py) and 0.20 (95% CI 0.19- 0.21) per 1,000 py in the non CLL cohort. An age and sex adjusted PRM estimated an IRR of 7.7 (95% CI 6.9- 8.68, p-value <0.001). A significant trend of increasing COP incidence was observed for age (p-value <0.001). However, no differences found for gender.

Conclusions: This study indicated that CLL patients had a higher rate of experiencing an episode of COP as opposed to non-CLL patients, adjusted for age and sex. As COP is difficult to distinguish from the infectious and non-infectious inflammatory pulmonary process in CLL patients, awareness of this increased risk may lead to earlier diagnosis and institution of treatment of COP. The role of co-morbidities and co-medications will be investigated in further analyses.

Legal entity responsible for the study: Gilead Sciences Gilead Sciences.

Funding: Gilead Sciences.

Disclosure: I. Faghmous, H. Ramroth, C. Aguilar, A. Van Troostenburg, P. Badyal: Gilead Sciences.

1018P Progression of disease within 2 years (POD24) is a clinically significant endpoint to identify follicular lymphoma patients with high risk of death

C. Sortais[1], A. Lok[1], T. Gastinne[1], B. Mahé[1], V. Dubruille[1], N. Blin[1], S. Howlett[2], A. Tabah[2], P. Arnaud[2], A. Moreau[3], P. Moreau[1], C. Leux[4], S. Le Gouill[1]

[1]*Service d'Hématologie Clinique, CHU de Nantes, Nantes, France,* [2]*Lymphoma Department, Celgene Medical, Summit, NJ, USA,* [3]*Service d'Anatomopathologie, CHU de Nantes, Nantes, France,* [4]*Service d'Information Médicale, CHU de Nantes, Nantes, France*

Background: Follicular lymphoma (FL) is an indolent non-Hodgkin's lymphoma with heterogeneous outcomes among patients. Casulo et al (JCO 2015) showed that progression of disease within 2 years (POD24) after diagnosis for FL patients treated by R-CHOP was associated with poor outcomes, needing further validations before using it as a standard endpoint to evaluate treatment efficacy. We investigated the POD24 predictive value for all patients treated or not with R-CHOP in our institution (Nantes Medical University, France).

Methods: Patients with grade 1, 2 or 3a FL treated from 2007 were registered in our local database (approved by French authorities, CNIL) and included in the present retrospective monocentric study, with up-dating of patient's outcomes. FL diagnosis was performed by local pathologist experts (members of the national LYSA-pathologist group, France).

Results: Between 2007 and 2016, 317 patients with confirmed FL were included. At diagnosis: 24 did not received any treatment (Wait and watch), 259 were treated with Rituximab (R) (including R alone in 98 cases), 143 received an anthracycline-containing regimen (mainly R-CHOP like), 5 received bendamustine-containing regimen, radiotherapy alone in 11 cases and another chemotherapy regimen in 36 cases (mainly R-COP). Second line treatment (N = 151) consisted of chemotherapy in 91 cases, R alone in 37 cases. After first line therapy, 61 patients relapsed or died within 2y (POD24+), 99 patients after 2y, including 21 transformations, and 154 patients did not progress or die (missing = 3). At the time of the present analysis, the median follow-up is 5y. Median PFS is 58.2 months. OS at 1y, 3y, and 5y are 98.4% [97.0-99.8], 95.1% [92.6-97.6] and 92.5% [89.3-95.9] respectively. The 5y OS was statistically worst for POD24+ patients (82 % [71.9-93.5]) than for POD24- patients (93.3% [88.98-97.8]) (p = 0.00001). Age at diagnosis (≥60), performance status (PS ≥ 1), FLIPI, FLIPI2 scores (high) and transformation are predictive of OS in univariate analysis. PS (≥1) at diagnostic is predictive of POD24+.

Conclusions: POD24 is predictive of a worse OS regardless of first line treatment nature and can be recommended as a relevant endpoint for clinical trials.

Legal entity responsible for the study: CHU de Nantes.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1019P Impact of genetic polymorphisms on prognosis and survival of diffuse large B-cell lymphoma

O. Novosad[1], I. Pastushenko[1], T. Skrypets[1], I. Tytorenko[1], T. Kadnikova[1], O. Skachkova[2], O. Gorbach[2], N. Svergun[2], N. Khranovska[2], I. Kriachok[1]

[1]*Onco-Hematology, National Cancer Institute of the MPH Ukraine, Kiev, Ukraine,* [2]*Experimental Oncology, National Cancer Institute of the MPH Ukraine, Kiev, Ukraine*

Background: DLBCL is the most common subtype of NHL in adults. The efficacy of chemotherapy in DLBCL patients has significantly increased in the last 10 years. Growing evidence has shown genetic and environmental factors are involved in the etiology and prognosis of DLBCL. Genetic polymorphisms can influence the individual susceptibility and clinical outcome for different types of Lymphomas. The aim of this study was to investigate the genetic polymorphism of glutathione S-transferase P1 (GSTP1), as a prognostic factor for patients with DLBCL.

Methods: 136 patients with DLBCL, 56 men and 80 women, median age - 47 y.o were included in the study. The patients received R-CHOP-like regimens. Genomic DNA was extracted from blood samples. GSTP1 polymorphism (c. 313 A > G, p. Ile105Val) were analyzed by Allelic Discrimination Real-Time PCR.

Results: A homozygous for the A313A GSTP1 genotype was detected in 65/136 (47.8%) patients, heterozygous A313G – in 57/136 (42%) and 14/136 (10.2%) were homozygous for the G313G genotype of DLBCL ($p < 0.05$). The GSTP1 genotype distribution was conformed to Hardy-Weinberg equilibrium ($\chi 2=0.05$;$p=1.01$). The frequency of the homozygous wild genotype of the GSTP1 was significantly higher in patients with advanced disease vs patients with early stages of DLBCL (57% vs 43%, $p < 0.05$). The ORR was 76% (104/136) during the follow-up (median – 16 months; range 25–96 months), 41% of patients (56/136) had relapse or progression and 42 (31%) of them died during the follow-up period. We found an association of GSTP1 homozygous wild genotype with an unfavorable prognosis of DLBCL. The A313A genotype was strongly associated with increased risk of the DLBCL r/r disease as compared with A313G or G313G genotypes (23% vs 14% vs 4%, respectively, $p < 0.05$). 5-years EFS for patients with A313A GSTP1 genotype was lower compared to patients with A313G or G313G genotypes (42 % vs 52%, $p < 0.05$). Thus, the A313A genotype impacts survival of DLBCL.

Conclusions: Results suggest the genotype of the GSTP1 (A313A) is associated with unfavorable prognosis of DLBCL, reduce EFS rate. Results can be promising, but further investigations might provide a possible application of this marker as a prognostic factor of DLBCL.

Legal entity responsible for the study: Olga Novosad.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1021P Long term treatment outcome of patients with refractory or relapsed Hodgkin's lymphoma in the anthracycline era: A single-center intention-to-treat analysis

T.I. Bogatyreva, A.Y. Terekhova, S.S. Shklyaev, V.V. Pavlov, N.A. Falaleeva

Department of Radiotherapy and Chemotherapy for Hematological Malignancies, A.F. Tsyb Medical Radiological Research Center - Branch of the National Medical Research Center of Radiology of the Ministry of Health of the Russian Federation, Obninsk, Russian Federation

Background: High dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) is currently the treatment of choice for refractory or relapsed Hodgkin's lymphoma (HL) and cures up to 50% of patients. However, its applicability is restricted to selected eligible patients and/or responding to salvage chemotherapy. The aim was to compare outcomes after salvage regimens with and without HDT and ASCT in HL patients who failed or relapsed after ABVD or BEACOPP regimens.

Methods: From 856 patients with newly diagnosed HL registered in the MRRC database between 1998 and 2017 there were identified 131 patients with refractory disease (gr.1, n = 89), early (gr. 2, n = 31) or late (gr.3, n = 11) relapse. At first relapse, patients had median age 30 years (range, 17 to 69); male, 46%; stage III/IV, 70%; B symptoms, 28%. Of 131 patients, 76 (58%) received standard CT regimens (ST) when HDT was not available (n = 64) or contraindicated (12). HDT was initiated in 55 (42%) patients, but withdrawn in 38 of them (adverse effects, 9; progression, 24; low cytopheresis, 5). ASCT was performed in 17 (31%) patients.

Results: Median follow-up time after first failure for survived patients (79 of 131, 60%) was 60 months (8-186). Durable second remissions were achieved in 10 (59%) of 17 patients after ASCT and in 30 (40%) of 76 patients after ST. In an intention-to-treat (ITT) analysis median freedom from second failure (FF2F) after HDT and ST was, respectively, 4 vs. 15 months in Gr.1 (p = 0.018) but did not differ (15 and 16 months) in Gr.2; Gr.3 was too small for ITT. Median overall survival (OS2) after HDT and ST was, respectively, 22 vs. 158 months in Gr.1 (p = 0.036) and 42 vs. 52 months in Gr.2 (n.s).

Conclusions: This single center analysis demonstrates the effectiveness of standard CT regimens as first-line salvage in patients not eligible for HDT/ASCT. It also demonstrates the high failure rate due to inadequate chemo-responsiveness at salvage in patients referred to HDT: An effect not accounted for in studies analyzing only outcome following HDT/ASCT.

Legal entity responsible for the study: Viacheslav Vladimirovich.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1022P Population-based use of intravenous bisphosphonates in patients newly diagnosed with symptomatic multiple myeloma in Denmark in 2005-2015: Impact of patient characteristics

V. Ehrenstein[1], A.G. Ording[1], S.P. Ulrichsen[1], I.T. Andersen[1], A. Seesaghur[2], C. Helleberg[3], T. Silkjær[4], R. Hernandez[5], D. Niepel[6], N. Abildgaard[7]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, [2]Amgen Limited, Cambridge, UK, [3]Department of Hematology, Herlev Hospital, Herlev, Denmark, [4]Department of Hematology, THG, University Hospital, Aarhus, Denmark, [5]Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA, [6]Amgen GmbH, Zug, Switzerland, [7]Department of Hematology, Odense University Hospital, Odense, Denmark

Background: Bone and kidneys are among the main affected organ systems in symptomatic multiple myeloma (MM) and may be associated with debilitating complications. Thus, bone health and renal protection are at the core of MM management. Bisphosphonates (BP) are recommended for prevention of bone complications in all newly diagnosed symptomatic MM patients, but BPs are also potentially nephrotoxic and are cleared by the kidneys. This study describes the routine clinical use of BP among MM patients in Denmark.

Methods: Adult patients newly diagnosed with MM between 01.01.2005 and 30.06.2015 were identified in the Danish National Multiple Myeloma Registry, and information on BP treatment in first-line (1L) anti-MM therapy was analyzed.

Results: Among 2,633 MM patients with information on BP treatment in 1L, 1,838 (69.8%) received BP. Median time from MM diagnosis to BP treatment was 19 days (IQR: 9, 35). Receipt of BP among 1L-treated patients by therapy was: 79.4% (635/799) in autologous stem cell transplant recipients, 75.0% (793/1,058) in patients treated with conventional chemotherapy, and 70.2% (903/1,286) in those treated with bortezomib-, lenalidomide-, or thalidomide-containing regimens. Among the BP-treated patients, 67.2% (543/1,838) had no recorded hypercalcemia at MM diagnosis, 81.0% (1,489/1,838) had a record of skeletal-related events (SRE) in the 12 months before MM diagnosis, and 80.0% (1,470/1,838) had a record of osteolytic foci at 1L. An additional 431 patients had a record of osteolytic foci but no record of BP treatment. Patients without a record of BP treatment had higher prevalence of overall hospital-registered comorbidity, anemia, or higher ISS stage at MM diagnosis than patients with a record of BP treatment. Severe renal impairment (stages 4 - 5) was recorded at MM diagnosis in 31.8% of patients with no BP record and in 12.6% of patients with BP record at 1L start.

Conclusions: In newly diagnosed MM patients receiving 1L, co-administration of BP and anti-MM therapy is widespread, though less prevalent in patients with renal impairment or comorbidity burden.

Legal entity responsible for the study: Aarhus University.

Funding: This study was funded by Amgen Inc. via institutional research grant to and administered by Aarhus University.

Disclosure: V. Ehrenstein, A.G. Ording, S.P. Ulrichsen: Employee of Aarhus University. I.T. Andersen, C. Helleberg, T. Silkjær, N. Abildgaard: Employee of the listed institution. A. Seesaghur, R. Hernandez, D. Niepel: Employee and stockholder: Amgen.

1023P Role of liposomal doxorubicin as a first line agent with VTd regimen in newly diagnosed multiple myeloma

M. Khanderia[1], G. Badarkhe[2], S. Bj[3], R. Naik[3]

[1]Medical Oncology, HCG Bangalore Institute of Oncology Speciality Centre, Bangalore, India, [2]Hematology and Bone Marrow Transplant, HCG Hospital, Bangalore, India, [3]Medical Oncology, HCG Hospital, Bangalore, India

Background: Triple drug regimens are standard of care in newly diagnosed Multiple Myeloma (MM). Studies show 4 drug regimens to be highly active. In an economically backward country like India, newer drugs and Autologous transplant may not always be feasible because of financial constraints. We studied the effect of adding Pegylated Liposomal Doxorubicin (PLD) to standard regimen on the Response Rates (RR).

Methods: 60 newly diagnosed cases of MM were included in this double armed prospective, observational, comparative study. Patients were randomly assigned into 2 arms (30 Patients in each arm). Arm A consisted of VTd regimen (Inj. Bortezomib Day (D)1, D8, D15, D22 1.3mg/ / m^2, Tab. Thalidomide Daily 100mg, Inj. Dexamethasone D1, D8, D15, D22 40 mg / once in 28 days). Arm B consisted of VTdD regimen (PLD D1 i.v 30mg / m^2 + VTd). Hematological and biochemical parameters were noted at baseline and after completion of 4 cycles. Response assessment was done as per the criteria defined by International Myeloma Working Group (IMWG). The outcomes between the two treatment arms in terms of RR were compared.

Results:

Table: 1023P

RR	VTd	VTdD
Overall Response Rates	86.6%	93.3%
>very good partial response	73.3%	86.6%
Stringent Complete Response	33.3%	53.3%

The differences in sCR rates were clinically very significant. However, on application of Pearson chi-square test significance p of 0.118 was seen, which maybe attributed to the lower power of the study. Poorest responses noted were highest in the 71-80 age group. Both the regimens were equally effective in ISS B patients. Neutropenia, thrombocytopenia, infections, mucositis, edema, dizziniess/somnolence and DVT were not significantly different between the two arms ($P > 0.05$). Palmar–plantar erythrodysesthesia (PPE) was the only new complication seen in (10%) VTdD group. Grade 3–4 toxicities were similar in both arms.

Conclusions: The role of liposomal doxorubicin in first line setting as a 4th agent along with triple drug regimen in treatment of MM looks promising, especially in countries with financial constraints for the newer drugs. Larger studies are needed to validate this.

Legal entity responsible for the study: Scientific and Ethics Committee at HCG Hospital, Bangalore, India.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1024P The β2-microgloulin is associated with the prognosis in patients with peripheral t-cell lymphoma, not otherwise specified

B.S. Sohn[1], S-N. Lim[2], J. Kim[3], D.H. Yoon[3], S. Kim[3], J. Huh[3], S-E. Park[1], Y.J. Yuh[1], C. Suh[3]

[1]Internal Medicine, Inje University Sanggye Paik Hospital, Seoul, Republic of Korea, [2]Internal Medicine, Inje University Haeundae Paik Hospital, Busan, Republic of Korea, [3]Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of tumors and subdivided into specified and not otherwise specified (NOS) types. Clinically, the International Prognostic Index (IPI), Prognostic Index for T-cell lymphoma, and Bologna score have been the prognostic model to discriminate the prognosis of patients with PTCL-NOS. However, no simple prognostic marker has been satisfactory in predicting treatment outcomes in patients with PTCL-NOS.

Methods: From Sep 2005 to Aug 2016, we identified 94 patients diagnosed with PTCL-NOS initially treated with CHOP or CHOP-like regimens. Event-free survival (EFS) was calculated from the date of diagnosis to the date of disease progression, treatment failure, relapse, or death from any cause. Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause. The cut-off of serum β_2-microgloulin (B_2MG) was defined as > 3.2 mg/L.

Results: Among 94 patients, 41 (43.6%) patients showed $B_2MG > 3.2$ mg/L, 37 (39.4%) patients showed B symptoms. According to IPI scores, 19 (20.2%) patients belonged to the low risk group (L), 25 (26.6%) to the low-intermediate (LI), 29 (30.9%) to the high-intermediate (HI), and 21 (22.3%) to the high (H). Complete response (CR), EFS, and OS were associated with B_2MG, B symptoms, performance status, lactate dehydrogenase, extranodal involvement, Ann Arbor stage, and IPI risk group in univariate analysis. After multivariate analysis, B_2MG was associated with CR (> 3.2 mg/L vs. ≤3.2 mg/L, odd ratio [OR]: 4.053, 95% confidence interval [CI]: 1.314–12.503, $P = 0.015$), EFS (hazard ratio [HR]: 1.721, 95% CI: 1.026–2.887, $P = 0.040$), but OS (HR: 1.449, 95% CI: 0.803–2.615, $P = 0.218$). IPI risk group was associated with CR (L/LI vs. HI/H, $P = 0.022$), EFS ($P < 0.001$), and OS ($P < 0.001$). In 50 patients of HI/H risk group, B_2MG showed association with CR (OR: 5.464, 95% CI: 1.256–23.774, $P = 0.024$), EFS (HR: 2.160, 95% CI: 1.095–4.260, $P = 0.026$), and OS (HR: 2.158, 95% CI: 0.979–4.759, $P = 0.057$).

Conclusions: B_2MG could be a simple prognostic factor for the patients with PTCL-NOS. $B_2MG > 3.2$ mg/L was associated with worse prognosis of patients with PTCL-NOS, especially in HI/H risk group. The larger scaled study is warranted to confirm our result.

Legal entity responsible for the study: Byeong Seok Sohn.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1026P Impact of prior bortezomib therapy on the incidence of lenalidomide-induced skin rash in multiple myeloma: A propensity score-matched multi-institutional cohort study

S. Dote[1], K. Ito[2], S. Itakura[3], T. Yasu[4], D. Hira[5], S. Noda[6], S. Yamada[2], Y. Kobayashi[1], T. Terada[6]

[1]Department of Pharmacy, Kyoto-Katsura Hospital, Kyoto, Japan, [2]Department of Pharmacy, Fujita Health University Hospital, Aichi, Japan, [3]Department of Pharmacy, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan, [4]Department of Pharmacy, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan, [5]College of Pharmaceutical Sciences, Ritsumeikan University, Shiga, Japan, [6]Department of Pharmacy, Shiga University of Medical Science Hospital, Shiga, Japan

Background: Rash is a well-known toxicity induced by lenalidomide (LEN) therapy in multiple myeloma (MM). LEN has immunomodulatory effects activating function of effector immune cell such as T-cells, which may result in rash onset. Conversely,

bortezomib (BOR), another key drug of MM therapy, has strong Immunosuppressive effects decreasing CD4 T-cell count. Although the two drugs have different immunological aspects, the association between prior BOR therapy and LEN-induced rash has not been reported.

Methods: We conducted a four-institutional cohort study. Eligible MM patients treated with initial LEN therapy were divided into two propensity score-matched cohorts according to presence or absence of prior BOR therapy. The primary endpoint was the incidence of rash. The secondary endpoint was the incidence of eosinophilia defined more than 10% of the leukocyte after LEN therapy.

Results: One-hundred forty-four patients were evaluated. The incidence of rash was 35 (50/144) %, of which 34 (17/50) % were discontinued LEN therapy due to rash. The median time to rash onset was 8.5 days after LEN initiation. Each cohort contained 43 patients after performing propensity-score matching. As compared to in the absence of prior BOR therapy, the incidence of rash was significantly lower in the presence of prior BOR therapy (30% vs 53%, $p = 0.04$). Median period of BOR therapy was significantly shorter in patients with rash, as compared with those without rash (109 days vs 164 days, $p = 0.046$). Also, the patients with rash showed significantly higher incidence of eosinophilia than those without rash, within one month after LEN initiation (26% vs 8%, $p < 0.01$).

Conclusions: Prior BOR therapy could reduce the incidence of LEN-induced rash. LEN-induced rash may be characterized by eosinophilia, suggesting that LEN enhance Th2 immune responses. Regarding the patients failed to continue LEN therapy due to rash, they may have a chance of LEN re-treatment after adequate BOR therapy.

Legal entity responsible for the study: Satoshi Dote.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1027P The significance of FMS-like tyrosine kinase 3 surface receptor expression in acute myeloblastic leukemia and precursor B-acute lymphoblastic leukemia patients

S.A. Al Hassanin[1], I.A. Ahmedy[2]

[1]Clinical Oncology Department, Faculty of Medicine - Menoufia University, Shebin El Kom, Egypt, [2]Clinical Pathology Department, Faculty of Medicine - Menoufia University, Shebin El Kom, Egypt

Background: FMS-Like Tyrosine Kinase III (FLT3 / CD135), also known as stem cell tyrosine kinase 1 (STK1) or fetal liver kinase 2 (FLK2), belong to the group of class3 receptor of tyrosine kinase activity. The expression of FLT3 receptor is confined to early hematopoietic progenitor's cells in normal BM. Even though new FLT3 mutations in Acute Myeloid Leukemia (AML) are increasing, the role of FLT3 receptor surface expression in AML and precursor B acute lymphoblastic leukemia (pre-B-ALL) had infrequently been addressed.

Methods: To further evaluate the significance of FLT3 (CD135) expression in AML and pre B-ALL we investigated FLT3 level of expression in newly diagnosed 76 AML patients, 80 pre B-ALL patients and 72 healthy control donors by flowcytometry. The cut-off value for FLT3 positivity was 20%. FLT3 expression was correlated with standards prognostic parameters.

Results: We demonstrated FLT3 protein expression >20% in 68.4% of AML patients, its level was different in FAB subtypes with increasing levels in the following order: M1<M2<M3<M5. Positive FLT3 expression correlated with older age, hepatosplenomegaly, high percentages of bone marrow blasts, high leukocyte counts. Furthermore, it correlated with, CD14, CD64, HLADR, CD $135^+/34^+$, $CD117^+$ and high LDH. Finally, $FLT3^+$ correlated with poor clinical outcome, shorter disease-free survival and overall survival than $FLT3^-$, Regarding pre B-ALL, $FLT3^+$ protein expression >20% was 65%. It correlated with age ≤10 years, with absence of lymphadenopathy and absence of CNS infiltration, high percentages of bone marrow blasts, leukocyte counts $\leq 50 \times 10^3$. Furthermore, it correlated with CD 10^+, $CD34^+$. Finally, $FLT3^+$ correlated with good clinical outcome, longer free disease survival and overall survival than $FLT3^-$.

Conclusions: High FLT3 expression can predict outcome and is associated with poor prognostic factors in AML while it is associated with good prognostic factors in ALL.

Legal entity responsible for the study: Faculty of Medicine, Menoufia University, Shebin Elkom, Egypt.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1028P Prognostic factors of clinical use in acute myeloid leukemia

P.A. Chorão[1], N.T. Tavares[2], E. Aguiar[1], M.L. Amorim[1], P. Gomes[1], F. Príncipe[1], J.E. Guimarães[1]

[1]Clinical Hematology Department, Centro Hospitalar São João, EPE, Porto, Portugal, [2]Medical Oncology Department, Centro Hospitalar São João, EPE, Porto, Portugal

Background: The heterogeneity in acute myeloid leukemia (AML) is influenced by disease and host-specific factors. In recent years, independent molecular factors and host characteristics that affect prognosis have been described. Nevertheless, data is needed to warrant their clinical use.

Methods: We retrospectively reviewed data on 356 AML patients from October 2008 to June 2017, including age, Charlson Comorbity Index (CCI), ECOG performance status (PS), laboratory parameters (complete blood count, bone marrow blasts, lactic dehydrogenase) and disease factors (de novo or secondary AML (sAML), genetic alterations). The 2017 European Leukemia Net genetics risk stratification (GRS) was used. Univariate and multivariate Cox regression analysis was performed.

Results: The intensive chemotherapy (IC) group comprised of 241 patients, median age 58 years (y), 95% having PS ≤ 1, 67% CCI ≤2 and 22% were sAML. GRS was 23% favorable, 44% intermediate, 27% adverse and 6% unknown. Median overall survival (OS) was 15 months (mo), with 28% 3y-OS. In multivariate analysis (Table), age older than 60y (median 6 versus (vs) 22mo), PS ≥ 2 (median 7 vs 15mo) and higher risk GRS (median 35mo favorable vs 13mo intermediate and 11mo adverse) impacted on survival. The non-IC group included 112 patients, median age 67y, 76% having PS ≤ 1, 6% CCI ≤2 and 37% were sAML. GRS was 12% favorable, 49% intermediate, 24% adverse and 15% unknown. Median OS was 3mo, with 10% 3y-OS. In multivariate analysis (Table), age older than 60y (median 2 vs 17mo), PS ≥ 2 (median 1 vs 5mo) and higher risk GRS (median not reached in favorable vs 4mo intermediate and 1mo adverse) impacted on prognosis.

Table: 1028P

		Intensive chemotherapy HR [95% CI]	Non-intensive therapy HR [95% CI]
Age	≤60 years	Ref	Ref
	>60 years	2.41 [1.76-3.31]	3.09 [1.70-5.65]
ECOG PS	≤ 1	Ref	Ref
	> 1	2.36 [1.23-4.53]	2.25 [1.27-3.98]
ELN2017 genetics	Favorable	Ref	Ref
	Intermediate	2.04 [1.33-3.14]	3.26 [1.30-8.15]
	Adverse	2.26 [1.42-3.59]	5.55 [2.13-14.44]

Conclusions: In spite of the high number of recognized risk factors, in real-life only GRS, age and PS were of clinical use to predict survival in both IC and non-IC sets. In our sample, there was no significant impact of sAML, CCI and laboratory parameters. Efforts are needed to identify more factors that aid clinical decision in the treatment of AML.

Legal entity responsible for the study: Clinical Hematology Department, Centro Hospitalar São João, EPE.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1029P Frequency and clinical impact of compound mutation in chronic myeloid leukemia patients resistant to tyrosine kinase inhibitor

S. Bonecker[1], M. Carneiro[2], M. Bonamino[2], I. Zalcberg[1]

[1]Centro de Transplante de Medula Ossea, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [2]Programa de Carcinogêse, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil

Background: Chronic myeloid leukemia is characterized by onco-protein BCR-ABL1 which is constitutively activated. This particularity allowed the development of the first specific tyrosine kinase inhibitor (TKI) which changed the course of this disease. However, resistance to TKI is still a growing clinical problem. The canonical mechanism of resistance is point mutation in ABL1 kinase domain (KD). After the introduction of second and third TKI, the presence of multiple mutations was grown and the clinical importance is still controversial.

Methods: We included 21 resistant patients with two BCR-ABL1 KD mutations detected by direct sequencing. 43% failed to two therapies, 8 to three and 4 failed only to imatinib. For two patients we had sequential samples. We cloned ABL1 region and sequenced minimum of 10 clones. In order to evaluate the frequency of false compound mutation we cloned sample with only T315I mutation, other with F317L and 1:1 dilution of both samples.

Results: We observed that 66.7% of double mutations detected by direct sequencing were compound mutations. Our ratio of false positive compound mutation was 9%. T315I plus other mutation was the most frequently compound mutation in our cohort. Patients who failed to more than one TKI had higher frequency of compound mutation. Analyzing sequential samples we observed mutated clones in samples up to 5 months earlier than direct sequencing. The frequency of clones harboring compound mutations with more than two missense mutations was low (6%), comparing with silent mutations, suggesting a limited tolerance for BCR-ABL1 KD missense mutations. The number of transition was higher than transversion. Among patients with compound mutations: 5/7 progressed to advanced phases presented compound mutation, 1/2 died, 5/8 achieved molecular response (MR) during second or third line therapy and 3/4 did not achieve MR (median follow up 26 months).

Conclusions: We did not find correlation between presence of compound mutation and probability to respond therapy or progression. Analyze higher number of sample is needed. Indeed, the importance to detect clones harboring high resistance mutation such T315I earlier could help the clinician to choose the therapy to avoid clone progression.

Legal entity responsible for the study: Instituto Nacional do Câncer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1030P Poor outcome of double-protein expressor diffuse large B-cell lymphoma

E.V. Kharchenko[1], T. Semiglazova[1], A. Artemeva[2], V. Kushnarev[2], P.S. Shilo[1]

[1]Department of Innovative Methods of Therapeutic Oncology and Rehabilitation, N.N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russian Federation, [2]Department of Pathology, N.N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russian Federation

Background: In previous several studies it was confirmed that double expression of both c-myc and bcl-2 in Diffuse Large B-cell lymphoma patients (DLBCL) predict aggressive course. We suggest that it can be independent risk factor and early treatment intensification can provide potential benefit for this poor risk group.

Methods: To analyze data we used chi-square test for independence, odds ratio (OR), full analisys test. Progression free survival (PFS) were estimated by Kaplan-Meier method, comparison of PFS in experimental groups (long-rank test), multifactor analysis of PFS (multinomial logistic regression). Statistically significant difference if $p < 0,05$.

Results: We analyzed 240 pts with DLBCL, from 18 to 85 y.o. (median age 56 y.o), who underwent treatment in National Medical Research center from 2008 to 2018. Seventy six (32%)-with early stage of disease (I,II) and 164 pts (68%)-advance stage (III,IV). Extranodal involvements were observed in 61 pts (25%) and B-symptoms in 109 (45%), GCB-subtype in 47% and non-GCB in 53% (Hans algorithm). DA-EPOCH-R, Hyper-CVAD-R as first line received 26 pts (11%) and up-front high-dose chemotherapy with AutoSCT received 17 pts (7%). 2-years PFS was 86% for all pts [95% CI 78-94]. PFS was significantly lower in pts with B-symptoms (38% vs 84%; RR 3,3 [95% CI 0,85 – 1,4], $p < 0,05$); advance stage (42% vs 89%; RR 3,0 [95% CI 1,7 – 2,1], $p < 0,05$); c-myc expression (45% vs 84%); RR 1,9 [95% CI 0,3 - 0,9], $p < 0,05$); bcl-2-expression (60% vs 83%) RR 1,6 [95% CI 1,2 – 1,9], $p < 0,05$); Ki-67 higher than 70% (59% vs 89%; RR 2,5 [95% CI 0,9 – 1,2], $p < 0,05$). Double-expressor lymphoma (DEL) (both c-myc and bcl-2) were observed in 33% (80 patients). Among patients with DEL, PFS were lower but not significantly different comparing with non-DEL ($p = 0,03$). These data were related to early treatment intensification in this subgroup (DA-EPOCH-R, Hyper-CVAD-R, up-front high-dose chemotherapy with AutoSCT). DEL subgroup was also associated with advance stage of the disease (III-IV 68% vs I-II 39%, $p < 0,05$), B-symptoms (69% vs 47%, $p = 0,03$) and Ki-67 higher than 70% (81% vs 71%, $p > 0,05$).

Conclusions: These data confirm more aggressive course of the disease in patients with DEL comparing with standard group and may suggest benefit for patients to undergo early-treatment intensification.

Legal entity responsible for the study: Tatiana Semiglazova. MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1031P Combination of chemotherapy and radiation improve the prognosis of primary diffuse large B-cell lymphoma of the tonsil

S-N. Lim[1], B.S. Sohn[2], H-J. Shin[3], C. Suh[4], W.S. Kim[5], W.S. Lee[6], J.S. Kim[7]

[1]Internal Medicine, Inje University Haeundae Paik Hospital, Busan, Republic of Korea, [2]Internal Medicine, Inje University - Sanggye Paik Hospital, Seoul, Republic of Korea, [3]Internal Medicine, Pusan National University School of Medicine, Pusan National University Hospital, Busan, Republic of Korea, [4]Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [5]Internal Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea, [6]Internal Medicine, Inje University College of Medicine, Busan Paik Hospital, Busan, Republic of Korea, [7]Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Seoul, Republic of Korea

Background: The most common histological type of tonsil lymphoma is diffuse large B-cell lymphoma (DLBCL). Treatment approaches that have used include surgery, chemotherapy (CTx) alone, radiation (RT) alone, and combination of both. We reviewed our data and evaluate treatment outcome of patient with DLBCL of the tonsil.

Methods: Retrospective review of 114 stage I-II DLBCL patients between 1995 and 2010. Forty-five (39.5%) patients had stage I disease and B-symptoms were present in only 7 patients. Seventy-two (65.5%) patients were treated with CTx alone, whereas the remaining 38 received treatment with a combination of CTx and RT. Chemotherapy was CHOP-based, with R-CHOP in 80 patients (70%). Median involved-field RT dose was 3,960 cGy, with 96% receiving more than 3,000 cGy.

Results: The median age was 59 years and 61% of patients were males. Low to low intermediate by International prognostic index (IPI) was 97.3%. LDH level. Overall CR rate was 73.5% and seven (13.5%) of the patients who had achieved CR had recurred. The median follow-up was 28 months. Five-year disease-free survival (DFS) and overall survival (OS) were 86.3% and 82.5%, respectively. Significant prognostic factors included: age $\geq$ 60 years old (OS, $P = 0.011$), LDH >upper normal limit (OS, $P = 0.003$; DFS, $P < 0.001$), IPI>0 (OS, $P = 0.007$; DFS, $P = 0.034$) and combination of CTx and RT (OS, $P = 0.025$; DFS, $P = 0.038$). Germinal center (GC) and non-GC phenotype were not predictors of outcome in localized DLBCL of the tonsil. Chemoimmunotherapy-treated patients with rituximab did not show a significantly better OS and DFS than those without rituximab. On multivariate analysis; LDH >upper normal limit (DFS: hazard ratio [HR], 14.958; 95% CI, 2.474-90.432, $P = 0.003$; OS: HR, 9.341; 95% CI, 1.635-53.361, $P = 0.012$), and combination of CTx and RT (DFS: HR, 0.088: 95% CI, 0.009-0.834, $P = 0.034$; OS: HR, 0.112; 95% CI, 0.014-0.918, $P = 0.041$), retained statistical significance.

Conclusions: The DFS and OS rates were significantly better for patients receiving combination of CTx and RT. A combined treatment, consisting of CTx and RT (with RT dose of $\geq$ 45 Gy), results in a satisfactory outcome in patients with localized primary DLBCL of tonsil.

Legal entity responsible for the study: Consortium for Improving Survival of Lymphoma.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1032P The impact of serum microRNA-21 on outcome of diffuse large B-cell lymphoma patients

S.F. Gohar[1], S. Kamal Eldin[2], F. El-Bassal[2], A. Shehata[3], A. Azzam[4], E. Tawfik[1], S.A. Al Hassanin[1]

[1]Clinical Oncology, Faculty of Medicine - Menoufia University, Shebin El Kom, Egypt, [2]Clinical Pathology, Faculty of Medicine - Menoufia University, Shebin El Kom, Egypt, [3]Clinical and Chemical Pathology, Menoufia University, Menoufia, Egypt, [4]Clinical Biochemistry and Molecular Diagnostics, National Liver Institute, Menoufia, Shebin El Kom, Egypt,

Background: The utilization of circulating microRNAs (miRNAs) as non-invasive diagnostic and predictive tools have become substantial and promising scope of cancer research. The link between the aberrant expressions of various miRNAs and the pathogenesis of diffuse large B-cell lymphoma (DLBCL) has been revealed by multiple studies. This study planned to investigate the relative expression levels of serum miRNA-21 and to demonstrate its potential prognostic impact in DLBCL patients who were treated by cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (R-CHOP) protocol.

Methods: Polymerase chain reaction (PCR) based technique was used to analyze serum miRNA-21 relative expression levels in 65 DLBCL patients prior to immunochemotherapy in comparison with 35 healthy individuals. Receiver operating characteristic curve analysis was used to gauge the optimal miRNA-21 cutoff and Kaplan-Meier method was performed to estimate overall patients' survival.

Results: Serum miRNA-21 overexpression was significantly observed in DLBCL patients compared to the control group ($P < 0.001$). MiRNA-21 expression levels were closely associated with stage, C-reactive protein (CRP), lactate dehydrogenase (LDH) and β2 microglobulin ($P < 0.001$; $P = 0.02$; $P = 0.003$; $P < 0.001$ respectively). However, there was no relationship with other characteristics, such as gender, age, B symptoms, extranodal site involvement, international prognostic index (IPI) and initial response to therapy (all $Ps > 0.05$). Overall survival was significantly worse in patients with high miRNA-21 expression levels compared to those with low expression levels ($P = 0.01$).

Conclusions: Serum miRNA-21 may be employed as valuable non-invasive diagnostic and prognostic marker in DLBCL patients treated with R-CHOP regimen.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1033P Efficacy and safety of bosutinib vs imatinib in Indian and non-Indian patients with newly diagnosed chronic phase chronic myeloid leukemia: Subgroup analysis from the BELA trial

H. Malhotra[1], A. Maru[2], N. Khattry[3], M.V. Ramanan[4], E. Leip[5], R.J. Crescenzo[6], C. Gambacorti-Passerini[7], J.E. Cortes[8]

[1]Division of Medical Oncology, Birla Cancer Center, Jaipur, India, [2]Department of Medical Oncology, Sarvodaya Multispeciality & Cancer Hospital, Hisar, India, [3]Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India, [4]Department of Medical Oncology, Jehangir Hospital, Pune, India, [5]Clinical Statistics, Pfizer Inc, Cambridge, MA, USA, [6]Clinical Development, Pfizer Inc, Collegeville, PA, USA, [7]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy, [8]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: The international, phase 3 BELA trial (NCT00574873) evaluated first-line bosutinib vs imatinib in Philadelphia chromosome–positive patients (pts) with chronic phase chronic myeloid leukemia.

Methods: Pts were randomized to receive bosutinib 500 mg once daily (QD) or imatinib 400 mg QD; the primary endpoint was complete cytogenetic response (CCyR) rate at 12 mo. We compared efficacy and safety of bosutinib and imatinib in Indian and non-Indian pts after 48 mo of follow-up. Efficacy was assessed in the intent-to-treat population; safety was assessed in all pts who received ≥1 dose of study drug.

Results: In all, 54 Indian pts (median age 34.5 y; 61% male) and 448 non-Indian pts (median age 48.5 y; 56% male) were randomized to receive bosutinib (n = 25 and n = 225 [2 untreated], respectively) or imatinib (n = 29 and n = 223 [1 untreated]). At 12 mo, major molecular response (MMR) and CCyR rates, respectively, for bosutinib vs imatinib were 44% vs 24% and 72% vs 86% in Indian pts, and 37% vs 26% and 70% vs 66% in non-Indian pts (Table). After 48 mo of follow-up, cumulative MMR and CCyR rates, respectively, for bosutinib vs imatinib were 64% vs 69% and 84% vs 97% in Indian pts, and 68% vs 67% and 78% vs 79% in non-Indian pts. The most frequently reported treatment-emergent adverse events (TEAEs; any grade) with bosutinib were diarrhea (44%) and thrombocytopenia (36%) in Indian pts, and diarrhea (73%) and nausea (39%) in non-Indian pts. 8 pts in the entire study were lost to follow-up while on-treatment; 7 (6 bosutinib; 1 imatinib) were from Indian sites.

Table: 1033P

	Indian pts		Non-Indian pts	
	Bosutinib n = 25	Imatinib n = 29	Bosutinib n = 225	Imatinib n = 223
Sokal Risk Group, n (%)				
Low	11 (44)	13 (45)	77 (34)	76 (34)
Medium	11 (44)	13 (45)	106 (47)	105 (47)
High	3 (12)	3 (10)	42 (19)	42 (19)
Cumulative response, any time on–treatment, % (95% CI)				
MMR	64 (45–83)	69 (52–86)	68 (61–74)	67 (61–73)
CCyR	84 (70–98)	97 (90–100)	78 (73–84)	79 (74–84)
Response at 12 mo, % (95% CI)				
MMR	44 (25–64)	24 (9–40)	37 (31–44)	26 (20–31)
CCyR	72 (54–90)	86 (74–99)	70 (64–76)	66 (60–72)
Probability of retaining response at 48 mo (95% CI)*				
MMR	80 (49–93)	100 (100–100)	93 (86–96)	98 (93–99)
CCyR	89 (62–97)	78 (58–90)	93 (88–96)	91 (85–95)
Transformation to AP/BP CML, n (%)	1 (4)	2 (7)	4 (2)	10 (5)
Overall survival				
Deaths, n (%)	1 (4)	1 (3)	14 (6)	14 (6)
At 48 mo (95% CI)*	96 (72–99)	96 (77–100)	95 (91–97)	94 (89–96)

*Kaplan-Meier estimate

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CI=confidence interval; CML=chronic myeloid leukemia; MMR=major molecular response

Conclusions: Response rates for bosutinib were comparable between Indian and non-Indian pts. MMR rates were higher for bosutinib vs imatinib at 12 mo, but not 48 mo, in Indian pts; comparison of bosutinib vs imatinib was limited by the small number of Indian pts. TEAEs were consistent with the known bosutinib safety profile, although Indian pts had a lower rate of diarrhea than non-Indian pts.

Clinical trial identification: NCT00574873.

Editorial acknowledgement: Medical writing support was provided by Emily Balevich, PhD, of Engage Scientific Solutions, and funded by Pfizer.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: E. Leip, R.J. Crescenzo: Employment and stock ownership: Pfizer. C. Gambacorti-Passerini: Consultancy: BMS, Pfizer; Honoraria and research funding: Pfizer. J.E. Cortes: Consultancy: Ariad, BMS, ImmunoGen, Novartis, Pfizer; Research funding: Ariad, BMS, ImmunoGen, Novartis, Pfizer, Sun Pharma, Teva. All other authors have declared no conflicts of interest.

1034P A prospective multicenter study of primary breast lymphoma in the rituximab era: Prognostic implication of beta 2 microglobulin and interlukin-6 & interlukin-10

L. Ezz Elarab[1], E. Hamada[2], A. Mostafa[1], A. Saber[2], M. Abdel-Gawad[3], R.M. Haggag[4], H.D. Darwish[5], S.A. Elhassanin[6], M. Swellam[7]

[1]Clinical Oncology, Ain Shams University Faculty of Medicine, Cairo, Egypt, [2]Clinical Oncology, Minya University Medical School, Minya, Egypt, [3]Clinical Oncology, Faculty of Medicine, Assuit University, Cairo, Egypt, [4]Medical Oncology, Zagazig University Faculty of Medicine, Zagazig, Egypt, [5]Medical Oncology, Damietta Cancer Institute (DCI), Damietta, Egypt, [6]Clinical Oncology, Faculty of Medicine, Menoufiia University, Cairo, Egypt, [7]Biochemestry, Genetic Engineering and Biotechnology, National Research Center, Cairo, Egypt

Background: Primary breast diffuse large B-cell lymphoma (DLBCL) is a rare entity representing ≤ 2% of extra-nodal non-Hodgkin lymphoma. We aimed to define clinical profile, prognostic factors and the incidence of the central nervous system (CNS) relapse in the era of rituximab and clarify the prognostic value of beta$_2$ microglobulin(B_2M), interlukins-6 (IL-6) and interlukin -10(IL-10).

Methods: Between Jan 2012 to Dec 2016, a prospective analysis of 28 patients presenting to 7 academic Egyptian centers. All patients were females. Only patients with newly diagnosed stage I and II disease DLBCL were included. Patients with evidence of baseline CNS disease and patients with hepatitis B and HIV were excluded. All patients were scheduled to receive R-CHOP protocol plus involved- field radiotherapy. The prognostic significance of B_2M, and IL-6 and 10 were assessed.

Results: About 75% presented with breast mass, 4 cases with inflammatory symptoms, 3 cases were discovered by mammography. Right breast was more involved (64%), 86% had ≤ 1 ECOG performance status, and LDH elevated was in 39% and 18% had B symptoms. HCV was positive in 32% (9 patients). Stage I was detected in 57%. The stage–modified International prognostic index was ≤1 in 54%. Ten cases underwent breast surgery (2 modified radical mastectomy, 8 conservative breast surgery). Complete response was achieved in 23/28 (82%) with median follow-up of 28 months, 39% of patients had relapsed, contralateral breast was the site of initial relapse in two cases, 11% developed CNS relapse and 21% in other nodal and extranodal sites. Three years disease free survival and overall survival were 68% and 79%. Favorable prognostic factors according to univariate analysis were stage I, IPI≤1, tumor size < 5cm, B_2M. IL6 and IL-10, while for multivariate analysis they were IPI≤1 and B_2 M and IL-6.

Conclusions: Primary breast DLBCL has high rate of CNS relapse in spite of era of rituximab so CT or MRI of CNS is necessary during follow-up. Prophylaxis to CNS should be considered in the initial treatment to improve outcome. In addition, assessment of pretreatment serum levels of B_2M, and IL-6 in newly diagnosed DLBCL may indicate a possible prognostic role.

Legal entity responsible for the study: Lobna Ezz el-arab.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1035P Experience in treatment of newly diagnosed multiple myeloma patients with renal failure required dialysis

S. Semochkin[1], E. Zhelnova[2], E. Misyurina[2], T. Tolstykh[2], N. Arkhipova[2], E. Baryakh[2], E. Grishina[2], E. Karimova[2], O. Kochneva[2], E. Mavrina[2], Y. Polyakov[2], E. Yaskova[2]

[1]Oncology, Hematology and Radiotherapy, Pirogov Russian National Research Medical University, Moscow, Russian Federation, [2]Hemalology, Moscow City Hospital #52, Moscow, Russian Federation

Background: About 2-4% of patients with newly diagnosed multiple myeloma (MM) present with severe dialysis required renal failure (RF), which is associated with significant morbidity and early death. The aim of this article was to analyze own experience in treating this category.

Methods: During 10.2014-12.2017 the sixty-two patients with severe RF with a glomerular filtration rate (eGFR) <30 ml/min/1.73m^2 were enrolled in this retrospective study. All patients received bortezomib-based regimens: 41 (66.1%) VDC; 2 (3.2%) PAD; 12 (19.4%) VD and 7 (11.3%) VMP. Seven (11.3%) patients underwent high-dose therapy with ASCT. IMWG (2010) renal response criteria were used. Myeloma response was evaluated using the standard IMWG (2006) criteria.

Results: At the time of presentation 48 (77%) patients required dialysis. The mean eGFR was 6.0 (95% CI 4.4-7.6) for patients requiring dialysis (Group A) and 22.2 (16.4-29.2) ml/min/1.73 m^2 for those (Group B) are a dialysis independent (P < 0.001). Mean level of involved free light chain (iFLC) was 7400 (3440-10840) mg/l vs 2900 (780-5020) mg/l respectively (P < 0.001). The median time from RF to start of MM chemotherapy comprise 39 and 21 days for two groups respectively. Six (9.7%) patients died within the first 60 days of therapy (induction mortality). At least minimal renal response (> =MRrenal) documented in 23.5% and 57.1% patients respectively. If the duration RF before initiation of MM treatment was >1 month no one patient required dialysis restored a renal function. Among all patients, overall myeloma response (> =PR) documented in 81% cases, including 39.6% very good partial response (VGPR) and 14.6% complete response (CR/sCR). Two-years overall survival (OS) was 67.8 ± 6.4% without any different between groups.

Conclusions: In conclusion, our data indicate that bortezomib-based triplets are associated with a significant probability of renal response. In at least a 23.5% of patients

with MM presenting with dialysis-requiring severe RF may improve their renal function and discontinue dialysis. Unfortunately, our results are inferior to the literature data according to which up to 50% of patients become independent of dialysis.

Legal entity responsible for the study: Evgeniya Zhelnova.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1036P Inmunohistochemical (IHQ) classification of DLBCL into CGB and non-CGB subtypes to predict survival after chemoimmunotherapy at the Virgen de la Victoria University Hospital

L. Galvez Carvajal, C. Quero Blanco, M. Robles Lasarte, I. Moreno Perez, L. Vicioso, I. Ramos Garcia, C. Bandera Lopez, J. Baena Espinar, C. Ithurbisquy, E. Alba

Oncología Médica, Hospital Universitario Virgen de la Victoria, Málaga, Spain

Background: It is known that diffuse large-B-cell lymphoma (DLBCL) is a clinically heterogeneous entity. The most important clinical predictor of survival is the International Prognostic Index, which does not provide information regarding the heterogeneous biology of tumors. Two major subtypes of DLBCL have been identified by gene expression profiling (GEP) and classified by cell of origin into germinal center B-cell–like (GCB) and activated B-cell–like (ABC). GEP has become a reliable method for predicting the outcome of patients with DLBCL treated with R-CHOP chemotherapy. However, that it́s not easily applicable in clinical practise. Several IHC algorithms have been developed to assign patients into GCB and non-GCB/ABC subtypes.

Methods: We retrospectively analyzed 142 patients diagnosed of de novo DLBCL from 1999 to 2017 at our Hospital treated with chemoimmunotherapy. DLBCL was classified using the Hans algorithm into GCB and non-GCB subtypes. The primary end point was progression-free survival (PFS) according to the Hans algorithm, that it was estimated by the Kaplan–Meier method.

Results: The percentage of GCB and non-GCB subtypes was 54% and 46%, respectively. After a median follow-up of 37 months, the median progression-free survival was 100 months in the global population. No significant differences were found in PFS, although there was a trend to favor CGB subtype (PFS at 24 months 70% in CGB group and 59% in non-CGB group, with a median of 60 months in non-CGG and not reached in CGB group, $p = 0.177$). Despite of being a retrospective study and the low median follow-up of patients, in CGB subtype there was a trend towards better overall survival (OS) (2-year OS: 72% vs. 68%), not statistically significant ($p = 0.661$).

Conclusions: In our study there is a lack of evidence supporting the use of the Hans algorithm for stratifying patients into distinct prognostic groups, probably due to the low median follow-up. Rather, GEP remains the preferred method for predicting prognosis. IHQ for subclassification of DLBCL is feasible and reproducible, but the harmonization of techniques and centralized consensus review is necessary.

Legal entity responsible for the study: Laura Galvez Carvajal.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1037P Quality of life evaluation in acute leukemia patients receiving induction chemotherapy

T. Lymanets[1], I. Skrypnyk[1], G. Maslova[1], I. Gusachenko[2]

[1]Ukrainian Medical Stomatological Academy, Poltava, Ukraine, [2]Hematology, Poltava Regional Clinical Hospital M.V. Sklifosovsky, Poltava, Ukraine

Background: Over the past decades, special attention has been paid to study of quality of life (QoL) indicators in hematological patients receiving chemotherapy (CT). Nowadays QoL is conceptually viewed as an important complement to traditional objective evaluation measures. Aim. To assess QoL in patients with acute leukemia (AL) depending on the presence of concomitant ischemic heart disease (IHD) during the induction CT.

Methods: Our study involved 83 patients with newly diagnosed AL, of which 19 were lymphoblastic, 64 – myeloid leukemia, aged 16-72, 43 (51.8%) men, 40 (48.2%) women, according to ECOG I-II. Patients received standard induction CT. According to concomitant IHD patients were divided into groups: I ($n = 47$) - AL without cardiological diseases; II ($n = 36$) - AL with concomitant IHD. Patients were evaluated using SF-36 questionnaire to calculate physical and mental health components before treatment and after 2 induction courses of CT reaching remission.

Results: The indicators of physical and mental QoL components in patients of both groups before CT were significantly lower compared with healthy respondents. After reaching the remission in patients of group I, all QoL parameters improved, with the exception of bodily pain and social functioning. The average physical status indicators in patients of groups I and II did not significantly change. At the same time, the psychological status of patients improved: in group I in 1.5 times (40.9 ± 2.25 vs 27.1 ± 2.77 before CT, $p < 0.05$), in group II - in 1.3 times (37.3 ± 2.82 vs 28.3 ± 2.37 before CT; $p < 0.05$). Minimum values of all scales after CT were characteristic for patients with concomitant IHD in group II. Differences between groups were not statistically significant in all scales, except for the index of physical activity (41.7 ± 1.36 vs 46.6 ± 2.02; $p < 0.05$). However, in comparison with the data of practically healthy respondents, QoL of patients with AL after CT remained significantly lower.

Conclusions: The QoL evaluation in patients with AL with comorbid IHD during induction CT is an important component of the management of oncological patients, which allows individualizing the approach to each patient in the presence of this type of syntropy.

Legal entity responsible for the study: Ukrainian Medical Stomatological Academy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1038P PET-CT as a prognostic factor in patients with early stages in primary diagnosed Hodgkin lymphoma

T. Skrypets[1], O. Novosad[1], I. Pastushenko[1], T. Kadnikova[1], O. Gorbach[2], Y. Kmetyuk[3], O. Karpova[3], L. Mykhalska[4], E. Lukjanec[5], V. Kozlov[6], N. Novikov[7], O. Oliinichenko[8], N. Kostiukova[9], O. Tkachenko[9], O. Karnabeda[10], V. Stratienko[11], I. Kriachok[1]

[1]Onco-Hematology, National Cancer Institute of the MPH Ukraine, Kiev, Ukraine, [2]Experimental Oncology, National Cancer Institute of the MPH Ukraine, Kiev, Ukraine, [3]Radiology, Clinical Hospital "Feofaniya", Kiev, Ukraine, [4]Hematology, Clinical Hospital "Feofaniya", Kiev, Ukraine, [5]Hematology, Cherkassy Regional Oncology Center, Cherkassy, Ukraine, [6]Hematology, Odessa Regional Hospital, Odessa, Ukraine, [7]Radiology, Oncology Hospital "LISOD", Kiev, Ukraine, [8]Radiology, Center of Nuclear Medicine KMCOC, Kiev, Ukraine, [9]Hematology, Kiev Centre of Bone Marrow Transplantation, Kiev, Ukraine, [10]Hematology, Oncology Clinic "Innovation", Kiev, Ukraine, [11]Hematology, Regional Clinical Hospital, Kherson, Ukraine

Background: Nowadays, there are different guidelines in diagnostics and PET-guided treatment of lymphomas. But questions about benefits and predictive role of PET-CT in pts with early-stage Hodgkin lymphoma (HL) still remain debatable. Here we report results of Ukrainian multicenter retrospective study about the role of PET-CT in early-stage HL pts.

Methods: 56 patients, with stages I-II, were registered in the study between August 2012 and Feb 2018 in 9 Ukrainian hematological centers. Metabolic PET-CT imaging was performed according to standard protocols. The threshold of positivity was set for a residual uptake higher than the liver background (Deauville score (DS) 4and 5). Patients were treated with ABVD or BEACOPPesc regimens based on risk group. The primary endpoint was event-free survival (EFS), defined as disease progression or death from HL.

Results: Median age of patients at diagnosis was 29 years (range 18-50), 16 (28,5%) male and 40 (71,5%) pts were female. Bulky disease (>10 cm in any dimension) were presented in 6/56 (10,7%) of pts, B symptoms - in 16/56 (28,5%) and extranodal disease had 4/56 (7%). Median follow-up was 24 months from diagnosis. Interim PET (PET2) was performed in 50 pts at 15.5 ±3 days (range, 5-26) after 2xABVD or 2xBEACOPP esc cycles. Interim PET-CT was assessed as DS 1-2 in 34 patients (60,7%), DS 3 in 11 (19,6%), DS 4-5 in 5 pts (8,8%). In total, disease progression was documented in 5/56 (9%). Among them, 2/5 (40%) patient were PET2-positive (PET2+) and 3/5 (60%) PET2-negative (PET2-), ($p > 0.05$). There were no registered deaths from the refractory disease. We did not find any significant difference between EFS rate in pts with PET2+ vs PET2- (log-rank test, $p = 0.4$). 47 pts have proceeded for end-of-treatment PET-CT (PET3). Results showed 3/47 pts (6,3%) were PET3+ and PET3- were 44/47 (93,7%), ($p < 0,05$). EFS was compared and assessed depending on DS. Achieved rate of 3-year EFS in pts with PET3 DS 1-2, DS 3 and DS 4-5 were 94,4%, 50% and 0%, respectively ($p < 0.006$).

Conclusions: End of treatment PET-CT plays an important role in patients with early-stage HL and could be a beneficial prognostic factor. However, there is still need for prospective confirmation of interim PET-CT as a prognostic factor.

Legal entity responsible for the study: Tetiana Skrypets.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1039P Assessment to predict survival and risk of progression in patients with newly multiple myeloma in different age groups

I. Kriachok, O. Novosad, K. Ulianchenko, T. Skrypets, T. Kadnikova

Onco-Hematology, National Cancer Institute of the MPH Ukraine, Kiev, Ukraine

Background: Treatment options and outcomes for multiple myeloma (MM) pts were greatly changed over the last 10 years. Treatment according to different age groups requires careful consideration of the balance between maximizing efficacy and acceptable tolerability.

Methods: 100 pts (median age: 63, range 34-80; m: 63, f: 37) were registered in NCI from Jan 2006 to Jan 2018. 19% (19/100) of patients received M2, MP, DAV therapy (group1), 46% (46/100) - thalidomide-based (group2) and 35% (35/100) -PI-based regimens (group3). In 28% patients t(4:14), del13, and del17p13] were assessed. The primary endpoint was EFS and OS.

Results: For 100 pts the ORR was 70 %. We recorded 39% relapses in the follow-up after the 1st line therapy (median – 10.9 months; range 2–129). 61.1% vs 47.8% vs 17.1% relapses were diagnosed in group1 vs group2 vs group3, respectively ($p < 0.05$). 3-year EFS for group1 was 18% vs 30% in group3 and 20% vs 30% for group2 vs group3, respectively ($p = 0.002$). ROC analysis confirmed bortezomib-based regimens improved EFS in MM patients without age correlation (Se = 81%; Sp = 54%; AUC=0.7, $p = 0.0001$). EFS was higher in the group 2 pts <65 y.o. vs > 65 y.o (40% vs 18%, $p < 0.05$). 3-year OS was 65% vs 45% in younger pts vs elderly pts, respectively ($p = 0.009$). Thrombosis complications in group 2 were compared in pts >65 y.o (20%) vs < 65 y.o (7.7%), ($p < 0.05$). 3-year EFS and OS were similar in the group 3 ($p = 0.4$). Also, neurotoxicity was the same in different age groups (58.6% vs 60%). 50% vs 33.8% cases of disease progression had patients who received doublet and triplet regimens, respectively ($p < 0.05$). ROC analysis confirmed doublet regimen association with lower EFS pts >65 y.o (Se = 50%; Sp = 100%; AUC=0.7, $p = 0.04$). Median EFS in pts with del17p13 was lower without any correlation with age (10.9 vs 29.7 months). We did not find any significant association between patients with del13 or t(4:14) and clinical outcome of MM.

Conclusions: Bortezomib-based regimens are still in a priority for the 1st-line treatment in different age groups. Thalidomide might be an option for younger pts, because thrombosis events are more frequent in elderly pts. To achieve better response in the 1st-line therapy, it is preferable to use triplet regimens in pts <65 and >65 years old.

Legal entity responsible for the study: Olga Novosad.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1040P Impact of bisphosphonate and anti-myeloma therapy on bone turnover markers in multiple myeloma

A. Jandial[1], S. HJ[1], K. Mishra[1], S. Bhadada[2], A. Sood[1], M. Prakash[3], A. Meshram[1], R. Sandal[1], D. Lad[1], R. Aggarwal[4], G. Prakash[1], S. Vikas[1], A.R. Khadwal[1], S. Kumari[1], N. Varma[1], S.C. Varma[1], P. Malhotra[1]

[1]Internal Medicine, PGIMER, Chandigarh, India, [2]Endocrinology, PGIMER, Chandigarh, India, [3]Radiodiagnosis, PGIMER, Chandigarh, India, [4]Immunopathology, PGIMER, Chandigarh, India

Background: Bone involvement is a defining feature of symptomatic multiple myeloma (MM). There is little information on changes in bone mineral metabolism that occur with bisphosphonates and anti-myeloma medication.

Methods: Newly-diagnosed MM patients were prospectively enrolled from January to December 2017. Serum bone turnover markers estimation [CTX, P1NP, and Osteocalcin (OC)], DEXA scan, and Tc99 bone scintigraphy were assessed at baseline. Antimyeloma drugs and monthly bisphosphonates were given as per institutional protocol. Bone turnover markers were re-assessed at 3 months.

Results: 24 patients were enrolled. Median age was 55 years (35 – 76 years); 79.16% males. Bone pains and anemia were most common [renal failure 45.8% and hypercalcemia 45.8%]. IgG subtype was most common (52%) [IgA 21%, light chain 16%]. 83.3% had ISS stage III disease; mean β-2 microglobulin was 17.81 (± 25.16) mg/mL. 70.83% patients had multiple lytic lesions and 29.16% had baseline fracture. On DEXA scan, 41.67% had osteopenia and 12.5% had osteoporosis. All bone markers showed a graded but statistically insignificant correlation with the extent of bone involvement, $P > 0.05$. Baseline CTX levels in patients with pathological fractures were significantly higher. Baseline β-2 microglobulin significantly correlated with CTX ($r = 0.44$) and P1NP ($r = 0.43$) levels; OC showed no such correlation. At 3 months, a significant decline was seen in CTX levels [0.46 (±0.84) v 1.16 (±1.19), $P = 0.001$]; minimal rise was seen in P1NP and OC levels, $P > 0.05$. Fall in CTX levels in patients receiving VTD regimen was significantly greater than VCD regimen, $P = 0.012$. The decline in CTX among patients exclusively treated with zoledronate was significantly larger than those who received initial ibandronate followed by zoledronate, $P = 0.017$. At 3 months, overall response rate was 75% [CR 16.7%, VGPR 50%, PR 33.3%].

Conclusions: The bone turnover markers significantly correlated with β-2 microglobulin. Bisphosphonates and anti-myeloma medications considerably reduced CTX (bone resorption marker) but had a trivial effect on P1NP and OC. Larger prospective studies with longer follow up are required to interpret dynamics of bone turnover markers in myeloma.

Legal entity responsible for the study: PGIMER, Chandigarh.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1041P Assessment of bleeding risk by sonoclot in acute lymphoblastic leukemia

K. Mishra[1], A. Jandial[1], A. Meshram[1], R. Sandal[1], D. Lad[1], G. Prakash[1], A.R. Khadwal[1], R. Dhiman[2], N. Varma[1], S.C. Varma[1], P. Malhotra[1]

[1]Internal Medicine, PGIMER, Chandigarh, India, [2]Hepatology, PGIMER, Chandigarh, India

Background: At the same level of thrombocytopenia, patients with acute lymphoblastic leukemia (ALL), receive more prophylactic platelet transfusion in comparison to immune thrombocytopenia (ITP). Routine investigation cann't differentiate the risk of bleeding between ALL and ITP. Sonoclot is a global test of coagulation, a bed side tool, also assesses platelet function. It is widely used in cardiac surgery and hepatology to assess need for blood plasma and platelet transfusion. Aim of the study was to evaluate role of sonoclot in assessing the risk of bleeding in ALL with severe thrombocytopenia.

Methods: In this prospective observational study, twenty-five cases of ALL and fifty cases of ITP (control) were included. All patients included had platelet counts lower than 20000/μL and there was no evidence of any active bleeding. Blood samples were evaluated by conventional coagulation tests as well as by Sonoclot. Sonoclot measures activated clotting time (ACT), clot rate (R1) and platelet function (PF).

Results:

Table: 1041P Comparison of ALL and Control (ITP)

	ITP (n = 50)	ALL (n = 25)		
Parameters	(mean ± SD)	(mean ± SD)	p	Normal Value
Platelet (/μL)	9536.73 ± 5048.05	12240 ± 4576.02	NS	150000-450000
Prothombin time (seonds)	14.1 ± 1.43	14.72 ± 2.13	NS	11-14
Activated partial thromboplastin time (seconds)	29.66 ± 1.99	29.77 ± 2.13	NS	25-35
ACT (seconds)	251.1 ± 37.97	260.16 ± 51.2	NS	100-155
CR (unit)	22.17 ± 6.43	19.56 ± 4.55	0.371	9-35
PF (unit)	1.54 ± 0.72	0.94 ± .83	0.007	>1.6

Both the groups were matched for platelet count. There was no statistically significant difference between two groups when prothrombin time and activated partial thromboplastin time were compared. On sonoclot analysis, the ACT did not show any difference in the two groups, and though clot rate (CR) was different in two groups, it was not statistically significant. However, platelet function (PF) was significantly lower in the ALL than the ITP group (Table).

Conclusions: This is the first study to the best of our knowledge demonstrating the use of sonoclot in ALL with severe thrombocytopenia. We conclude that sonoclot, a point of care device, can assess the risk of bleeding amongst patients with ALL.

Legal entity responsible for the study: Kundan Mishra.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1042P Clinically actionable mutations identified in Korean patients with high-risk acute lymphoblastic leukemia

K-J. Park, I-S. Kim

Department of Laboratory Medicine, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea

Background: Identification of clinically actionable mutations in cancer is essential for catalyzing precision oncology based on risk stratification. Currently, little is known about the mutation profile of high-risk acute lymphoblastic leukemia (ALL) in Korean patients. We aimed to develop a multigene panel for ALL and to investigate clinically actionable mutations in the Korean patients with high-risk ALL.

Methods: We developed a multigene panel targeting 102 genes with diagnostic, prognostic, or therapeutic significance in ALL and validated it using reference materials and clinical samples. The mutation analyses were done in a total of 18 patients with high-risk ALL {T lymphoblastic leukemia (T-ALL, n = 7), B lymphoblastic leukemia in relapse (relapsed B-ALL, n = 5), and Philadelphia chromosome-positive ALL (Ph+ ALL, n = 6)}. High-risk ALL was categorized based on clinical findings and laboratory tests including immunophenotyping, chromosome analyses, fluorescence in situ hybridization, and RT-PCR. Clinically actionable mutations were selected based on a four-tiered system recommended by Association for Molecular Pathology in 2017.

Results: A total of 28 clinically actionable mutations including 6 novel mutations were identified in 83% of the patients. The most frequent alterations in Korean patients were loss of function mutations of KMT2C (78%), followed by mutations of NOTCH1 (17%) and SUZ12 (11%). There is no difference in the frequency of KMT2C mutation among T-ALL, relapsed B-ALL, and Ph+ ALL, while mutations in NOTCH1 and

SUZ12 were observed only in T-ALL. Additional 8 genes including NT5C2 and KRAS were mutated. Furthermore, potential germline pathogenic variants were discovered in 3 patients including one previously diagnosed as neurofibromatosis type 1.

Conclusions: This study showed that KMT2C mutations were recurrently observed in Korean patients with high-risk ALL. The KMT2C mutation status could be an effective risk stratification strategy for Korean patients with ALL. This study provides clinically actionable mutational portrait of high-risk ALL, albeit in a limited number of patients and gives novel insight into genetic heterogeneity of the disease.

Legal entity responsible for the study: Pusan National University Yangsan Hospital Institutional Review Board.

Funding: Biomedical Research Institute in Pusan National University Yangsan Hospital.

Disclosure: All authors have declared no conflicts of interest.

1043TiP A phase IIA dose optimization study of ASLAN003 in acute myeloid leukemia (AML)

C.H. Ng[1], S.B. Ting[2], W.Y.K. Hwang[3], A. Bajel[4], R. Eek[5], M. McHale[6], H-J. Shih[7], N. McIntyre[8], J. Kwek[9], B. Lindmark[6]

[1]Haematology-Oncology, National University Hospital, Singapore, [2]Haematology Department, Eastern Health, Box Hill Hospital, Box Hill, Australia, [3]Haematology, Singapore General Hospital and National Cancer Centre, Singapore, [4]Department of Clinical Haematology, Royal Melbourne Hospital, Parkville, Australia, [5]Medical Oncology, Border Medical Oncology Research Unit, Albury, Australia, [6]Medical, ASLAN Pharmaceuticals, Singapore, [7]Medical, ASLAN Pharmaceuticals, Taipei, Taiwan, [8]Statistical, ASLAN Pharmaceuticals, Singapore, [9]Clinical Operations, ASLAN Pharmaceuticals, Singapore

Background: AML is a heterogeneous hematologic malignancy. For patients who are ineligible for standard treatment, relapsed from prior remission, or failed prior treatment, only few options are available for further treatment and the responses are limited. A recent study has identified dihydroorate dehydrogenase (DHODH) as a critical enzyme in the myeloid differentiation of human AML blast. At present there is no specific molecular marker to identify likely responders to DHODH inhibition. ASLAN003, a potent small molecular DHODH inhibitor, which has completed phase 1, has demonstrated the ability to induce differentiation in AML cell lines, xenograft models, and the primary AML blast obtained from patients. ASLAN003 has shown a safe and tolerable profile in prior phase I studies.

Trial design: A multicenter, single arm phase IIA study to evaluate ASLAN003 as monotherapy in patients with AML who are ineligible for standard therapy. The primary objective is to determine the optimum dose of ASLAN003 based on the efficacy, safety and tolerability profile, of doses already studied in healthy volunteers. Safety will be assessed based on Adverse Events and other safety measures including vital signs, laboratory tests, electrocardiography. Efficacy will be assessed using the Overall Complete Remission Rate (OCRR, % of complete remission (CR) + complete remission with incomplete hematologic recovery (CRi)). Secondary objective is to assess the pharmacokinetics (PKs) of ASLAN003 and its metabolite and to further assess the efficacy based on relapse-free survival and clinical benefit rate (CBR, % of partial remission +CR+ CRi). Exploratory objectives is to exam the myeloid differentiation effects of ASLAN003 ex vivo and explore the possible relationships between the clinical response and AML molecular profile. The study contains 3 cohorts (ASLAN003 100 mg, 200 mg, and 300 mg once daily). Accrual has started on December 2017, with planned enrollment for 6 patients for each cohort. Safety data will be listed and summarized. Overall AML response data will be listed and summarized showing frequency and proportion of the best response, OCRR and CBR by dose levels. Concentrations and PK parameters will be listed and summarized using descriptive statistics.

Clinical trial identification: Clinical trial information: NCT03451084.

Legal entity responsible for the study: ASLAN Pharmaceuticals.

Funding: ASLAN Pharmaceuticals.

Disclosure: M. McHale: Chief Operating Officer and holds stocks: ASLAN Pharmaceuticals. H-J. Shih, J. Kwek: Employee: ASLAN Pharmaceuticals. N. McIntyre: Statistical consultant: Aslan Pharmaceuticals. B. Lindmark: Employee, senior management team and CMO: ASLAN Pharmaceuticals; Holds stock and stock options: ASLAN Pharmaceuticals. All other authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii372–viii399, 2018
doi:10.1093/annonc/mdy287

HEAD AND NECK CANCER, EXCLUDING THYROID

1044O A phase Ib/II study (SCORES) of durvalumab (D) plus danvatirsen (DAN; AZD9150) or AZD5069 (CX2i) in advanced solid malignancies and recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC): Updated results

E.E.W. Cohen[1], K.J. Harrington[2], D.S. Hong[3], R. Mesia[4], I. Brana[5], P. Perez Segura[6], T. Wise-Draper[7], M.L. Scott[8], P.D. Mitchell[9], G.M. Mugundu[10], P. McCoon[8], C.E. Cook[8], M. Mehta[8], U. Keilholz[11]

[1]San Diego Moores Cancer Center, University of California, La Jolla, CA, USA, [2]Chester Beatty Laboratories, Institute of Cancer Research ICR, London, UK, [3]Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA, [4]Servicio De Oncologia Medica, ICO L'Hospitalet, Barcelona, Spain, [5]Department of Medical Oncology, Vall D'Hebron Institute of Oncology, Barcelona, Spain, [6]El Instituto de Investigación Sanitaria del Hospital Clínico San Carlos, Hospital Clinico San Carlos, Madrid, Spain, [7]Division of Hematology-Oncology, University of Cincinnati Cancer Institute, Cincinnati, OH, USA, [8]Oncology Translational Medicine Unit, IMED Biotech Unit, AstraZeneca Pharmaceuticals, Waltham, MD, USA, [9]Biometrics, IMED Biotech Unit, AstraZeneca Pharmaceuticals, Waltham, MD, USA, [10]Quantitative Clinical Pharmacology, Early Clinical Development, IMED Biotech Unit, AstraZeneca Pharmaceuticals, Waltham, MD, USA, [11]Oncology, Charite Comprehensive Cancer Center, Berlin, Germany

1045O A phase II window of opportunity study of preoperative olaparib (O) with cisplatin (C) or durvalumab (D) or olaparib alone in in patients with operable squamous cell head and neck carcinoma (HNSCC) (OPHELIA)

A. Psyrri[1], P. Economopoulou[2], I. Kotsantis[2], G. Koutsodontis[2], M. Cheila[1], G. Papaxoinis[3], D.G. Pectasides[4], G. Fountzilas[5], L. Krikoni[6], V. Souliotis[6]

[1]Internal Medicine/Medical Oncology, Attikon University Hospital, Athens, Greece, [2]Medical Oncology, Attikon University Hospital, Athens, Greece, [3]Oncology, The Christie NHS Foundation Trust, Manchester, UK, [4]2nd Department of Internal Medicine, Hippokration General Hospital, Athens, Greece, [5]Medical Oncology, Papageorgiou Hospital Aristotle University of Thessaloniki, Thessaloniki, Greece, [6]Biology, Institute of Biology, Medicinal Chemistry and Biotechnology (IBMCB), Athens, Greece

1046O Preliminary results from a phase II trial of tipifarnib in squamous cell carcinomas (SCCs) with HRAS mutations

A.L. Ho[1], N. Chau[2], J. Bauman[3], K. Bible[4], A. Chintakuntlawar[4], M.E. Cabanillas[5], D.J. Wong[6], I. Braña Garcia[7], M.S. Brose[8], V. Boni[9], C. Even[10], M. Razaq[11], V. Mishra[12], K. Bracken[13], D. Wages[13], C. Scholz[13], A. Gualberto[13]

[1]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [3]Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [4]Medical Oncology, Mayo Clinic, Rochester, MN, USA, [5]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]Medicine, Hematology/Oncology, UCLA - School of Medicine, Los Angeles, CA, USA, [7]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [8]Medical Oncology, Abramson Cancer Center at the University of Pennsylvania School of Medicine, Philadelphia, PA, USA, [9]Medical Oncology, START Madrid-CIOCC HM Hospital Sanchinarro, Madrid, Spain, [10]Department of Head and Neck Surgical & Medical Oncology, Gustave Roussy Institute, Villejuif, France, [11]Medical Oncology, Stephenson Cancer Center, Oklahoma City, OK, USA, [12]Diagnostics, Kura Oncology, San Diego, CA, USA, [13]Development, Kura Oncology, Cambridge, MA, USA

1047PD Pembrolizumab for recurrent head and neck squamous cell carcinoma (HNSCC): Post hoc analyses of treatment options from the phase III KEYNOTE-040 trial

C. Le Tourneau[1], E.E.W. Cohen[2], K.J. Harrington[3], J. Dinis[4], L. Licitra[5], M.-J. Ahn[6], A. Soria[7], J-P. Machiels[8], N. Mach[9], R. Mehra[10], B. Burtness[11], P. Zhang[12], J. Cheng[12], R. Swaby[12], D. Soulières[13]

[1]Drug Development and Innovation, Institut Curie, INSERM U900 Research Unit, and Versailles-Saint-Quentin-en-Yvelines University, Paris, France, [2]Moores Cancer Center, UC San Diego Health, La Jolla, CA, USA, [3]Targeted Therapy, The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust, National Institute of Health Research Biomedical Research Centre, London, UK, [4]Medical Oncology, Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal, [5]Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy, [6]Hematology & Oncology, Samsung Medical Center, Seoul, Republic of Korea, [7]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [8]Oncology, Cliniques Universitaires Saint-Luc and Université Catholique de Louvain, Brussels, Belgium, [9]Hôpitaux Universitaires de Genève, Geneva, Switzerland, [10]Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA, [11]Medicine, Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA, [12]Medical Oncology, Merck & Co, Inc, Kenilworth, NJ, USA, [13]Department of Medicine - Department of Hemato-Oncology, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada

1048O M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients (pts) with advanced SCCHN: Results from a phase I cohort

B.C. Cho[1], A. Daste[2], A. Ravaud[2], S. Salas[3], N. Isambert[4], E. McClay[5], A. Awada[6], C. Borel[7], J. Gulley[8], L. Ojalvo[9], C. Helwig[10], P.A. Rolfe[11], N. Penel[12]

[1]Medical Oncology, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea, [2]Medical Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France, [3]Medical Oncology, CEPCM Assistance Publique des Hôpitaux de Marseille, Marseille, France, [4]Medical Oncology, Centre Georges-François Leclerc (Dijon), Dijon, France, [5]Medical Oncology, Institute for Melanoma Research & Education, California Cancer Associates for Research & Excellence, Inc, Encinitas, CA, USA, [6]Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, [7]Medical Oncology, Centre Paul Strauss Centre de Lutte contre le Cancer, Strasbourg, France, [8]Genitourinary Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA, [9]Immuno-Oncology, EMD Serono, Billerica, MA, USA, [10]Biostatistics, Merck KGaA, Darmstadt, Germany, [11]Bioinformatics Immunology and Immuno-Oncology, EMD Serono, Billerica, MA, USA, [12]General Oncology Department, Centre Oscar Lambret, Lille, France

1049PD **Results of a phase II study evaluating monalizumab in combination with cetuximab in previously treated recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)**

J. Fayette[1], G. Lefebvre[2], M.R. Posner[3], J. Bauman[4], S. Salas[5], C. Even[6], E. Saada-Bouzid[7], T. Seiwert[8], D. Colevas[9], F. Calmels[10], R. Zerbib[10], A. Boyer Chammard[10], R. Cohen[11]

[1]ENT, Lung, Sarcomas and GIST, Centre Léon Bérard, Lyon, France, [2]Oncology, Centre Oscar Lambret, Lille, France, [3]Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [4]Oncology, Fox Case Cancer Center, Philadelphia, PA, USA, [5]Early Phases Cancer Trial Center, APHM, AMU, Marseille, France, [6]Oncology, Institut Gustave Roussy, Villejuif, France, [7]Medical Oncology, Hopital Lacassagne, Nice, France, [8]Hematology/Oncology, The University of Chicago Medical Centre, Chicago, IL, USA, [9]Oncology, Stanford University Medical Center, Stanford, CA, USA, [10]Medical, Innate Pharma, Marseille, France, [11]Oncology, Abramson Cancer Center, Philadelphia, PA, USA

1050PD Phase Ib/II, open label, multicenter study of intratumoral SD-101 in combination with pembrolizumab in anti-PD-1 treatment naïve patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)

E.E.W. Cohen[1], A. Algazi[2], D. Laux[3], D.J. Wong[4], A. Amin[5], L. Nabell[6], M. Chisamore[7], E. Gamelin[8], R. Janssen[8], S. Bishnoi[9]

[1]Moores Cancer Center, University of California, San Diego, San Diego, CA, USA, [2]Medicine: Hematology / Oncology, UCSF Medical Center at Mount Zion, San Francisco, CA, USA, [3]Medicine, University of Iowa, Iowa City, IA, USA, [4]Medicine, Hematology/Oncology, UCLA - School of Medicine, Los Angeles, CA, USA, [5]Medical Oncology, Levine Cancer Institute, Charlotte, NC, USA, [6]Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL, USA, [7]Clinical Research, Oncology, Merck & Co, Kenilworth, NJ, USA, [8]Clinical Development, Dynavax Technologies Corporation, Berkeley, CA, USA, [9]Oncololgy, Adelaide Cancer Center, Kurralta Park, Australia

1051PD Comparison of patient populations identified by different PD-L1 assays in head and neck squamous cell carcinoma (HNSCC)

M. Scott[1], S. Wildsmith[2], M. Ratcliffe[2], H. Al-Masri[3], P.W. Scorer[1], C. Barker[1], M.C. Rebelatto[4], J. Walker[2]

[1]IMED Biotech Unit, Precision Medicine Laboratories, Precision Medicine and Genomics, AstraZeneca, Cambridge, UK, [2]IMED Biotech Unit, Oncology Companion Diagnostics Unit, Precision Medicine and Genomics, AstraZeneca, Cambridge, UK, [3]Anatomic Pathology & Clinical Pathology, Hematogenix, Tinley Park, IL, USA, [4]Experimental Pathology, Translational Sciences-Research, MedImmune, Gaithersburg, MD, USA

1052PD Predictor of effectiveness of treatment intensification on overall survival in head and neck cancer (HNC)

K. Zakeri[1], F. Rotolo[2], B. Lacas[2], L.K. Vitzthum[1], Q-T.X. Le[3], V. Gregoire[4], J. Overgaard[5], J. Tobias[6], B. Zackrisson[7], M.K. Parmar[8], B.A. Burtness[9], M.G. Ghi[10], G. Sanguineti[11], B. O'Sullivan[12], C. Fortpied[13], J. Bourhis[14], H. Shen[1], J. Harris[15], J-P. Pignon[2], L.K. Mell[1]

[1]Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA, USA, [2]Plateforme Ligue contre le Cancer, Service de Biostatistique et d'Epidémiologie, Gustave Roussy, Villejuif, France, [3]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA, USA, [4]Radiation Oncology Department, Leon Berard Cancer Center, Lyon, France, [5]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [6]Department of Radiotherapy, University College Hospital, London, UK, [7]Department of Radiation Sciences - Oncology, Umeå University, Umeå, Sweden, [8]MRC Clinical Trials Unit, University College London, London, UK, [9]Department of Medical Oncology, Yale University School of Medicine, New Haven, CT, USA, [10]Oncology Unit 2, Istituto Oncologico Veneto-IRCCS, Padua, Italy, [11]Department of Radiation Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy, [12]Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [13]Headquarters, EORTC - European Organisation for Research and Treatment of Cancer, Brussels, Belgium, [14]Department of Radiotherapy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [15]Statistics and Data Management Center, NRG Oncology, Philadelphia, PA, USA

1053PD **Genomics features (GF) and integration with MRI radiomics features (RF) to develop a prognostic model in oral cavity squamous cell carcinoma (OSCC)**

S. Cavalieri[1], L. De Cecco[2], G. Calareso[3], M. Silva[4], S.E. Gazzani[4], M. Bologna[5], I. Nauta[6], F. Wesseling[7], L. Lopez Perez[8], R. Shefi[9], V. Tountopoulos[10], G. Fico[8], K. Scheckenbach[11], R.H. Brakenhoff[6], F. Hoebers[12], S. Canevari[2], T. Poli[13], L. Licitra[14], L. Mainardi[5], on behalf of the BD2Decide Consortium

[1]Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [2]Platform of Integrated Biology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [3]Radiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [4]Radiology Unit, University of Parma and Azienda Ospedaliero Universitaria di Parma, Parma, Italy, [5]Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy, [6]Department of Otolaryngology and Head & Neck Surgery, VU University Medical Center Amsterdam, Amsterdam, Netherlands, [7]GROW - School of Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, Netherlands, [8]Universidad Politécnica de Madrid, LifeSTech, Madrid, Spain, [9]All in Image Ltd, All in Image, Israel, Israel, [10]Athens Technology Center SA, Innovation Lab, Athens, Greece, [11]Department of Otorhinolaryngology, Universitätklinikum Düsseldorf, Düsseldorf, Germany, [12]Department of Radiation Oncology, Maastricht University Medical Centre, Maastricht, Netherlands, [13]Maxillofacial Surgery Unit, University of Parma and Azienda Ospedaliero Universitaria di Parma, Parma, Italy, [14]Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy

1054PD **Concurrent cisplatin and dose escalation with intensity-modulated radiotherapy (IMRT) versus conventional chemo-radiotherapy for locally advanced (LA) head and neck squamous cell carcinomas (HNSCC): GORTEC 2004-01 randomized phase III trial**

Y. Tao[1], A. Auperin[2], P. Blanchard[1], M. Alfonsi[3], X-S. Sun[4], M. Rives[5], Y. Pointreau[6], J. Castelli[7], P. Graff[5], S. Wong Hee Kam[8], J. Thariat[9], O. Veresezan[10], A. Cornely[1], O. Casiraghi[11], M. Lapeyre[12], J. Bourhis[13]

[1]Radiation Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [2]Biostatistics, Gustave Roussy Cancer Campus, Villejuif, France, [3]Radiotherapy, Clinique Sainte Catherine, Avignon, France, [4]Radiotherapy, Hopital Nord Franche-Comté de Montbéliard & CHRU de Besançon, Montbéliard, France, [5]Radiotherapy, Institut Claudius Régaud, Toulouse, France, [6]Radiotherapy, Centre Jean Bernard, Le Mans, France, [7]Radiotherapy, Centre Eugène Marquis, Rennes, France, [8]Radiotherapy, AP-HM Hôpital de la Timone, Marseille, France, [9]Radiation Oncology, Centre François Baclesse, Caen, France, [10]Radiotherapy, Centre Henri Becquerel, Rouen, France, [11]Biopathology, Institut Gustave Roussy, Villejuif, France, [12]Radiotherapy, Centre Jean Perrin, Clermont-Ferrand, France, [13]Radiation oncology, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland

1055PD **Surrogates of immunologic cell death (ICD) and chemoradiotherapy outcomes in head and neck squamous cell carcinoma (HNSCC)**

G. Koutsodontis[1], G. Papaxoinis[2], I. Kotsantis[1], P. Economopoulou[1], A. Strati[3], C. Avgerinou[1], N. Spathas[4], E. Kirodimos[5], O. Tsavaris[1], E. Maratou[6], L. Hoxhallari[1], M. Anastasiou[1], M. Prevezanou[1], E. Lianidou[3], A. Psyrri[1]

[1]Section of Medical Oncology, 2nd Department of Internal Medicine, Attikon University Hospital, Athens, Greece, [2]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [3]Department of Chemistry, Lab of Analytical Chemistry, University of Athens, Athens, Greece, [4]Oncology Unit, Attikon University Hospital, Athens, Greece, [5]Department of Otolaryngology-Head and Neck Surgery, Hippokration General Hospital, University of Athens, Athens, Greece, [6]Prevention and Treatment of Diabetes Mellitus and its Complications, Hellenic National Center for Research, Athens, Greece

1056PD Phase I experience with rogaratinib in patients with head and neck cancer selected based on FGFR mRNA overexpression

M. Joerger[1], S. Takahashi[2], C.M. Sayehli[3], S. Slosarczyk[3], A. Navarro Mendivil[4], P.A. Cassier[5], H. Nogai[6], C. Zhang[7], F. Sei[8], S. Bender[9], P. Ellinghaus[10], M. Tahara[11]

[1]Department of Medical Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, Switzerland, [2]Department of Medical Oncology, Cancer Institute Hospital of JFCR, Tokyo, Japan, [3]Klinik für Hämatologie und Onkologie, University Clinic Würzburg, Würzburg, Germany, [4]Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Department of Medical Oncology, Centre Léon Bérard, Lyon, France, [6]Oncology, Bayer AG, Berlin, Germany, [7]Product Development, Bayer Yakuhin, Osaka, Japan, [8]Clinical Science, Bayer Yakuhin, Osaka, Japan, [9]Pharmaceuticals, Bayer AG, Berlin, Germany, [10]Translational Medicine, Bayer AG, Wuppertal, Germany, [11]Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

1057P Cetuximab + platinum-based therapy (PBT) as a first-line treatment for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): An observational study (ENCORE)

C. Le Tourneau[1], M. Ghiani[2], M.C. Cau[2], R. Depenni[3], G. Ronzino[4], P. Bonomo[5], V. Montesarchio[6], L. Leo[7], J. Schulten[8], D. Messinger[9], A. Sbrana[10], M.G. Ghi[11]

[1]Department of Drug Development and Innovation, Institut Curie, Paris & Saint-Cloud, France, [2]Medical Oncology Department, H Armando Businco, Azienda Ospedaliera Brotzu, Cagliari, Italy, [3]Medical Oncology, Università degli Studi di Modena e Reggio Emilia, Modena, Italy, [4]Medical Oncology, Ospedale Vito Fazzi, Lecce, Italy, [5]Radiation Oncology, Department of Oncology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy, [6]Pneumo-Oncology Department, AORN dei Colli-Monaldi Hospital, Naples, Italy, [7]Medical Oncology, Ospedale Monaldi-Azienda Ospedaliera dei Colli, Naples, Italy, [8]Medical Affairs, Merck KGaA, Darmstadt, Germany, [9]Biostatistics, Prometris GmbH, Mannheim, Germany, [10]Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [11]Oncology Unit 2, Istituto Oncologico Veneto – IRCCS, Padua, Italy

Background: The EXTREME regimen (cetuximab + PBT ≤ 6 cycles followed by cetuximab-alone maintenance until progressive disease [PD]) was the first treatment in 30 years to significantly improve disease control and overall survival (OS) vs PBT in patients (pts) with first-line (1L) R/M SCCHN (median progression-free survival [PFS], 5.6 vs 3.3 months; median OS, 10.1 vs 7.4 months). ENCORE is a multinational, observational, prospective, open-label study investigating the real-world treatment practices, efficacy, and safety of the EXTREME regimen in 1L R/M SCCHN. The primary objective was to characterize the ways the 1L R/M treatment regimen is administered in SCCHN.

Methods: This study (EMR 062202-566) enrolled 225 pts with previously untreated R/M SCCHN from Italy, France, Portugal, Russia, Algeria, and South Africa, who were planned to receive 1L treatment with cetuximab + PBT.

Results: 221 pts were evaluable. Median age was 64 years, 76% were male, and 85% had an ECOG performance status of 0 or 1. 51% of patients had recurrent disease, 9% had recurrent and metastatic disease, and 40% had metastasis at first presentation. 40% of patients received cisplatin, and 59% received carboplatin. Only 54% of patients received 5-fluorouracil (5-FU). 14% had previously received cetuximab as part of their concomitant treatment, and 12% had PD < 6 months since the last platinum dose in the locally advanced setting. 206 pts (93%) were planned to receive cetuximab maintenance until PD, and 97 of the 202 pts with known stop date (48%) received cetuximab maintenance. Median PFS was 6.5 months (95% CI, 5.4–7.6), and median OS was 10.2 months (95% CI, 8.5–12.6). Serious adverse events occurred in 36% of pts, with 5% related to cetuximab.

Conclusions: The ENCORE trial showed, in an international real-world setting, OS and PFS with 1L cetuximab + PBT that were comparable to what was observed in the randomized, phase 3 EXTREME study. Notably, the EXTREME regimen was feasible in an unselected population and was adapted in a substantial proportion of patients, with almost half of them not receiving 5-FU. Final data will be presented at the congress.

Clinical trial identification: Trial Protocol Number: EMR 062202-566.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA.

Funding: Merck KGaA.

Disclosure: C. Le Tourneau: Honoraria: MSD, Bristol-Myers Squibb, Roche, Amgen, Novartis, Merck Serono, Nanobiotix. All other authors have declared no conflicts of interest.

1058P Elderly patients with locally advanced head and neck squamous cell carcinoma treated with NBTXR3 nanoparticles activated by radiotherapy: A phase I trial

C. Le Tourneau[1], V. Calugaru[1], V. Moreno[2], X. Mirabel[3], B. Dodger[2], E. Calvo[2], T. Jouffroy[1], J. Rodriguez[1], A. Chilles[1], M. Yemi[1], C. Hoffmann[1]

[1]Medical Oncology, Institut Curie, Paris, France, [2]Medical Oncology-Start Madrid-FJD, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [3]Medical Oncology, Oscar Lambret Center, Lille, France

Background: Elderly patients (pts) with head and neck squamous cell carcinoma (HNSCC) represent 25% of the affected population. They are not always eligible to the same treatment of younger pts, thus require new therapies. NBTXR3, injectable hafnium oxide nanoparticles activated by radiotherapy (RT), was developed to increase the local deposit of energy within the tumor. It is currently evaluated in a phase I trial for locally advanced HNSCC in elderly and frail pts.

Methods: So far, 16 pts ≥65 years ineligible for surgery and cisplatin, the non-surgical standard of care, or intolerant to cetuximab, but eligible for RT with stage III or IV HNSCC of the oral cavity/oropharynx were treated with a single NBTXR3 intratumoral (IT) injection. A 3 + 3 dose escalation design was applied with dose levels at 5%, 10%, 15%, 22% of baseline tumor volume followed by intensity-modulated RT (IMRT; 70 Gy / 35 fractions / 7 weeks). Primary endpoints were determining the Recommended Dose and of Dose Limiting Toxicities (DLTs). NBTXR3 leakage in

nearby healthy tissues and efficacy per RECIST 1.1 response via MRI were evaluated. Pts are followed until disease progression/study cut-off date.

Results: Enrollment is at the fourth level at 22% (5 pts) and complete for the first three at 5% (3 pts), 10% (3 pts), 15% (5 pts) with no early DLTs. Two adverse events (AE; asthenia, grade 1; oral pain, grade 2) related to NBTXR3 and four AEs (two tumor hemorrhage, grade 1; asthenia, grade 1; oral pain, grade 2) related to the IT injection were reported. NBTXR3 persistence in the tumor with no leakage was assessed per CT scan between 24h and 7 weeks post injection. In 13 evaluable pts, the best response per RECIST 1.1 on investigator assessment were 6 CR, 4 PR, 3 NC.

Table: 1058P

	5% (n = 3)	10% (n = 3)	15% (n = 5)	22% (n = 2)	Total (n = 13)
Complete response (CR)	0	1 (33%)	4 (80%)	1 (50%)	6 (46%)
Partial response (PR)	2 (67%)	1 (33%)	1 (20%)	0	4 (31%)
No change (NC)	1 (33%)	1 (33%)	0	1(50%)	3 (23%)

Conclusions: Current results indicate a safe and well tolerated profile for NBTXR3 even at the highest doses highlighting an encouraging perspective in the elderly. This population stress a medical need of which few HNSCC trials answer.

Clinical trial identification: NCT01946867.

Legal entity responsible for the study: Nanobiotix.

Funding: Nanobiotix.

Disclosure: All authors have declared no conflicts of interest.

1059P Long lasting responses to adoptive T-cell therapy in relapsed EBV-related nasopharyngeal carcinoma

S. Secondino[1], P. Bossi[2], A. Gurrado[3], S. Basso[3], I. Imarisio[1], A. Pagani[1], M. Zecca[4], I. Pisani[3], J. Bagnarino[3], M. Casanova[5], C. Bergamini[2], C. Perotti[6], L.F. Licitra[2], P. Comoli[3], P. Pedrazzoli[1]

[1]Oncology Departement, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [2]Head and Neck Medical Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Cell Factory, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [4]Pediatric Hematology Oncology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [5]Pediatric Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [6]Immunohaematology and Transfusion Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Background: Epstein-Barr virus (EBV)-related Nasopharyngeal carcinoma (NPC) is a highly chemo-radiosensitive cancer. However, when relapsing without surgical or reirradiation options, NPC carries a dismal prognosis; survival >2 years being reported in 7-14% metastatic pts (1,2). We have previously achieved disease control using autologous EBV-specific cytotoxic T lymphocytes (CTL) in refractory/relapsed pts following conventional treatments (3). The aim of the present study was to evaluate outcomes in pts receiving T-cell therapy after first line chemotherapy (CT) for recurrent disease.

Methods: Sixteen patients (13 males, median age 41 yrs) with metastatic (n = 12; 7/12 with visceral metastasis, and 5/12 with bone and nodes lesions) or locally recurrent (n = 4) NPC received 2 administrations of EBV-specific CTL at a total cell dose/infusion of 1.5-3 x 10^8, following completion of first line CT. The best response after first-line CT had been progressive disease (PD) in 4 pts, stable disease (SD) in 3, partial response (PR) in 5 and complete response (CR) in 4.

Results: No severe adverse events were recorded, following CTL therapy. Among patients in CR after first-line CT, 3 remain in CR at 58, 76 and 77+ months, while one patient relapsed, but attained a long-lasting CR after treatment with 2nd-line CT. In the 12 patients treated with persistent disease (PR, SD, PD), the best response observed after CTL therapy, in some cases (3/12) associated with 1subsequent line of CT or radiotherapy, was PD in 8 patients, and CR (range 39-78+ months) in 4. At a median follow-up of 64 months, 8/16 patients are alive with no evidence of disease. Among the factors associated with positive outcome are response to first-line CT, and metastatic disease with limited tumor burden.

Conclusions: EBV-specific CTL therapy administered following first line CT for recurrent NPC, is safe and associated with remarkable clinical benefit in some patients, including long-lasting CR.

Legal entity responsible for the study: Fondazione IRCCS Policlinico San Matteo Pavia.

Funding: Fondazione IRCCS Policlinico San Matteo, Ricerca Corrente RCR.

Disclosure: All authors have declared no conflicts of interest.

1060P Radiotherapy alone for human papillomavirus-related locally advanced oropharyngeal squamous cell carcinoma: A single-arm, phase II study

N. Takemoto[1], M. Suzuki[1], Y. Seo[2], K. Ogawa[2], H. Inohara[1]

[1]Otorhinolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, Osaka, Japan, [2]Radiation Oncology, Osaka University Graduate School of Medicine, Osaka, Japan

Background: Oropharyngeal squamous cell carcinoma (OPSCC) is divided into two entities: human papillomavirus-related (HPV-related) and HPV-unrelated. Although it is established that patients with HPV-related locally advanced OPSCC (LA-OPSCC) survive significantly better than those with HPV-unrelated LA-OPSCC when treated with chemoradiotherapy (CRT), CRT remains the standard treatment for HPV-related LA-OPSCC. Given the young generation being more prone to be affected by HPV-related OPSCC, patients suffer from severe late toxicity associated with CRT for a long time. The hypothesis has emerged that patients with HPV-related LA-OPCC could be well managed by de-intensified treatment, resulting in long-term less morbidity without compromising survival. A series of clinical trials are in progress to certify this hypothesis.

Methods: We did a single-arm, phase 2 trial, enrolling patients with newly diagnosed, biopsy-proven, stage III or IV (excluding T4 and/or N3) OPSCC, positive for both p16 and HPV DNA. Patients received intensity-modulated radiotherapy alone for 70 Gy in 35 fractions. The primary endpoint was response at 11th week after treatment, assessed on RECIST and PERCIST.

Results: Between August 2013 and November 2016, 39 patients were enrolled with a median age of 64 years (range, 49-83). The majority of patients (24, 62%) had ≥10 pack-years smoking history. 35 (90%) patients showed complete response on RECISIT and/or complete metabolic response on PERCIST. One patient had regional recurrence, and two had distant metastasis. The 2-year overall survival rate and progression-free survival rate was 96% and 91% (95% CI, 76-99 and 75-97), respectively. During treatment 10 patients had grade 3 adverse events, but no grade 4 events were reported. 7 patients had gastrostomy tube placed during treatment, but no patient was dependent on gastrostomy tube at 4 weeks after treatment.

Conclusions: Radiotherapy alone was associated with high disease control and an improved toxicity profile. Radiotherapy alone has the potential to replace CRT as the standard treatment for HPV-related LA-OPSCC.

Clinical trial identification: UMIN000008953; Release date: 09/20/2012.

Legal entity responsible for the study: Osaka University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1061P Molecular screening in advanced cancer patients with head and neck cancers: A retrospective analysis of the MOSCATO-01 trial

A. Houessinon[1], L. Verlingue[1], A. Hollebecque[1], C. Even[2], L. Lacroix[3], S. Postel-Vinay[1], A. Varga[1], Y. El Dakdouki[1], R. Balheda[1], J-M. Michot[1], A. Gazzah[1], A. Marabelle[1], S. Michiels[4], E. Rouleau[5], I. Breuskin[2], T. de Baere[6], E. Angevin[1], J-Y. Scoazec[7], J-C. Soria[1], C. Massard[1]

[1]Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, [2]Department of Head and Neck Surgical & Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France, [3]Biology, Institut Gustave Roussy, Villejuif, France, [4]Biostatistics and Epidemiology, Gustave Roussy, Université Paris-Saclay, Villejuif, France, [5]Department of Medical Biology and Pathology, Laboratory of Translational Research and Biological Resource Center, AMMICA, INSERM US23/CNRS UMS3655, Gustave Roussy, University Paris-Saclay, Villejuif, France, [6]Radiation Oncology, Institut Gustave Roussy, Villejuif, France, [7]Pathology, Laboratory of Translational Research and Biological Resource Center, AMMICA, INSERM US23/CNRS UMS3655, Gustave Roussy, University Paris-Saclay, Villejuif, France

Background: Advanced and metastatic head and neck (HN) cancers are a heterogeneous tumour with poor outcome as few therapeutic options are available. Until now, no accepted genomic profiles can lead to an oriented treatment. We performed a retrospective analysis of the MOSCATO-01 trial for patients with advanced and metastatic HN cancer.

Methods: Patients included in MOSCATO-01 trial underwent biopsies for molecular screening analyses by Comparative Genomic Hybridisation Array, Next Generation Sequencing or RNA Seq. Patients were treated by targeted treatment on the molecular alteration screening. Progression-free survival (PFS) ratio was the primary endpoint corresponding to PFS2/PFS1 (PFS2: PFS in patients treated according to molecular alteration; PFS1: PFS in patients treated with usual treatment).

Results: 129 patients (12.4%) with advanced or metastatic HN cancers were included in MOSCATO-01 trial among 1035 patients. The most frequent histologic type was squamous cell carcinoma (62.7%), followed by adenocarcinoma and kystic adenoid carcinoma (6.5% each) and muco epidermoid carcinoma (3.7%). Patients were in most of the cases heavily pre-treated, as 65% of them received 3 lines of prior systemic treatment. More than 60% of the patients had a RMH score at 0. Of 107 patients (82.9%) who underwent a biopsy, 45 (42%) presented potential targetable molecular alterations: PI3KCA, ERBB2, NOTCH and MET where the most frequent targeted

molecular alterations. Moreover, 33.3% of them (n = 15) had a targeted treatment: 9 patients in phase 1 trial and 6 with off label use therapeutic. The median progression free survival of the 15 patients treated according to molecular alteration was 1.7 months [0.26-6.93]. The PFS ratio was above 1.3 for 46% of the patients.

Conclusions: MOSCATO-01 for HN cancers showed that a large proportion of patients have cancer with actionable molecular alteration, with benefit on PFS ratio of oriented treatment guided by molecular screening. Precision medicine in advanced HN cancers could bring new therapeutic options in these hard to treat cancers.

Legal entity responsible for the study: Christophe Massard.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1062P Pembrolizumab and afatinib for recurrent or metastatic head and neck squamous cell carcinoma

H-F. Kao, R-L. Hong

Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

Background: Head and neck squamous cell carcinoma (HNSCC) is an important malignancy in Taiwan. Anti-PD-1, including nivolumab or pembrolizumab (pembro), had shown the efficacies against recurrent or metastatic (R/M) HNSCC. Afatinib, an irreversible EGFR tyrosine kinase inhibitor (TKI), had showed its activity against head and neck squamous cell carcinoma. In vitro and animal study showed that afatinib can inhibit macrophage function, increase antigen presentation, and augment the T cell response. The role of afatinib for cancer immunotherapy have not been explored in human. We hypothesized that adding afatinib with pembro may improve the treatment efficacy for patients with R/M HNSCC.

Methods: For HNSCC patients who decided to take pembro, the combination with afatinib would be discussed between the physician and the patient. Pembro was planned for 4 cycles. Afatinib was prescribed concurrently with pembro, and will be kept after discontinuation of pembro, until disease progression. For patients taking pembrolizumab and afatinib (P+A), the medical records were reviewed. Patients who have monotherapy with pembrolizumab or afatinib before the P+A were excluded. RECIST 1.1 were used for evaluating tumor response.

Results: From Nov. 1, 2016 to Sep. 30, 2017, 41 R/M HNSCC patients (pts) took P+A. The median age was 59 years, and 38 pts were men. The cancer types were: oral cavity: 29 pts, oropharynx: 5 pts, and hypopharynx: 7 pts. The initial treatments were: pembrolizumab 200mg: 27pts; 2mg/kg: 14pts. Eighteen pts are platinum naïve, and 23 pts are platinum refractory. Until Mar. 30, 2018, the median follow-up was 7.6 months. The clinical response was: CR+PR 24/41 (58.5%, 95% CI: 42.8% -74.3%), SD: 9/41, PD: 8/41. The median PFS was 7.2 (5.0-9.3) months. The median of OS was not reached. The most common toxicities were: diarrhea 56%, skin rash 44%, mucositis 32%, and hand-foot-skin reaction 24%. The incidence of grade 3 or 4 toxicities was 3/41. No pneumonitis were noted in the cohort.

Conclusions: The addition of afatinib with pembrolizumab showed good efficacies and tolerable toxicities. Biomarker studies are ongoing. Further confirmatory prospective trial is indicated.

Legal entity responsible for the study: Hsiang-Fong Kao.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1063P A multicenter phase II trial of paclitaxel, carboplatin and cetuximab (PCE) followed by chemoradiotherapy in patients with unresectable locally advanced squamous cell carcinoma of the head and neck (SCCHN)

T. Enokida[1], T. Ogawa[2], A. Homma[3], K. Okami[4], S. Minami[5], S. Iwae[6], A. Nakanome[2], Y. Shimizu[7], A. Motegi[8], D. Maki[4], Y. Ueda[1], T. Fujisawa[1], S. Nomura[9], S. Okano[1], M. Tahara[1]

[1]Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [2]Otolaryngology and Head and Neck Surgery, Tohoku University School of Medicine, Sendai, Japan, [3]Department of Otolaryngology, Head & Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [4]Department of Otolaryngology-Head Neck Surgery, Tokai University, Isehara, Japan, [5]Department of Otorhinolaryngology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan, [6]Head and Neck Surgery, Hyogo Cancer Center, Akashi, Japan, [7]Department of Medical Oncology, Hokkaido University Hospital, Sapporo, Japan, [8]Division of Radiation Oncology and Particle Therapy, National Cancer Center Hospital East, Kashiwa, Japan, [9]Clinical Biostatistics Division, Center for Research Administration and Support, National Cancer Center, Kashiwa, Japan

Background: Induction chemotherapy (IC) often compromises the compliance of following chemoradiotherapy (CRT) in LA-SCCHN. In particular, impaired compliance of cisplatin (CDDP) during CRT negatively affects outcomes. Here, we aimed to assess the feasibility and efficacy of paclitaxel (PTX), carboplatin (CBDCA), and cetuximab (Cmab) as IC for unresectable LA-SCCHN.

Methods: Patients with biopsy-proven, unresectable LA-SCCHN were enrolled. IC consisted of CBDCA AUC = 1.5, PTX 80mg/m^2 and Cmab with an initial dose of 400mg/m^2 followed by 250mg/m^2 administered weekly for 8 weeks. Following IC, CDDP (20mg/m^2, 4 days x 3 cycles) and concurrent radiotherapy (70Gy/35fr) were started. Primary endpoint was the rate of CRT completion, defined by (1) completion of planned CDDP relative dose intensity (RDI) $\geq$ 80%, and (2) completion of radiotherapy within 2 weeks after planned completion date. PCE was planned to be deemed effective if the Bayesian posterior probability (PP) that the rate of CRT completion was $>$ 65% exceeded 84%.

Results: 35 patients were eligible and received study treatment. Cases were hypopharynx/oropharynx/larynx in 17/17/1 patients, all Stage IV (stage IVA: 24, stage IVB: 11). Of 35 patients, 34 (97%) completed IC and 32 received CRT (FAS). Of 32 FAS cases, the rate of CRT completion was 96.9%, and the study's primary endpoint was therefore met (PP = 99.9% $>$ 84%). Mean cumulative dose and RDI of CDDP in CRT was 232.5mg (160-240mg) and 100% (66.7-100%), respectively. Response rate was 88.6% in the IC phase and 93.8% in the CRT phase. 2-year rates of local progression, distant metastasis, event-free survival and overall survival were 34.9%, 16.7%, 55.1% and 83.5%, respectively. Main grade 3 toxicities included neutropenia (11%), skin rash (6%), and anemia (6%) in the IC phase; and oral mucositis (31%), neutropenia (13%), and radiation dermatitis (13%) in the CRT phase. No grade 4 toxicity or treatment-related death was seen.

Conclusions: PCE as IC was feasible, with promising efficacy and no effect on compliance of following CRT in unresectable LA-SCCHN. A Phase III comparison with CRT alone is warranted.

Clinical trial identification: UMIN000014430.

Legal entity responsible for the study: IC-PCE Study Executive Committee.

Funding: National Cancer Center Research and Development Fund (25-B-2).

Disclosure: K. Okami: Honoraria: Merck Serono Co, Ltd; Consulting or advisory role: Merck Serono Co, Ltd. S. Minami: Speakers' bureau: Nihon Cochlear; Research funding: Taiho Pharmaceutical, Kyorin Pharmaceutical. S. Iwae: Research funding: Ono Pharmaceutical CO, Ltd, Otsuka Pharmaceutical CO, Ltd. S. Nomura: Employment: Asahi Kasei Pharma (Immediate Family Member). S. Okano: Honoraria: Merck Serono, Brystol-Myers Squibb, Ono Pharmaceutical Co, Nippon Kayaku Co. M. Tahara: Honoraria: Bristol-Myers Squibb, Ono Pharmaceutical CO, Ltd, Merck Serono Co, Ltd, Eisai Co, Ltd, AstraZeneca PLC. All other authors have declared no conflicts of interest.

1064P Cetuximab in combination with platinum-based chemotherapy or radiotherapy in patients with recurrent and/or metastatic SSCHN in clinical routine: Updated interim results of the prospective SOCCER study

M. Hecht[1], D. Hahn[2], P. Wolber[3], M. Hautmann[4], D. Reichert[5], J. Weniger[6], C. Belka[7], T. Bergmann[8], T. Göhler[9], M.K. Welslau[10], D. Hofmann[11], R. Fiektkau[1]

[1]Strahlentherapie, Universitätsklinikum Erlangen, Erlangen, Germany, [2]Hematology and Oncology, Klinikum Stuttgart - Katharinenhospital Klinik für Onkologie, Stuttgart, Germany, [3]Hals-Nasen-Ohren Klinik, Universitätsklinikum Köln, Cologne, Germany, [4]Strahlentherapie, Universitätsklinikum Regensburg, Regensburg, Germany, [5]Onkologie, Medizinische Studiengesellschaft Nord-West GmbH, Westerstede, Germany, [6]Onkologie, Gemeinschaftspraxis Dres. Weniger, Bittrich, Schütze, Erfurt, Germany, [7]Radio-Oncology, University of Munich, Munich, Germany, [8]II. Medizinische Klinik, SRH Wald-Klinikum Gera GmbH, Gera, Germany, [9]Onkozentrum Dresden, Onkozentrum Dresden/Freiberg, Dresden, Germany, [10]Onkologie, Klinikum Aschaffenburg, Aschaffenburg, Germany, [11]Medical Affairs Oncology, Merck Serono GmbH, Darmstadt, Germany

Background: Cetuximab in combination with platinum-based chemotherapy followed by cetuximab maintenance until progression significantly prolonged overall survival (OS) in patients with first line recurrent and/or metastatic squamous-cell carcinoma of the head and neck (SCCHN) (EXTREME trial).

Methods: SOCCER is an ongoing German prospective, non-interventional study to evaluate symptom control in patients with recurrent and/or metastatic SCCHN treated with cetuximab in combination with platinum-based chemotherapy or radiotherapy in clinical routine. Desciptive statistics were used for the current interim analysis (data cut-off 6 DEC 2017) focusing on efficacy outcomes.

Results: This interim analysis involves 399 patients (median age: 62.0 years (range 29-89 years), 82.2% male, ECOG 0-1: 74.2%, 61.9% metastatic disease) who received at least one dose of cetuximab. In 289 of 399 patients cetuximab was applied in combination with platinum-based chemotherapy (CT) only (165 cis- (41.3%), 124 carboplatin (31.1%)), in 80 patients (20.1%) in combination with radiotherapy (RT) only; and other regimens in 30 patients (7.5%). Current median duration of cetuximab therapy was 6.1 weeks in combination with RT and 12.9 weeks in combination with CT. Median observation time was 11.7 months (reverse Kaplan-Meier estimate). In the 251 patients with available response data (CR, PR, SD, PD) the objective response and disease control rate were 45.0% and 80.5%, respectively. Median progression-free survival and OS after start of cetuximab therapy was 5.5 and 9.3 months (5.2/9.3 months for the cetuximab + CT and 8.7/9.3 months for the cetuximab + RT).

Conclusions: Interim results of the non-interventional SOCCER study indicate that efficacy outcomes of cetuximab in combination with platinum-based CT under routine conditions are in line with the results of the EXTREME trial.

Editorial acknowledgement: Medical writing by Sonja Hartmann, Alcedis GmbH.

Legal entity responsible for the study: Merck Serono GmbH, Darmstadt, Germany.

Funding: Merck Serono GmbH, Darmstadt, Germany.

Disclosure: M. Hecht: Research funding: Novartis, MSD, AstraZeneca; Honoraria: BMS, Merck Serono; Travel support: Merck Serono, MSD, TEVA. D. Hahn: Travel grants, honoraria for advisory boards and speaker: Merck Serono. M. Hautmann: Honoraria as speaker and consultant: Merck Serono, C. Belka: Honoraria and advisory boards: Merck Serono. D. Hofmann: Employee and stock ownership: Merck. R. Fiektkau: Honoraria as speaker and advisory boards: Merck Serono; Research funding: MSD, AstraZeneca; Honoraria: Roche, Merck Serono, Fresenius, MSD; Travel support: Roche, Merck Serono, Fresenius, MSD. All other authors have declared no conflicts of interest.

1065P TOPNIVO: A safety study of nivolumab in patients with recurrent and/or metastatic platinum-refractory squamous cell carcinoma of the head and neck (R/M SCCHN): First results on behalf of the UNICANCER Head&Neck Group and the GORTEC

C. Even[1], A. Daste[2], E. Saada-Bouzid[3], J. Fayette[4], M-C. Kaminsky-Forrett[5], S. Zanetta[6], A. Prevost[7], G. Lefebvre[8], C. Borel[9], D. Cupissol[10], F. Huguet[11], J-P. Delord[12], N. Baste Rotllan[13], J. Delaye[14], I. Jallut[14], N. Vintonenko[15], J. Bourhis[16], J. Guigay[17], M. Texier[18], A. Auperin[18]

[1]Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France, [2]Medical Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France, [3]Medical Oncology, Hopital Lacassagne, Nice, France, [4]Medical Oncology, Centre Léon Bérard, Lyon, France, [5]Medical Oncology, Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandoeuvre les Nancy, France, [6]Medical Oncology, Centre Georges-François Leclerc (Dijon), Dijon, France, [7]Medical Oncology, Institut Jean Godinot, Reims, France, [8]Medical Oncology, Centre Oscar Lambret, Lille, France, [9]Medical Oncology, Centre Paul Strauss Centre de Lutte contre le Cancer, Strasbourg, France, [10]Medical Oncology, ICM Val d'Aurelle, Montpellier, France, [11]Medical Oncology, APHP, CancerEst, Tenon University Hospital, Paris, France, [12]Medical Oncology, Institut Universitaire du Cancer -Toulouse- Oncopole, Toulouse, France, [13]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [14]R&D, UNICANCER, Paris, France, [15]Clinical Operations, GORTEC, Tours, France, [16]R&D, GORTEC, Tours, France, [17]Medical Oncology, Centre Anticancer Antoine Lacassagne, Nice, France, [18]Biostatistics, Gustave Roussy Cancer Campus, Villejuif, France

Background: In the randomized phase III Study CA209141, Nivolumab (N) demonstrated significant overall survival benefit as treatment for platinum refractory R/M SCCHN and is now approved for these patients. N has demonstrated a manageable safety profile compared to chemotherapies commonly used in patients with platinum-refractory R/M SCCHN. The main objective of the study is to provide additional insight into the frequency of high-grade AEs related to N and their outcome.

Methods: Between August 2017 and October 2017, 75 patients were included in the multicenter, open-label, non-controlled phase II safety study TOPNIVO. The main inclusion criteria were patients with platinum refractory R/M SCCHN with progressive disease, ECOG 0-2. Patients received N 3mg/kg every 2 weeks intravenously over 30 minutes. We report here the safety results of the three first months of treatment.

Results: Of 73 patients treated with N, median age was 64.0 yr, 75% were male, 23% were ECOG 0, 62% 1, 15% 2, 81% were current or former smoker. The primary site of cancer was oral cavity 27%, oropharynx 34%, larynx 19%, hypopharynx 19%. 36% had loco regional relapse, 34% had metastatic disease and 30% had both. 48% had received one prior line of chemotherapy and 32% two prior lines. 37 pts (51%) received at least 6 administrations of N during the first three months of treatment. 5% of administrations were delayed, mainly for intercurrent disease. 38 pts (52%) ended N within the first three months, 28 pts for progressive disease, 8 due to death (thrombus 1pt, progressive disease or related to cancer 7 pts), 1 for pneumonitis, 1 for pain. 35 pts experienced at least 1 AE grade 3/4/5. On the 52 AEs grade 3-4, 7 (mainly asthenia and lipase increase) were related to N. On the 7 AEs grade 5, 1 (pneumonitis) was related to N. 28 pts (38%) experienced at least 1 SAE. On the 38 SAEs, 3 were related to N. 6 patients experienced tumor bleeding (grade 1 2 pts, grade 2 1 pt, grade 3 1 pt, grade 4 1 pt, grade 5 1 pt), none were related to N.

Conclusions: The first results of the TOPNIVO study show an acceptable toxicity profile without additional toxicities compared to what has been described previously.

Clinical trial identification: NCT03226756; EudraCT: 2017-000424-10.

Legal entity responsible for the study: UNICANCER.

Funding: Bristol-Myers Squibb.

Disclosure: C. Even: MSD, Merck Serono, BMS, AstraZeneca, Innate Pharma. E. Saada-Bouzid: Advisory board and consulting: BMS, Merck Serono, AstraZeneca. C. Borel: Advisory board immunotherapy: AstraZeneca, BMS; Symposia honoraria: Merck Serono, BMS; Congress: Merck Serono. D. Cupissol: Boards: Merck, AstraZeneca, BMS. F. Huguet: Merck Serono, BMS, AstraZeneca, MSD. J. Guigay: Consulting or advisory role: Merck Serono, BMS, Innate Pharma, AstraZeneca; Research funding: BMS, GSK, Merck Serono. All other authors have declared no conflicts of interest.

1066P A phase II trial of docetaxel plus cisplatin in recurrent and/or metastatic non-squamous cell carcinoma of head and neck

Y. Imamura[1], N. Kiyota[1], K. Tanaka[2], H. Hayashi[2], I. Ota[3], K. Nario[3], S. Hirano[4], A. Arai[4], S. Iwae[5], T. Onoe[6], S. Minami[7], T. Shimada[7], K. Yane[8], T. Yamazaki[9], Y. Nagatani[1], M. Toyoda[1], N. Otsuki[10], K-I. Nibu[10], H. Minami[1]

[1]Medical Oncology/Hematology, Kobe University Hospital, Kobe, Japan, [2]Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan, [3]Otolaryngology Head and Neck Surgery, Nara Medical University, Kashihara, Japan, [4]Otorhinolaryngology, Kyoto Prefectural University of Medicine, Kyoto, Japan, [5]Head and Neck Surgery, Hyogo Cancer Center, Akashi, Japan, [6]Medical Oncology, Hyogo Cancer Center, Akashi, Japan, [7]Otolaryngology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan, [8]Otolaryngology, Nara Hospital, Faculty of Medicine, Kindai University, Nara, Japan, [9]Head and Neck Cancer Oncology, Miyagi Cancer Center, Natori, Japan, [10]Otolaryngology-Head and Neck Surgery, Kobe University Hospital, Kobe, Japan

Background: Due to the rarity and heterogeneity of recurrent and/or metastatic head and neck non-squamous cell carcinoma (R/M HN non-SCC), no standard chemotherapy for this condition has yet been established. This multicenter phase II trial evaluated the efficacy and safety of docetaxel and cisplatin combination (DC) in R/M HN non-SCC.

Methods: Eligibility criteria were R/M HN non-SCC; progressive disease within the last 6 months; no prior systemic therapy, or interval of at least 24 weeks since the last induction chemotherapy or chemoradiotherapy with curative intent; measurable disease; and ECOG performance status of 0 or 1. Patients (pts) received docetaxel (75 mg/m^2 on day 1) and cisplatin (75 mg/m^2 on day 1), repeated every 21 days for 6 cycles. The primary endpoint was objective response rate (ORR).

Results: From Nov 2012 to Oct 2016, a total of 23 pts were enrolled, characterized as 15 females, median age 57 years (range, 32-76), and 96% metastatic. Among 22 evaluable pts, ORR was 45.5% (95% confidential interval [CI], 24.4-67.8%), and the lower bound of the 95% CI of 24.4% exceeded the predefined hypothesis of 10%. ORRs according to primary tumor site and histology are shown in the table below. With a median follow-up period of 18.8 months, median progression-free survival and overall survival were 6.7 and 20.1 months, respectively. Grade 3/4 adverse events included neutropenia (91%), febrile neutropenia (FN) (39%), anemia (22%), appetite loss (17%), and fatigue (13%). The FN rate was significantly lower in the pts with prophylactic antibiotics (57 vs 11%, P = 0.04). No treatment-related deaths were observed.

Table: 1066P Objective response rates according to primary tumor site and histology

	Adenoid cystic carcinoma	Aadenocarcinoma, not otherwise specified	Salivary duct carcinoma	Sebaceous carcinoma	Mucoepidermoid carcinoma	NUT midline carcinoma	Acinic cell carcinoma	Total
Salivary gland	2/4	2/3	2/3			0/1		6/11
Nasal cavity/paranasal sinus	1/3							1/3
Ocular	0/1			2/2*				2/3
Oral cavity/lip					1/1		0/1	1/2
Oropharynx	0/1	0/1						0/2
Ear	0/1							0/1
Total	3/10	2/4	2/3	2/2	1/1	0/1	0/1	10/22

*complete response

Conclusions: This phase II study of DC met its primary endpoint. This DC regimen is effective and represents a new treatment option in the treatment of progressive R/M HN non-SCC, although prophylactic antibiotics for FN should be considered.

Clinical trial identification: UMIN000008333.

Legal entity responsible for the study: Kobe University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1067P Multicenter phase II trial of nab-paclitaxel and cisplatin (AP) followed by chemoradiation therapy (CRT) for locally advanced head and neck squamous cell carcinoma (HNSCC)

D. Adkins[1], J. Ley[1], H.A. Gay[2], M. Daly[2], R. Jackson[3], J. Rich[3], P. Pipkorn[3], R.C. Paniello[3], K. Trinkaus[4], P. Neupane[5], J. Zevallos[3], W. Thorstad[2], P. Oppelt[1]

[1]Internal Medicine/Medical Oncology, Washington University School of Medicine, St. Louis, USA, [2]Radiation Oncology, Washington University School of Medicine, St. Louis, MO, USA, [3]Otolaryngology, Washington University School of Medicine, St. Louis, MO, USA, [4]Biostatistics, Washington University School of Medicine, St. Louis, MO, USA, [5]Medical Oncology, University of Kansas Cancer Center, Fairway, KS, USA

Background: The results of two consecutive phase II trials of patients with locally advanced HNSCC showed relapse rates of 13% after nab-paclitaxel, cisplatin, 5-FU and cetuximab (APFC) followed by CRT (Cancer 2013) and 3% after APF (no cetuximab) and CRT (Oral Oncology 2016). The complete response (CR) rates at the primary tumor site after 2 cycles of APFC was 53% and APF 77%. A comparison of APFC and CRT to APF and CRT showed no benefit of cetuximab (Oral Oncology 2017). In this phase II trial, we hypothesized similar efficacy with AP (no 5-FU) and CRT.

Methods: Eligibility criteria were similar to prior trials: stage III-IV oropharynx (OP), larynx, or hypopharynx SCC and adequate organ function and performance status (ECOG 0-1). T_1 tumors were excluded. Treatment: 3 cycles of AP followed by CRT. AP: nab-paclitaxel 100 mg/m^2 days 1,8 and 15 + cisplatin 75 mg/m^2 day 1 in 3 week/cycles. CRT: Cisplatin 100 mg/m^2 days 1, 22 and 43 or cetuximab weekly (if cisplatin-ineligible) and intensity modulated RT 70 Gy (200 cGy/day). The primary endpoint was clinical CR rate at the primary tumor site after 2 cycles of AP, determined by visual exam. With a non-inferiority margin of 19% (lower boundary: 58%), a 40 patient sample provided power = 0.80 at p = 0.05 to conclude the CR rate at the primary tumor site with AP was non-inferior to APF (77%).

Results: Characteristics of the 40 enrolled patients: mean age 57 years (range 42-77), smoker 68%, male 90%, and ECOG 0 (78%). Tumor characteristics: $T_{3\text{-}4}$ (68%), > N_{2c} (58%), and human papillomavirus (HPV)-related OPSCC (73%) or HPV-unrelated HNSCC (28%). CRT included cisplatin (36) or cetuximab (4). Clinical CR rate at the primary tumor site after 2 cycles AP was 70% (28 patients). Primary tumor site biopsies obtained following 2 cycles AP in 29 patients showed no cancer in 24 (83%). Post-cycle 2 biopsies showed no cancer in 19 of 20 evaluable patients with clinical CR. Median follow-up was 12.0 months (range: 0.1-19.6). Relapse rate was 8% (3 patients).

Conclusions: The CR rate at the primary tumor site after 2 cycles of AP was not inferior to that with APF. Deletion of 5-FU from APF did not reduce tumor response.

Clinical trial identification: NCT02573493.

Legal entity responsible for the study: Washington University School of Medicine.

Funding: Celgene.

Disclosure: D. Adkins: Advisory board: Pfizer, Merck; Research funding: Celgene, Pfizer, Merck, Novartis, Lilly, Gliknik, Astra Zeneca, MedImmune, Celldex, Chiltern, Blueprint Medicine. W. Thorstad: Spouse works for Elekta, Inc. All other authors have declared no conflicts of interest.

1068P Cetuximab in combination with methotrexate (MTX) as first-line treatment in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): A phase Ib randomized phase II study versus single agent MTX

J. Ham[1], E. Meerten[2], E. Fiets[3], F. Jeurissen Mc Haaglanden[4], M. Slingerland[5], W.T.A. van der Graaf[6], C.M.L. van Herpen[1], L.V. Beerepoot[7]

[1]Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [2]Medical Oncology, Erasmus Cancer Institute, Rotterdam, Netherlands, [3]Medical Oncology, Medical Center Leeuwarden, Leeuwarden, Netherlands, [4]Internal Medicine, Medisch Centrum Haaglanden, Westeinde, Den Haag, Netherlands, [5]Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [6]Division of Clinical Studies, Royal Marsden Hospital Institute of Cancer Research, Sutton, UK, [7]Internal Medicine, St. Elisabeth Tweesteden Hospital, Tilburg, Netherlands

Background: First-line palliative treatment in R/M SCCHN consists of the combination of cetuximab with cisplatin and 5-FU with a median progression free survival (PFS) and overall survival (OS) of 5.5 and 10.1 months, respectively, at the expense of substantial toxicity. Single agent MTX has minimal side effects, but response rate, gain in PFS and OS are limited. We hypothesized that adding cetuximab to MTX could improve PFS without adding major toxicities. Because this combination had not been tested before, we first performed a phase Ib study followed by a randomized phase II study.

Methods: In the phase Ib study, patients (pts) with previously untreated R/M SCCHN were treated with weekly MTX 40 mg/m^2 and cetuximab 250 mg/m^2, after a loading dose of cetuximab 400 mg/m^2. The primary objectives of the phase Ib study were feasibility and safety of the combination of cetuximab and MTX. In the phase II study pts were randomized to either MTX or the combination (1:2). The primary objective of the phase II study was to detect an increase in median PFS from 3 to 5 months with combination vs single agent MTX. Secondary endpoints were toxicity and OS.

Results: Six pts were included in the phase Ib study. No dose limiting toxicities were observed, median PFS was 24.4 weeks (range 7.1-55.0). In the phase II study 45 pts were included; 15 pts received MTX (73% male, median age 64 years (range 50-77)) and 30 pts cetuximab and MTX (77% male, median age 69 years (range 46-80)). In the phase II study median PFS was significantly different: 8.0 weeks (range 3.0-39.0) in the MTX arm and 17.0 weeks (range 3.9-76.6+) in the combination arm (p=.009). Nine pts in the combination arm experienced a serious adverse event (SAE), 3 were possible treatment-related (pneumonia, pneumonitis and hypersensitivity reaction) compared with 5 pts with an SAE in the MTX group, all unrelated. OS and detailed toxicity results will be presented later.

Conclusions: The combination of cetuximab and MTX in pts with R/M SCCHN is feasible. This randomised phase II study met its primary endpoint: a significantly longer PFS in the cetuximab and MTX combination arm, while toxicity was acceptable.

Clinical trial identification: NCT02054442.

Legal entity responsible for the study: Carla M.L. van Herpen.

Funding: Merckgroup.

Disclosure: E. Meerten: Advisory board: Merck. C.M.L. van Herpen: Corporate-sponsored research: AstraZeneca, BMS, MSD, Merck. All other authors have declared no conflicts of interest.

1069P Phase II study of biweekly TPFL induction chemotherapy for locally advanced squamous cell carcinoma of head and neck

C.Y. Hsieh[1], M.Y. Lein[1], C-H. Hua[2]

[1]Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, Taichung City, Taiwan, [2]Department of Otolaryngology, China Medical University Hospital, Taichung City, Taiwan

Background: The induction chemotherapy (ICT) with triweekly TPF had been considered as an effective treatment in locally advance squamous cell carcinoma of head and neck (SCCHN). However, the treatment needs inpatient care and may have more toxicities for Asian patients. We conducted a phase 2 study of alternative biweekly TPFL as induction chemotherapy and evaluated the outcome and toxicities.

Methods: Patients with locally advanced SCCHN were enrolled in the study. Induction chemotherapy with Docetaxel 50mg/m2, cisplatin 50mg/m2, 5-fluorouracil 2500 mg/m^2 and leucovorin 250 mg/m^2 was administered biweekly for six cycles, followed by local treatment including concurrent chemoradiotherapy, bio-radiotherapy or surgery plus adjuvant RT. Our primary endpoint is response rate after ICT.

Results: Total 58 patients were enrolled in the study from June 2014 to September 2015. The median age is 53 years (from 28 to 69 y/o). The patients' characteristics was mentioned as: primary site of oral cavity/oropharynx/hypopharynx: 18/25/15; stage IVa/IVb: 35/23; male /female: 54/4; performance status ECOG 0-1/2:57/1. In the oropharyngeal cancer patients neither p16 nor HPV16 status was not studied. Of those 58 patients, 56 patients received at least 4 cycles of chemotherapy. The overall response rate after ICT was 89.6 % (CR: 31% PR: 58.6%). Two patients escaped during induction chemotherapy. Grade 3/4 neutropenia was 25/9%; grade 3/4 mucositis was 1.7%; grade 3/4 diarrhea was 1.7%. Infection rate was 19%. The response rate after following treatment was 75 % (CR: 66.0%, PR: 9.0 %) The median follow-up time was 31.8 months. The overall 3 years PFS/OS was 34.3 %/56.1%. Local recurrence rate was 29.3% and distant metastasis rate was 10.3%. Six patients had second primary tumor. (10.3%) The 3 years PFS of patients with CR/PR were 59.3%/25.5%. The 3 years OS of patients with CR/PR were 81.7%/49.1%.

Conclusions: Biweekly TPFL induction chemotherapy has excellent response rate in locally advanced SCCHN. In addition, the grade 3/4 adverse event was acceptable. The patients achieved CR after induction chemotherapy had very good outcomes.

Clinical trial identification: CMUH103-REC2-038.

Legal entity responsible for the study: Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital.

Funding: Sanofi, Taiwan branch.

Disclosure: All authors have declared no conflicts of interest.

1070P Evaluate the role of induction chemotherapy in the treatment of stage II nasopharyngeal carcinoma in intensity modulated radiotherapy era

T. Jin, P-J. Li

Radiation Department, Zhejiang Cancer Hospital, Hangzhou, China

Background: While the combined modality treatment of concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy has now been accepted as the standard treatment for advanced Nasopharyngeal carcinoma (NPC), induction chemotherapy +concurrent chemoradiotherapy (ICRT) is commonly used as well. The prognosis of II NPC patients is favorable. We should be more mindful to living quality during/after treatment, length of hospital stay, treatment cost and so forth. Therefore, the purpose of this study is to contrast prognosis of stage II NPC patients underwent the following two treatment modalities: ICRT vs CCRT.

Methods: 173 patients with American Joint Committee on Cancer 7th stage II NPC are included and divided into two groups: ICRT and CCRT. Induction chemotherapy consisted of 1 to 3 cycles of cisplatin plus fluorouracil or paclitaxel plus cisplatin. Concurrent chemotherapy includes cisplatin only. We retrospectively assess overall survival (OS), progression-free survival (PFS), locoregional free survival (LRFS) and distant metastasis free survival (DMFS).

Results: With a median follow up of 64.7 months, no significant differences are found in grade 3–4 hematologic toxicity, liver dysfunction and renal impairment between ICRT and CCRT groups. Univariable analyses show adding induction chemotherapy to CCRT significantly decreases 5-year OS (87.9% vs 95.5%, P = 0.033), PFS (74.0% vs 86.1%, P = 0 .035), LRFS (80.0% vs 91.2%, P = 0.016), but there is no statistically significant difference in DMFS (87.1% vs 94.7%, P = 0.095). In multivariable analyses, we find the consistent results that induction chemotherapy is a negative factor associated with OS (HR of death =3.768, 95% CI = 1.117 to 12.709; P = 0.032), PFS (HR of progression = 2.156, 95% CI = 1.060 to 4.386; P = 0.034), LRFS (HR of locoregional relapse = 2.435, 95% CI = 1.009 to 5.874; P = 0.048) and also DMFS (HR of metastasis = 2.873, 95% CI = 1.005 to 8.211; P = 0.049), in stage II NPC patients.

Conclusions: In present study, we find that induction chemotherapy causes deleterious effect on stage II NPC patients. However, this is a retrospective study and the adverse effects of induction chemotherapy has not been previously reported. It warrants further investigation.

Legal entity responsible for the study: Zhejiang Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1071P Phase II study of CC-486 in previously treated patients (pts) with locally advanced/metastatic nasopharyngeal cancer (NPC): Final results

R. Mesia Nin[1], P. Bossi[2], A. Hansen[3], C. Hsieh[4], L.F. Licitra[5], E.H. Tan[6], P. Chen[7], J. Miller[8], L.L. Siu[9], R. Haddad[10]

[1]Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain, [2]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [4]Medical Oncology, China Medical University Hospital, Taichung, Taiwan, [5]Head and Neck Medical Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [6]Medical Oncology, National Cancer Center, Singapore, [7]Biostatistics, Celgene Corporation, Summit, NJ, USA, [8]Oncology Clinical Research and Development, Solid Tumor, Celgene USA, Basking Ridge, NJ, USA, [9]Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [10]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Second/third-line treatment (Tx) options are limited for pts with NPC. The efficacy and safety of CC-486 were assessed using Simon's optimal 2-stage design in a phase 2 study. The predefined criterion for advancement to stage 2 (> 4 complete/partial responses) was not met. Here, we present final results from stage 1.

Methods: The single-arm, open-label study (NCT02269943) included pts with locally advanced/metastatic NPC who had ≥ 1 prior Tx, including ≥ 1 platinum-containing regimen. Pts received CC-486 300 mg orally on d 1-14 of a 21-d cycle until disease progression/unacceptable toxicity. The first 6 Asian-Pacific (AP) pts received CC-486 200 mg; if well tolerated, subsequent AP pts received 300 mg. Primary endpoints (per independent reviewer assessment): overall response rate, progression-free survival. Key secondary endpoints: overall survival, disease control rate, safety, pharmacokinetics (PK).

Results: Median age of 36 enrolled pts was 54.0 y. Most were male (81%), had ECOG PS of ≤ 1 (97%), and had ≥ 2 prior systemic anticancer Tx (58%); 36% were AP. Pts received a median of 7.0 Tx cycles; 44% had ≥ 1 dose interruption and 39% had ≥ 1 dose reduction. 22 pts died: 1 on- and 21 post-Tx (> 28 d after last dose); 18 died due to disease complications. The table shows efficacy outcomes. PK analysis showed rapid absorption; exposure was comparable between doses. However, large inter-pt variability and small pt numbers did not allow definitive conclusions. All 36 safety-evaluable pts had ≥ 1 Tx-emergent adverse event (TEAE). Common TEAEs included vomiting (72%) and nausea (67%). Common grade 3/4 TEAEs included neutropenia (33%) and febrile neutropenia (11%).

Conclusions: The safety profile of CC-486 in pts with NPC was consistent with that in other solid tumors and of azacitidine. CC-486 monotherapy did not show sufficient clinical activity in the selected pt population to support further development in these pts.

Table: 1071P

Primary Endpoints	Efficacy-Evaluable Population (n = 25)
Overall response rate, n (%)	3 (12)
Partial response	3 (12)
Median progression-free survival (90% CI), mo	4.7 (3.1 - 7.3)
Secondary Endpoints	
Disease control rate, n (%)	13 (52)
Median overall survival (90% CI), mo	18 (14.8 - not reached)

Clinical trial identification: NCT02269943.

Editorial acknowledgement: Medical writing assistance was provided by Rebecca Tweedell, PhD, MediTech Media, Ltd, funded by Celgene Corporation. All listed authors were fully responsible for all content and editorial decisions for this abstract.

Legal entity responsible for the study: Celgene Corporation.

Funding: Celgene Corporation.

Disclosure: R. Mesia Nin: Advisory role: AstraZeneca, Merck, MSD, BMS; Conferences fee: BMS, Merck. P. Bossi: Consultant/advisory and/or lectures: AstraZeneca, Kyowa Kyrin, Merck, Mundipharma, Roche; Travel coverage: Merck. L.F. Licitra: Consultant/advisory and/or lectures: AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Debiopharm, Eisai, Merck Serono, MSD, Novartis, Roche, Sobi; Research funds to institution: AstraZeneca, Boehringer Ingelheim, Eisai, Merck Serono, MSD, Novartis, Roche; Travel coverage: Bayer, BMS, Debiopharm, Merck Serono, MSD, Sobi. P. Chen: Employee, stock units and stock options: Celgene. J. Miller: Employee, holds company stock: Celgene Pharmaceutical Company. L.L. Siu: Research funding (to institution): Celgene. R. Haddad: Consulting: BMS, Merck, Pfizer, Celgene, Genentech, AstraZeneca; Research support: BMS, Merck, Pfizer, Genentech, AstraZeneca. All other authors have declared no conflicts of interest.

1072P Concurrent cisplatin-based chemoradiotherapy versus cetuximab-based bioradiotherapy for p16-positive, locally advanced oropharyngeal cancer: A meta-analysis

P. Suton[1], M. Skelin[2], I. Luksic[3]

[1]Department of Radiotherapy and Medical Oncology, University Hospital for Tumors, University Hospital Center Sisters of Mercy, Zagreb, Croatia, [2]Pharmacy Department, OB General Hospital Sibenik, Sibenik, Croatia, [3]Department of Maxillofacial Surgery, University Hospital Dubrava, Zagreb, Croatia

Background: Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. A special entity among HNSCCs is HPV-associated oropharyngeal cancer (OPC) with p16 positivity as a surrogate marker of cancer's viral etiology. A standard of definitive treatment for these tumors is cisplatin (CDDP) given concurrently with radiotherapy (RT). Another possible option being investigated is replacement of CDDP with cetuximab (C225). However, the optimal treatment for HPV-positive OPC remains unclear, until ongoing studies provide more evidence on this matter. The aim of this meta-analysis is to provide guidance regarding treatment decision-making in this subgroup of patients.

Methods: We performed a systematic literature search using the MEDLINE, PubMed, EMBASE, Web of Science, ScienceDirect, and Scopus databases. Meta-analysis included studies which directly compared the efficacy of CDDP vs. C225 given concurrently with RT as definitive treatment of p16-positive and locally advanced/unresectable OPC. Primary endpoints included 2-year overall survival (OS) (death from any cause) and 2-year locoregional recurrence (LRR) (recurrence at primary site and/or regional lymph nodes), analysed separately. Six studies were included in the final analysis, including a total of 526 patients (range 18-205).

Results: 2-year OS. There were 313 patients in the CDDP + RT group and 113 patients in the C225 + RT group. The pooled odds ratio (OR), calculated for CDDP + RT vs. C225 + RT, was 0.35 (95% CI, 0.17-0.71; P = 0.003). 2-year LRR. There were 382 patients in the CDDP + RT group and 144 patients in the C225 + RT group. The pooled OR, calculated for CDDP + RT vs. C225 + RT, was 0.25 (95% CI, 0.15-0.45; P < 0.0001).

Conclusions: According to our results, patients receiving CDDP with irradiation had 2.9 and 4-fold decreased risk for death from any cause and locoregional recurrence, respectively. Further investigations are needed in order to determine the optimal treatment modalities in both p16-positive and negative OPC. Until then, CDDP-based chemoradiotherapy should be considered as first line therapy option and standard of care in p16-positive and locally advanced/unresectable OPC.

Legal entity responsible for the study: Petar Suton.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1073P Survival benefit of adjuvant chemotherapy vs active surveillance in locally advanced nasopharyngeal carcinoma: A multicenter retrospective study

P. Danchaivijitr[1], A. Dechaphunkul[2], C. Paoin[1], J. Setakornnukul[3], T. Dechaphunkul[4], R. Jiratrachu[5], S. Niyomnaitham[6], B. Suktitipat[7], C. Sookthon[8], P. Pattaranutaporn[9], C. Jiarpinitnun[9], N. Ngamphaiboon[8]

[1]Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Medicine, Prince of Songkla University, Songkhla, Thailand, [3]Radiology, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [4]Otorhinolaryngology Head and Neck Surgery, Songkhlanagarind Hospital, Songkla, Thailand, [5]Radiology, Songklanagarind Hospital, Hat Yai, Thailand, [6]Pharmacology, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [7]Biochemistry, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [8]Medicine, Ramathibodi Hospital, Bangkok, Thailand, [9]Radiology, Ramathibodi Hospital, Bangkok, Thailand

Background: Adjuvant chemotherapy (AC) is not a standard of care, but commonly utilized, in locally advanced nasopharyngeal carcinoma (LA-NPC) after definitive concurrent chemoradiotherapy (CCRT). Prospective randomized studies showed unclear overall survival benefit of AC compared with active surveillance (AS).

Methods: We conducted retrospective medical record review from 2005 to 2017 from the 3 university hospitals. LA-NPC patients who underwent definitive CCRT were included. Patients who received adjuvant platinum doublet chemotherapy (AC) were compared with AS patients. The primary objectives were overall survival (OS) and disease-free survival (DFS). Toxicities were also analyzed.

Results: Patients' demographic data as shown in the table. Median follow up was 54.4months. Median OS in AC arm was 120 months vs 49.3 months in AS arm (HR = 0.51, P < 0.001, 95% CI 0.37 - 0.70). Median DFS in AC arm was 107.1 months vs 35.4 months in AS arm (HR = 0.49, P < 0.001, 95% CI 0.36 - 0.66). Weight loss and decline of renal function were observed but not statistically significant between two groups.

Conclusions: AC should be considered for patients with LA-NPC who completed definitive CCRT. AC in LA-NPC should be further validated in a randomized clinical study.

Legal entity responsible for the study: Research University Network, Thailand.

Funding: Research University Network, Thailand.

Disclosure: All authors have declared no conflicts of interest.

1074P Paclitaxel in combination with anti-EGFR therapy as induction chemotherapy for patients unfit for cisplatin with locally advanced head and neck squamous cell carcinoma (LA-HNSCC)

J.A. Marín[1], M. Oliva Bernal[1], M. Plana Serrahima[1], M. Ferrer[1], N. Vilariño Quintela[1], S. Vazquez[1], E. Vilajosana[1], A. Lozano[2], J. Nogués[3], A. Marí[4], O. Bermejo[5], R. Mesia Nin[6], M. Taberna Sanz[1]

[1]Medical Oncology, Institut Catala de Oncologia, Barcelona, Spain, [2]Radiation Oncology, Institut Catala de Oncologia, Barcelona, Spain, [3]Otorhinolaryngology, Hospital Universitari de Bellvitge, Barcelona, Spain, [4]Maxillofacial Surgery, Hospital Universitari de Bellvitge, Barcelona, Spain, [5]Plastic Surgery, Hospital Universitari de Bellvitge, Barcelona, Spain, [6]Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain

Background: Induction chemotherapy (ICT) followed by bioradiotherapy (BRT) is a validated conservative approach for fit LA-HNSCC patients (pts). However, in pts unfit for cisplatin-based chemotherapy, this treatment strategy remains a challenge. Paclitaxel in combination with anti-EGFR therapy is active and well-tolerated in the recurrent/metastatic setting. This study aims to evaluate this regimen as ICT followed by BRT.

Methods: A retrospective single institution analysis (2010-2016) of LA-HNSCC pts unfit for cisplatin-based chemotherapy (≥70 years-old and/or significant comorbidity) was performed. Pts were treated with paclitaxel plus anti-EGFR monoclonal antibody up to 9 weeks followed by radical BRT (IMRT with concurrent anti-EGFR therapy). Overall survival (OS) and progression free survival (PFS) were estimated by Kaplan-Meier method.

Results: A total of 44 pts were evaluated: median age 72 years-old (50-83), male 42; tumor location, pts (%): larynx 14 (32), oropharynx 10 (23) (HPV+ 0), hypopharynx 9 (21), oral cavity 7 (16), cervical unknown primary 4 (9); 7thed TNM stage, pts (%): EIII 11 (25), EIVa 19 (43) and EIVb 14 (32). ECOG status 0/1/2: 1/38/5 pts. Response rate to ICT: 32 pts (73%); 5 complete responses (CR) and 27 partial responses (PR). During ICT 5 pts (11%) presented grade 3/4 adverse events, and 1 patient (2%) died due to febrile neutropenia. 37 pts (84%) continued with radical BRT: 20 pts (45%) achieved CR, and 6 of them recurred. Median follow-up: 13.5 (1-52) months. For the whole cohort, median OS and PFS were 15.6 (95% CI 4.7-26.6) and 10.4 (95% CI 7.0-13.7) months, respectively. For the 35 pts who completed ≥6 weeks of ICT, median OS and PFS were 22.2 (95% IC 7.2-37.2) and 15.6 (95% IC 8.4-22.9) months, respectively. Larynx pts showed better outcome in comparison with other locations: median OS not reached (NR) vs 10.7 (p = 0.003) and median PFS NR vs 0 (p = 0.001); 9 pts (64%) preserved a functioning larynx and were alive by the time of the analysis.

Conclusions: Paclitaxel plus anti-EGFR therapy was well-tolerated and might be an effective ICT regimen for LA-HNSCC pts unfit for cisplatin. In our cohort, larynx pts obtained the greatest benefit from this regimen.

Legal entity responsible for the study: Institut Catala de Oncologia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1075P Safety and efficacy of nivolumab (nivo) in platinum-refractory recurrent/metastastic head and neck squamous cell (PR R/M HNSCC) patients (pts): Real-life experience

G. Bruixola[1], J. Caballero Daroqui[2], A.J. Cunquero Tomas[3], S. Sandiego[4], J. García Sánchez[5], S. Blasco[6], S. Ochenduszko[7], A. Iranzo[1], J. Lavernia[4], A. Berrocal Jaime[3], M. Pastor Borgoñón[2]

[1]Medical Oncology, Hospital Clinico Universitario de Valencia - INCLIVA, Valencia, Spain, [2]Medical Oncology, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [3]Medical Oncology, Hospital General Universitario Valencia, Valencia, Spain, [4]Medical Oncology, Instituto Valenciano de Oncología, València, Spain, [5]Oncology, Hospital Arnau de Vilanova, Valencia, Spain, [6]Medical Oncologiy, Hospital de Sagunto, Valencia, Spain, [7]Medical Oncology, Hospital Dr. Peset Aleixandre, Valencia, Spain

Background: PR R/M HNSCC pts present a poor prognosis. In the randomized phase 3 trial CheckMate141, nivo showed benefit in OS with manageable toxicity. In our region, nivo is available for clinical practice since April 2017. Aim: to evaluate the safety and activity of nivo in a real-world setting.

Methods: This multicenter, retrospective analysis included PR R/M HNSCC pts treated with nivo 3mg/kg every 2 weeks at 7 centers from Valencia region. We assessed demographics, safety (CTCAE v4.0 criteria), response evaluation (RECIST 1.1) progression-free survival (PFS) and OS. Pts included in the analysis should have received >1 dose of nivo.

Results: A total of 50 pts were treated between May 2017 and April 2018. At the time of this analysis 38 patients were evaluable (updated data of the complete cohort and follow-up will be presented in ESMO congress). Nivo was administered as first-line palliative treatment in 8 pts (21,1%), as second-line in 18 pts (47,4%) and in third or subsequent lines in 12 pts (31,6%). The median number of doses administered was 5 (range 1-26) with 6 one-week treatment delays due to respiratory infections. Analysis of concurrent antibiotic therapy is pending. The objective response rate was (ORR) 23,7% with 9 partial responses, whereas 9 pts (23,7%) had stable disease. No confirmed hyperprogression was observed. Median time since last dose of platinum was 2,9 months (range 0-24) with 10 pts with a period time longer than 6 months. With a median follow-up of 6 months (range 1-16), median PFS was 3,4 months

Table: 1073P

Characteristics	All (n = 675)	Adjuvant chemotherapy (n = 595)	Active surveillance (n = 80)	p-value
Age (mean±SD)	49.52269 ± 11.91209	48.96639 ± 11.63714	53.425 ±13.4473	0.002
Male (%)	465 (69)	416 (69.92)	49 (61.25)	0.116
BMI kg/m^2 (mean±SD)	23.26 ±4.08	23.25 ±4.10	23.35 ± 4.00	0.824
Smoking Status Non-smoking Previous Current Missing	419 135 100 29	367 120 84 26	49 13 15 3	0.454
T stage T1-T2 T3-T4	359 316	309 286	50 30	0.075
N stage N0 N1-N2 N3, N3a, N3b	75 516 73	62 463 60	13 53 13	0.054
Stage at diagnosis Stage 1 Stage 2 Stage 3 Stage 4 Stage 4a Stage 4b	4 117 306 33 137 78	3 100 275 32 120 65	1 17 31 1 17 13	0.255

(CI95% 1,3-5,6) and median OS was 8,8 months (CI95% 3,8-13,9). 6-month and 9-month overall survival rates were 55% and 45% respectively. No immunorelated adverse events (irAE) grade 3-4 were reported. Most frequent grade 1-2 irAE observed were: asthenia (31,6% 12 pts) arthralgias (15,6%, 6 pts), thyroid disorders (10,5%, 4 pts) and skin rash (1pt).

Conclusions: To date, there are few data on the use of nivo in routine clinical practice in PR R/M HNSCC pts. In our population, more heavilyy pretreated than in ChekcMate141, RR and OS were maintained. These promising results encourage the use of nivo in this population, but further follow-up is still needed.

Legal entity responsible for the study: G. Bruixola, Hospital Clinico Universitario de Valencia - INCLIVA.

Funding: Has not received any funding.

Disclosure: A. Berrocal Jaime: Honoraria: MSD; Advisory role: Bristol-Myers-Squibb. All other authors have declared no conflicts of interest.

1076P Comparison of 3-weekly cisplatin versus 3-weekly carboplatin in patients with locally advanced nasopharyngeal carcinoma (LA-NPC) receiving concurrent chemoradiotherapy (CCRT): A multicenter retrospective study

A. Dechaphunkul[1], P. Danchaivijitr[2], R. Jiratrachu[3], T. Dechaphunkul[4], C. Sookthon[5], C. Jiarpinitnun[6], C. Paoin[2], J. Setakornnukul[7], S. Niyomnaitham[8], B. Suktitipat[9], P. Pattaranutaporn[6], N. Ngamphaiboon[10]

[1]Medicine, Division of Medical Oncology, Prince of Songkla University, Hat Yai, Thailand, [2]Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Radiology, Prince of Songkla University, Hat Yai, Thailand, [4]Otorhinolaryngology Head and Neck Surgery, Songkhlanagarind Hospital, Songkla, Thailand, [5]Medicine, Ramathibodi Hospital, Bangkok, Thailand, [6]Radiology, Ramathibodi Hospital, Bangkok, Thailand, [7]Radiology, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [8]Pharmacology, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [9]Biochemistry, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [10]Medicine, Division of Medical Oncology, Ramathibodi Hospital, Bangkok, Thailand

Background: Although CCRT with high-dose cisplatin remains the standard protocol for patients with LA-NPC, carboplatin has been alternatively used especially for cisplatin-ineligible patients. However, the comparable efficacy of these 2 regimens is still unclear. This study aimed to compare the efficacy and tolerability of 3-weekly carboplatin with 3-weekly cisplatin.

Methods: From May 2005 to November 2014, we retrospectively reviewed medical information for 787 LA-NPC patients treated with CCRT from 3 university hospitals in Thailand. Chemotherapy regimen would be either cisplatin (75-100 mg/m^2) or carboplatin (AUC-5 or 6), followed by adjuvant chemotherapy (platinum plus 5-fluorouracil). Tolerability and survival were analyzed and compared.

Results: Patient demographics, baseline characteristics, and treatment for the patients was shown in the table. During CCRT, 52% of patients in the cisplatin arm completed the 3 planned cycles of treatment, compared to 88% in the carboplatin arm ($P < 0.0001$). Fifty-six percent of patients in the cisplatin, whereas only 5% in the carboplatin arm required dose reduction of chemotherapy due to toxicities ($P < 0.0001$). At the time of analysis, the 5-year disease-free survival was 60% (95% confidence interval [CI], 56 to 63) and 62% (95% CI, 50 to 72) ($P = 0.21$), and 5-year overall survival was 74% (95% CI, 70 to 77) and 67% (95% CI, 56 to 77) ($P = 0.19$), in the cisplatin and carboplatin groups, respectively.

Table: 1076P

Variables	Treatment group		P-value
	Cisplatin (n = 710)	Carboplatin (n = 77)	
Median age (years)	50	48	0.915
Sex [n (%)] Male	500 (70)	56 (73)	0.391
Smoking Yes [n (%)]	225 (32)	47 (61)	<0.0001
Comorbidity Yes [n (%)]	96 (14)	18 (23)	0.019
Stage I [n (%)] II [n (%)]	2 (0.3) 110 (15.6)	1 (1) 11 (15)	0.454
III [n (%)] IVa-IVb [n (%)]	289 (41)	28 (36) 37 (48)	
	308 (43)		
WHO classification I [n (%)]	5 (0.7) 206 (29)	0 (0) 39 (51)	0.401
II [n (%)] III [n (%)]	161 (22.7)	38 (49) 0 (0)	
Missing [n (%)]	338 (47.6)		
Median baseline Cr (mg%)	0.87	0.94	<0.0001

Conclusions: Carboplatin showed similar efficacy to that of cisplatin with better tolerability and could be used as an alternative regimen.

Legal entity responsible for the study: Research University Network: Head and Neck Working Group.

Funding: Research University Network (Thailand).

Disclosure: All authors have declared no conflicts of interest.

1077P Comparison of concurrent chemoradiation therapy plus induction chemotherapy with cisplatin, fluorouracil and docetaxel versus gemcitabine and cisplatin in advanced nasopharyngeal carcinoma

Z. Zeng[1], R. Yan[2], L. Tu[1], Y. Wang[2], P. Chen[3], F. Luo[4], L. Liu[5]

[1]Department of Medical Oncology, Cancer Center and State Key Laboratory of Biotherapy, and Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [2]Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [3]School of Public Health, Sichuan University, Chengdu, China, [4]Department of Medical Oncology, Cancer Center and Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [5]Department of Medical Oncology, Cancer Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China

Background: Induction chemotherapy treatment for nasopharyngeal carcinoma (NPC) is controversial. The aim of this study was to evaluate the treatment outcomes and toxicities between two induction chemotherapy regimens, with both followed by concurrent chemoradiotherapy.

Methods: A retrospective study of 113 patients with eligible NPC (stage III–IV NPC with non-distant metastases) treated at the West China Hospital Cancer Center between May 2009 and Dec 2014 was conducted. Among them, 58 patients received cisplatin, fluorouracil, and docetaxel (TPF) and 55 received gemcitabine and cisplatin (GP) induction chemotherapy. Both groups received CCRT incorporating IMRT and cisplatin-based chemotherapy.

Results: The average follow-up time was 51.4 (16.8–98.3) months. Ninety-four patients (83.2%) were alive after 36-months follow-up. The median overall survival (OS) and progression-free survival (PFS) time were 48.3 and 39.7 months, respectively. The 3-year OS for the TPF regimen was 87.9% and 87.4% with GP chemotherapy($P = 0.928$). The 3-year PFS of the TPF treatment was 84.5%, while it was 83.5% for the GP group($P = 0.551$). OS (Log-Rank $P = 0.928$) and PFS (Log-Rank $P = 0.551$) did not differ significantly between the two groups. Patients in the TPF induction chemotherapy plus CCRT group, did not show better LRFS outcomes in comparison to those in the GP induction group (Log-Rank $P = 0.073$). Furthermore, DMFS rates were not different between the treatment groups (Log-Rank $P = 0.892$).

Conclusions: There were no significant differences in adverse toxicities or treatment efficacy between the chemotherapy regimens in the treatment of locoregionally advanced NPC. Furthermore, the adverse toxicities were similar and could be tolerated. However, the TPF group had a high proportion of grade 3 or 4 adverse reactions.

Legal entity responsible for the study: Lei Liu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1078P Genomic profiling and matched therapy for recurrent or metastatic malignant salivary gland tumors

E.R. Malone[1], R. Jang[1], A. Spreafico[1], I. Weinreb[2], S. Jennings[1], L.L. Siu[1], A. Hansen[1]

[1]Medical Oncology, Princess Margaret Cancer Center, Toronto, ON, Canada, [2]Laboratory Medicine Program, University of Toronto, Toronto, ON, Canada

Background: MSGT are rare with limited systemic treatments. This ongoing trial is a single-institution, prospective study in advanced MSGT involving 2 phases: genomic profiling followed by treatment with either genomically-matched or unmatched therapy. The aim is to determine response rates as per RESIST v1.1 in patients (pts) with MSGT treated with matched or unmatched therapy.

Methods: Pts with recurrent/metastatic MSGT with archived paraffin-embedded tumor samples were enrolled in the profiling phase. Following pathology review and DNA extraction, targeted next generation sequencing was performed in a CLIA certified laboratory. Immunohistochemistry for androgen receptor (AR) and fluorescence in-situ hybridization for HER2 and ALK was done. Successfully profiled pts then proceeded to treatment phase when their disease was progressing to receive a matched therapy via early phase clinical trials or approved agents. If no actionable mutations were identified or no matched agents were available, pts could receive selinexor, an oral selective inhibitor of nuclear export (SINE) that inhibits XPO1 at a dose of 60mg twice weekly. Non-progressing pts remained on active surveillance.

Results: Since July 2014, 38 pts (19M/19F, median age 62 yrs [range 37-85]) have been enrolled in the profiling phase. Disease subtypes include adenoid cystic (n = 19), salivary duct (n = 8) and other (n = 11). Four pts failed screening due to lack of tissue, 4 tumor samples are currently being analysed. Of the 30 evaluable pts, 13 (43%) had at least one actionable mutation. Aberrations identified include PIK3CA (6), TP53 (5), AR (4), BRAF (2), HRAS (2), HER2 amplification (1), HER2 mutation (1), KIT (1), EGFR (1) and PTEN (1). Eight pts were treated with genomically matched therapy and 7 received selinexor. See table for outcomes.

Table: 1078P

	Matched Treatment	Selinexor
Median Duration of treatment	9 months (mo)	4mo
Median overall survival	19.2mo	21.3mo
Stable disease rate	88% (7/8)	86% (6/7)
Progressive disease rate	12% (1/8)	14% (1/7)

Conclusions: Genomic profiling may be integrated into clinical care for pts with MSGT permitting pts to receive targeted therapy. This is an ongoing study, we will present updated data at the conference.

Clinical trial identification: NCT02069730.

Legal entity responsible for the study: Princess Margaret Cancer Center.

Funding: Princess Margaret Cancer Center/Karyopharm.

Disclosure: A. Spreafico: Consultant and advisory board: Merck, BMS, Novartis; Research support to UHN: Karyopharm. A. Hansen: Research support: Genentech/Roche, Merck, GlaxoSmithKline, Bristol-Myers Squibb, Novartis, Boston Biomedical, Boehringer-Ingelheim, Karyopharm. All other authors have declared no conflicts of interest.

1079P Analysis of functional androgen receptor-pathway activity to predict response to androgen deprivation therapy in salivary duct carcinoma

W. van Boxtel[1], I. van Engen-van Grunsven[2], D. van Strijp[3], J.B.A. van Zon[3], M.J.L. Ligtenberg[4], G. Verhaegh[5], J. Schalken[5], S. Neerken[6], A. van de Stolpe[3], C.M.L. van Herpen[1]

[1]Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands, [2]Pathology, Radboud University Medical Center, Nijmegen, Netherlands, [3]Philips Research, Philips, Eindhoven, Netherlands, [4]Oncogenetics, Radboud University Medical Center, Nijmegen, Netherlands, [5]Urology, Radboud University Medical Center, Nijmegen, Netherlands, [6]Molecular Pathway Dx, Philips Healthcare, Eindhoven, Netherlands

Background: Treatment response to androgen deprivation therapy (ADT) in androgen receptor (AR)-positive salivary duct carcinoma (SDC) is 18-50%. The cause of ADT-resistance is unknown. We aim to predict treatment response through analysis of functional AR-pathway activity.

Methods: Patients who received palliative ADT (n = 28) for locally recurrent or metastatic SDC were selected. ADT consisted of bicalutamide or combined androgen blockade. AR-pathway analysis was performed in all patients. For this, RNA was extracted from annotated, formalin-fixed paraffin embedded sections from tumor tissue prior to treatment. For quantitative measurement of functional AR pathway activity, mRNA expression of the AR pathway target genes was measured using one-step RT-qPCR, and a pathway activity score between 0 and 100 was provided (Verhaegh et al, Cancer Res. 2014). Patients were analyzed for treatment response, progression free survival (PFS) and overall survival (OS).

Results: AR pathway activity score was divided in tertiles. Patients with highest AR activity had the longest progression free survival (PFS) and overall survival (OS) upon ADT treatment. Partial responders (PR) were only observed in the group with the highest AR activity (n = 3, p = 0.0267, two-sided Fisher exact), while highest incidence of progressive disease (PD) was found in the lowest AR activity group.

Table: 1079P

	AR-pathway activity (range)	Response (number of patients)			Median PFS (months)	Median OS (months)
Tertile 1	33.10-43.55	0 PR	1 SD	9 PD	2	12
Tertile 2	43.71-50.35	0 PR	2 SD	7 PD	2	13
Tertile 3	51.91-65.58	3 PR	4 SD	2 PD	5	33

Conclusions: Functional AR pathway activity measured by this new method was predictive for clinical response to ADT in this small retrospective SDC cohort. Extended validation of clinical utility in a larger patient cohort is in preparation.

Legal entity responsible for the study: Radboud University Medical Center, Nijmegen, the Netherlands.

Funding: Dutch Salivary Gland Cancer Patient Platform and Radboud Oncology Fund.

Disclosure: D. van Strijp, J.B.A. van Zon, A. van de Stolpe: Employee, corporate research funding: Philips Research. S. Neerken: Employee, corporate research funding: Philips Healthworks. All other authors have declared no conflicts of interest.

1080P Prognostics factors in adenoid cystic carcinoma of the head and neck (ACCHN): Retrospective study of 15 years

P. Neji[1], R.S. Conde[1], S. Esteves[2], M.T.A. Alexandre[1], M. Ferreira[1], E. Netto[3], J. Santos[4], M. Magalhães[5], A. Moreira[1]

[1]Medical Oncology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E, Lisbon, Portugal, [2]Biostatistics, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E, Lisbon, Portugal, [3]Radiotherapy, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E, Lisbon, Portugal, [4]Head and Neck Surgery, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E, Lisbon, Portugal, [5]Otorhinolaryngology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E, Lisbon, Portugal

Background: ACCHN is a rare entity mainly found in the major and minor salivary glands. Localized disease is frequent and very late recurrences are common. The treatment of choice is surgery, when feasible, followed by radiotherapy (RT). RT alone is used in unresectable [RC1] patients (pts).

Methods: Retrospective analyses of consecutive pts with ACCHN from Jan 2000 to Dec 2015 at Instituto Português de Oncologia de Lisboa was done [RC1]. Aims: to characterize clinical, demographic and treatment data, the related prognostic factors and evaluate the 5-years overall survival (OS) and the disease-free survival (DFS) for non-metastatic pts, and the 5-years OS for the entire cohort.

Results: Of the 112 pts with ACCHN, 100 had localized and 12 metastatic disease. The median age at diagnosis was 62 years (range 18-91). Of the 100 pts with localized disease, the most frequent location was in major salivary glands (40%) followed by minor salivary glands in oral cavity (28%). At presentation, T3/T4 tumors was found in 35% of pts and positive lymph nodes in 5%. Curative surgery was performed in 91% of pts and adjuvant RT in 86%. Positive surgical margins were R1 in 52% of pts and R2 in 15%. Perineural invasion was present in 68%. Of the 100 pts, 32 recurred, 16 locally and 13 of these had a second [RC1] surgery. Palliative cisplatin-based chemotherapy was used 12%. With a median follow-up of 6 years, the disease-free survival at 5 years was 63% (CI 95%, 53-75). The median time to recurrence in relapse pts was 24 months. Positive surgical margin (R1/R2) (p = 0.0045) and T3/T4 tumors (p = 0.000165) significantly reduced DFS and OS. Perineural invasion, positive lymph nodes and radiotherapy treatment did not impact on local control. The 5-years OS for the localized ACCHN was 71% (CI 95%, 62-82) and 68% (CI 95%, 59-78) for the global cohort.

Conclusions: Tumor size and surgical margins were found to be prognostic factors for local control and for survival. The low percentage of positive lymph nodes probably prevents its prognostic value. Our survival data was similar to those found in the literature.

Legal entity responsible for the study: Instituto Português de Oncologia de Lisboa Francisco Gentil.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1081P Molecular analysis of NRAS, BRAF, C-KIT, ROS1, ALK and RET alterations in serial biopsies in sinonasal mucosal melanoma

G. Anguera Palacios[1], L.P. del Carpio[1], M-A. Molina[2], C. Aguado[2], J.R. Gras-Cabrerizo[3], X. Leon[3], M. Gonzalez-Cao[4], N. Karachaliou[5], A. Mozos[6], A. Gonzalez[6], A. Barnadas[1], R. Rosell[4], M. Majem[1]

[1]Oncology Department, Hospital de la Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain, [2]Quirón Dexeus University Hospital, Pangaea Biotech S.L, Barcelona, Spain, [3]Otolaryngology/Head and Neck Surgery, Hospital de la Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain, [4]Instituto Oncológico Dr. Rosell, Hospital Universitario Quirón Dexeus, Barcelona, Spain, [5]University Hospital Sagrat Cor, Institute of Oncology Rosell, Barcelona, Spain, [6]Department of Pathology, Hospital de la Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain

Background: Sinonasal mucosal melanoma (SNMM) is a rare entity with no specific treatment. Little is known about SNMM molecular profile, a low rate of genetic alterations has been describe compared to cutaneous melanoma. We aimed to screen for several genetic alterations in SNMM.

Methods: From 1988 to 2017, we collected 20 formalin-fixed paraffin primary tumors blocks from SNMM patients and 12 local recurrences and/or distant metastasis from the same patients. We analyzed the spectrum of mutations in KIT gene (exon 9, 11 13 and 17) by standard PCR followed by Sanger sequencing, NRAS gene (exon 2, 3 and 4) by pyrosequencing and BRAF gene (exon 15) by Taqman PCR. Finally, RET, ALK and ROS1 fusions and gene expression levels were determined by nCounter.

Results: We identified gene mutations in 6/20 cases (30%). We found 2 cases (10%) with mutations in NRAS gene (both in exon 2: G12V), 3 cases (15%) with mutations in KIT (all in the exon 11: R586K, G565R, M552I) and 1 case (5%) with KRAS mutation (G12A). No BRAF mutations were detected. Interestingly, we found discrepancies in the NRAS mutational status of tumor samples obtained from 2 patients. In the first case, at diagnosis, we identified the NRAS mutation in 1 of 2 samples, and in 2 of 3 samples at the time of local recurrence. In the second case, the NRAS mutation was present at diagnosis but only in 2 of 4 samples of distant recurrence. Finally, nCounter did not reveal RET, ALK no ROS1 gene fusions or mRNA overexpression in any sample.

Conclusions: In our series of SNMM, we have found mutations in 6/20 tumors (30%) in KIT, NRAS and KRAS genes. No fusions or overexpression were found for ALK, ROS1 or RET genes. To our knowledge, this is the first reported study on these genes. We plan to further characterize this orphan population by analyzing immune-related genes.

Legal entity responsible for the study: Georgia Anguera.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1082P Programmed death-ligand 1 (PD-L1) expression and HPV-associated p16 in oropharyngeal squamous cell carcinoma (OSCC) treated with primary curative radiotherapy (RT)

T. Steiniche[1], J.G. Eriksen[2], J.K. Lilja-Fischer[2], J. Georgsen[1], P-T. Vo[3], M. Busch-Sørensen[4], D.R. Chirovsky[5], J. Cheng[6], D. Aurora-Garg[7], R. Swaby[8], J. Overgaard[2]

[1]Pathology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [3]Pharmacoepidemiology, MSD - Merck & Co USA, Kenilworth, NJ, USA, [4]Busch-Sørensen Consulting ApS, Virum, Denmark, [5]Outcomes Research, MSD - Merck & Co USA, Kenilworth, NJ, USA, [6]Medical Oncology, Merck & Co Inc, North Wales, PA, USA, [7]Translational Biomarkers, Merck & Co, Inc, Kenilworth, NJ, USA, [8]Medical Oncology, Merck & Co, Inc, Kenilworth, NJ, USA

Background: PD-L1 expression in malignancies contributes to an immunosuppressive microenvironment and disruption of anti-tumoral immune responses. Data are limited on the association between PD-L1 expression and survival in OSCC, overall and by HPV p16 status. We explored the prognostic effect of PD-L1 and p16 in localized or locally advanced OSCC treated with primary RT.

Methods: Patients (pts) diagnosed with OSCC from 2000-12 were identified from the Danish Head and Neck Cancer database (DAHANCA). PD-L1 expression was measured in tumor tissue using Agilent's investigational PD-L1 imunohistochemistry (IHC) PharmDx Assay (clone 22C3). PDL1+ expression was defined as a score >1 using Tumor Proportion Score (TPS) as % of neoplastic cells expressing PDL1 at any intensity, Mononuclear Inflammatory Density Score (MIDS) as the estimate of PDL1 expressing mononuclear inflammatory cells associated with neoplastic cells, and Combined Positive Score (CPS) calculated using both TPS and MIDS. HPV oncogene expression was assessed using a > 70% cut-point for p16 IHC (clone E6H4). Data were analyzed using Cox proportional hazard model.

Results: 303 OSCC pts with full clinical data, and PD-L1 and p16 staining were evaluated. Median follow up was 55 months (2-184). Median age (range) was 59 years (34-85), 72% were male, 91% had WHO 0-1 performance status, 55% were current smokers. All had primary RT, 66-68Gy, 2Gy/fx, 6 fx/wk, and 3% had concomitant cisplatin. 81% were UICC 7 stage 3-4 tumors. 55% were p16+. 76% were PD-L1+ by CPS, 35% by TPS, and 31% by MIDS. TPS was significantly associated with MIDS (Chi square p = 0.003). p16 was a strong prognostic factor for loco-regional control [crude hazard ratio (HR) of 0.31 (95% CI: 0.21-0.49)], disease-specific survival [0.39 (0.26-0.57)] and overall survival [0.34 (0.25-0.46)]. PD-L1 expressed as CPS, TPS or MIDS, was not prognostic of the clinical endpoints, overall or by p16 status. Adjustment for other covariates did not change the results.

Conclusions: PD-L1 expression is not prognostic in localized or locally advanced OSCC, including p16 positive disease. p16 is affirmed the strongest biological prognostic factor in OSCC.

Legal entity responsible for the study: The Danish Head and Neck Cancer Group (DAHANCA).

Funding: Merck & Co, Inc.

Disclosure: T. Steiniche: Research funding: Merck & Co, Inc. P-T. Vo, D.R. Chirovsky: Employement, stock ownership, research funding, travel and accommodations expenses: Merck & Co, Inc. J. Cheng: Employment, stock ownership: Merck & Co. D. Aurora-Garg, R. Swaby: Employment Merck & Co. All other authors have declared no conflicts of interest.

1083P Dynamics of immune checkpoint molecule (ICM) expression in immune cell subsets during curative conventional therapy of head and neck squamous cell carcinoma (HNSCC)

A. Grages[1], S.S. Jeske[1], L.K. Puntigam[1], C. Brunner[1], J. Kraus[2], H. Kestler[2], J. Döscher[1], T.K. Hoffmann[1], P.J. Schuler[1], S. Laban[1]

[1]Department of Otorhinolaryngology and Head & Neck Surgery, University Medical Center Ulm, Ulm, Germany, [2]Institute for Medical Systems Biology, Ulm University, Ulm, Germany

Background: Immune checkpoint modulation is a promising treatment strategy in HNSCC. PD-1 inhibition is currently studied in combination with conventional oncologic treatments. However, the impact of curative conventional treatment (surgery, (chemo-)radiotherapy (CRT)) on the expression of targetable ICM has not been studied previously.

Methods: In a prospective non-interventional immune monitoring trial (Immune Response Evaluation to curative Conventional Therapy; IRECT; NCT03053661) peripheral blood mononuclear cells (PBMC) from 22 patients with HNSCC were collected at 8 pre-specified time points during curative conventional treatment (baseline, post-surgery, mid-CRT, end of CRT, 3-, 6-, 9-, 12-months post end of treatment (EOT)). PBMC were analyzed by flow cytometry. Nine ICM (PD1, CTLA4, BTLA, CD137, CD27, GITR, OX40, LAG3, TIM3) were determined in different immune cell subsets (CD8, CD4, CD19, CD39 Treg) over the course of treatment.

Results: Paired samples tests revealed significant changes compared to pre-treatment samples. Compared to baseline, surgery had no significant impact on ICM expression. Median CD8/PD1 were significantly lower at 3 and 6 months post EOT, CD4/PD1, CD19/PD1 and Treg/PD1 were significantly higher at the end of CRT, whereas Treg/PD1 were significantly lower at 3 and 6 months post EOT. CD8/BTLA were significantly decreased from mid-CRT until 12 months post EOT, whereas CD4/BTLA and Treg/ BTLA were significantly decreased from 3 to12 months post EOT. CD4/CD27 were significantly lower from mid-CRT until 12 months post EOT, whereas CD19/CD27 and Treg/CD27 were significantly decreased from 3 to 12 months post EOT. CD4/OX40 and Treg/OX40 increased mid-CRT until 3 months post EOT, but significance was not confirmed after correcting for multiple testing.

Conclusions: Whereas surgery alone seems not to alter ICM expression, CRT has a significant impact on the expression of PD1, BTLA and CD27. OX40 seems to increase during CRT. These results reveal a rational for the combination of PD1 inhibitors with CRT. Combining such a treatment with OX40 inhibitors may be a promising strategy.

Clinical trial identification: NCT03053661.

Legal entity responsible for the study: University Medical Center Ulm.

Funding: Deutsche Forschungsgemeinschaft (GRK2254).

Disclosure: T.K. Hoffmann: Advisory board member: Merck Sharp & Dohme; Lecture fees: Merck Sharp & Dohme, Merck Serono. P.J. Schuler: Advisory board member: Bristol Myers Squibb. S. Laban: Advisory board member: AstraZeneca, Merck Sharp & Dohme; Lecture fees: Bristol-Myers Squibb, Merck Serono. All other authors have declared no conflicts of interest

1084P Multiobjective optimization reveals distinct cancer-testis antigen patterns by primary site and human papilloma virus status in head and neck squamous cell carcinoma

S. Laban[1], G. Völkel[2], J. Ezic[1], T.K. Hoffmann[1], H-G. Rammensee[3], J. Döscher[1], P.J. Schuler[1], C. Brunner[1], J. Kraus[2], H. Kestler[2]

[1]Department of Otorhinolaryngology and Head & Neck Surgery, University Medical Center Ulm, Ulm, Germany, [2]Institute for Medical Systems Biology, Ulm University, Ulm, Germany, [3]Department of Immunology, University of Tübingen, Tübingen, Germany

Background: Most previous vaccination attempts in cancer immunotherapy have been focused on a single antigen. Consequently, the expression of the selected antigen needs to be determined before trial inclusion resulting in a high screening failure rate. The establishment of a multi-antigen vaccine may improve the coverage of potential patients, especially if the selected antigens are semipersonalized for clinical patient subgroups.

Methods: Analysis and Visualization of Alteration Data (AVATAR), a novel bioinformatic software tool for multi-objective optimization of large datasets, was used to analyze publicly available datasets of transcriptome data from The Cancer Genome Atlas (TCGA) and a dataset from Gene Expression Omnibus (GSE 40774). Cancer-testis antigens (CTA) were selected as model antigens for multi-objective optimization based on the primary tumor site and HPV-status. Dichotomized data were pooled and edited resulting in a cohort of 865 patients, of which 125 were HPV-positive (HPV+). Primary tumor sites included were oral cavity (n = 208), oropharynx (n = 150) and larynx (n = 208).

Results: Selecting 10 CTA genes for the whole cohort results in a coverage of 89.3%. When optimizing gene selections for each primary tumor site, distinct 10-gene-selections are revealed improving the coverage in the respective group markedly. Antigen selections overlap only to a minor degree with the solutions for all patients or other patient groups. Even in predominantly HPV- primary sites such as OC and L, antigen selections are remarkably different from each other. When optimizing for HPV-status, distinct selections were found for optimal coverage in the respective patient group overlapping only in one gene.

Conclusions: AVATAR can be used to identify antigen selections with optimal coverage within a specified patient group. A semi-personalized antigen selection based on multi-objective optimization may be a useful strategy to plan trials for antigen-specific vaccination.

Legal entity responsible for the study: University Medical Center Ulm.

Funding: Deutsche Forschungsgemeinschaft (GRK2254).

Disclosure: S. Laban: Advisory board member: AstraZeneca, Merck Sharp & Dohme; Lecture fees: Bristol-Myers Squibb, Merck Serono. G. Völkel, H. Kestler, J. Kraus: Developers of Analysis and Visualization of Alteration Data (AVATAR) software. T.K. Hoffmann: Advisory board member: MSD, Merck Serono. H.-G. Rammensee: Cofounder and shareholder: Immatics, CureVac, Synimmune. P.J. Schuler: Advisory board member: Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1085P The use of HPV16-E5, EGFR and pEGFR as prognostic biomarkers for oropharyngeal cancer patients

M. Taberna[1], M. Torres[2], M. Alejo[3], M. Mena[2], S. Tous[2], S. Marquez[2], M.A. Pavon[2], X. Leon[4], J. Garcia[4], M. Guix[5], R. Hijano[6], T. Bonfill[7], A. Aguilà[8], A. Lozano[9], R. Mesia Nin[10], L. Alemany[2], I.G. Bravo[11]

[1]Medical Oncology, Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain, [2]PREC, Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain, [3]Pathology, Hospital General de Hospitalet, L'hospitalet De Llobregat, Spain, [4]Otorhinolaryngology Department, Hospital de Sant Pau, Barcelona, Spain, [5]Medical Oncology, Hospital del Mar, Barcelona, Spain, [6]Otorhinolaryngology Department, Hospital del Mar, Barcelona, Spain, [7]Medical Oncology, Hospital Parc Taulí, Barcelona, Spain, [8]Otorhinolaryngology Department, Hospital Parc Taulí, Barcelona, Spain, [9]Radiation Oncology, Institut Catala de Oncologia, Barcelona, Spain, [10]Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain, [11]Laboratory MIVEGEC, National Center for Scientific Research (UMR CNRS IRD UM), Montpellier, France

Background: HPV-related oropharyngeal cancer (OPC) patients have favorable prognosis, but around 20% fail to treatment. The HPV16-E5 oncoprotein increases recycling of activated epidermal growth factor receptor (EGFR) to the cell surface, enhancing factor signal transduction. Our aim was to evaluate viral HPV16-E5 oncogene expression as well as EGFR and its activated form, phosphorylated EGFR (pEGFR), protein levels as biomarkers for clinical outcome in a retrospective cohort of OPC patients.

Methods: Formalin-fixed-paraffin-embedded OPC were collected from pathology archives. Samples containing HPV-DNA were further subject to HPV E6*I mRNA detection and $p16^{INK4a}$ immunohistochemistry (IHC). HPV16-positive cases were evaluated for HPV16-E5 (RT-PCR) and EGFR/pEGFR (IHC). A stratified random sample of HPV-negative samples was evaluated for EGFR/pEGFR. Overall survival (OS) and disease-free survival (DFS) estimates were assessed.

Results: Among the 788 OPC patient samples from a retrospective cohort, 54 where double positive for HPV16-DNA and $p16^{INK4a}$. HPV16-E5 expression was found in 41 samples (77.4%). Expression of EGFR was observed in 37.7% vs 70.8% HPV16-positive and HPV-negative samples, respectively; (adjusted Odds Ratio (OR) 0.15[95%Confident Interval (CI):0.04-0.56]). Expression of pEGFR followed an inverse pattern with 39.6% and 24.9% detection in HPV16-positive and HPV-negative samples, respectively; (adjusted OR 1.58[0.48-5.17]). Within HPV16-positive cases, no association between HPV16-E5 and EGFR or pEGFR was observed. The combination of HPV status and EGFR or pEGFR expression were predictors of OS and DFS.

Conclusions: HPV16-E5 is highly expressed on HPV16-positive OPCs. Interestingly, HPV16-positive cases expressed more pEGFR while HPV-negative cases expressed significantly more EGFR. The combinations of HPV status and EGFR or pEGFR expression are useful biomarkers for prognosis outcome in OPC patients.

Legal entity responsible for the study: Institut Català d'Oncologia.

Funding: This work was supported by a grants from "Ayudas Merck Serono Investigación_Salud 2000" , Instituto de Salud Carlos III-ISCIII (Spanish Government) cofunded by FEDER funds / European Regional Development Fund (ERDF) - a way to build Europe (References: PI1102096, PI1401918, PI1500500, PI1501205, RD12/0036/0056, CIBERESP, CIBERONC), Agència de Gestió d'Ajuts Universitaris i de Recerca (2014SGR756; 2014SGR1077), Beca de recerca clínica 2016 de l'Acadèmia de Ciències Mèdiques de Catalunya i Balears, Beca PERIS-2016-2020 Pla Estratègic de Recerca en Investigacions Sanitàries (SLT002/16/00404), Asociación Española Contra el Cáncer (personal grant to LA), Rio Hortega-SEOM (ISCIII-Spanish Society of Medical Oncology) (personal grant to MT).

Disclosure: All authors have declared no conflicts of interest.

1086P Combined analysis of gene expression profiles in 2 preoperative trials with afatinib and cetuximab in head and neck squamous cell carcinoma

P. Bossi[1], S. Schmitz[2], J-P. Machiels[3], L.F. Licitra[1], C. Fortpied Lefevre[4], C. Caballero[5], S. Canevari[6], L. De Cecco[6]

[1]Head and Neck Medical Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Department of Head and Neck Surgery, Cliniques Universitaires St. Luc, Brussels, Belgium, [3]Oncology, Cliniques Universitaires St. Luc, Brussels, Belgium, [4]Statistical, EORTC, Brussels, Belgium, [5]Head and Neck Group, EORTC, Brussels, Belgium, [6]Functional Genomics and Bioinformatics, Department of Applied Research and Technology Development, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

Background: Only a minority of head and neck squamous cell carcinoma (HNSCC) patients (pts) respond to targeted agents acting on epidermal growth factor pathway. We investigated the changes of gene expression profiles in 2 preoperative window of opportunity trials, to allow a further investigation in mechanisms of response.

Methods: Thirty and 20 pts with similar characteristics were treated for 2 weeks before surgery with afatinib (EORTC 90111-24111 NOCI HNCG trial, Ann Oncology 2017) and cetuximab (Schmitz S, Ann Oncology 2013), respectively. The gene expression profile obtained by microarray platform was compared by a paired analysis pre and post treatment. Gene sets were defined according to GSEA and only sets with q-value FDR < 0.05 differences were considered. Clinical response was analysed according to primary endpoint of the trials (FDG-PET response).

Results: Pre- and post-targeted treatment paired histological samples from 20 and 15 pts were evaluable for gene expression, from afatinib and cetuximab series, respectively. The following gene sets were commonly downregulated by the treatment: G2M checkpoint, MYC and E2F targets and MTORC. On the opposite, the gene sets which resulted upregulated were: angiogenesis, epithelial-mesenchymal transition, inflammatory response and NOTCH signalling. A substantial overlapping of molecular alteration between the 2 series has been observed, thus allowing a further meta-analysis combining the 2 datasets to analyse profiles associated to response. Preliminary data in afatinib series showed a strong downregulation of hypoxia gene signature only in responding pts.

Conclusions: In 2 independent studies with afatinib and cetuximab in window of opportunity setting, we observed similar molecular alterations induced by the drugs. Further insights in the pathways involved in response to both drugs are ongoing.

Legal entity responsible for the study: Paolo Bossi.

Funding: AIRC and Italian Ministry of Health.

Disclosure: P. Bossi: Advisory Board: Merck Serono. J.-P. Machiels: Advisory board: Boerhingher-Ingelheim. L.F. Licitra: Advisory board and research supports: Merck Serono, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1087P Association of LIPI score with immune checkpoint inhibitors (ICI) outcomes in recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) patients (pts)

R.G. Herrera Gomez[1], L. Mezquita[2], E. Auclin[3], K. Saleh[2], N. Baste Rotllan[1], M. Iacobs[1], S.C. Bursuc[1], L. Mayache Badis[1], F.R. Ferrand[4], O. Casiraghi[5], S. Temam[1], I. Breuskin[1], Y. Tao[6], B. Besse[7], C. Even[1]

[1]Department of Head and Neck Surgical & Medical Oncology, Gustave Roussy Institute, Villejuif, France, [2]Department of Medical Oncology, Gustave Roussy Institute, Villejuif, France, [3]Medical Oncology, European Hospital Georges Pompidou, Paris, France, [4]Medical Oncology, Bégin Military Teaching Hospital, Saint-Mandé, France, [5]Department of Biopathology, Gustave Roussy Institute, Villejuif, France, [6]Department of Radiation-Oncology, Gustave Roussy Institute, Villejuif, France, [7]Department of Medical Oncology, Gustave Roussy Institute, Villejuif, France

Background: Lung Immune Prognosis Index (LIPI), based on pretreatment dNLR (neutrophils/(leucocytes-neutrophils)) and LDH, correlated with outcome after immune checkpoint inhibitors (ICI) in advanced NSCLC pts. We tested if LIPI, could have the same role in R/M SCCHN pts.

Methods: We conducted a retrospective study of 86 R/M HNSCC pts treated with ICI in our institution between Sep 2014 and Dec 2017. Complete blood cell counts and LDH were collected before ICI treatment. LIPI characterized 3 groups: good risk if dNLR < 3 and normal LDH, intermediate if dNLR > 3 or LDH $>$ upper limit of normal (ULN), and poor if dNLR >3 and LDH $>$ULN. ICI benefit was analyzed according to overall survival (OS) and progression free survival (PFS).

Results: In our cohort, 65 pts (76%) were males, 61 (71%) current/former smokers, 81 (94%) had PS ≤ 1, with median age 59 years. According to the location: 19 (22%) had oral cavity carcinoma, 43 (50%) oropharynx, 11 (13%) hypopharynx and 13 (15%) larynx. HPV by immunohistochemistry was positive in 11/52 pts (10 oropharynx, 1 oral cavity). Twenty-eight (33%) pts received PD1, PDL1, or CTLA-4 inhibitors in monotherapy, and 58 (67%) in combination. The median of prior lines was 1 (0-6). The median follow-up was 8 months (m) [95% CI:7-12], median PFS 3 m [95% CI:2-4] and median OS 12 m [95% CI 8-NA]. The dNLR >3 (36%) and LDH $>$ULN (10%) were associated with poor OS ($P = 0.005$). Based on them, LIPI considered: 44 pts (51%) as good, 38 (44%) intermediate and 4 (5%) poor prognosis group. LIPI was an independent factor for OS (hazard ratio [HR 2.49, 95% CI 1.2-5.2] for intermediate LIPI and [HR 7.97, 95%CI 1.9-32.6] for poor LIPI, $P = 0.005$) and PFS ($P = 0.004$). Median OS for poor, intermediate, and good LIPI was 3.5 m [95% CI, 2- not reached (NR)], 7 m (95% CI, 5-NR), and 12 m (95% CI, 8-NR), respectively ($P = 0.003$).

Conclusions: High LIPI was correlated with worse ICI outcomes in R/M SCCHN pts. Further studies are warranted to confirm the prognostic impact of this score and the potential predictive role for ICI.

Legal entity responsible for the study: Caroline Even.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1088P Analysis of immune and genomic landscapes of patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with pembrolizumab in the INSPIRE study

M. Oliva Bernal[1], S. Lien[2], B.X. Wang[2], S.C. Yang[3], A. Spreafico[1], R. Jang[1], S. Elston[1], S. Jennings[1], H. Jiang[4], B. Haibe-Kains[5], T. Pugh[3], P. Ohashi[2], L.L. Siu[1], A. Hansen[1]

[1]Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [2]Department of Immunology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [3]Medical Biophysics, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [4]Biostatistics, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [5]Department of Computer Sciences, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Despite the survival gain observed with antiPD-1 agents in R/M HNSCC, responses are modest and no predictive biomarkers have been validated. We investigated immune and genomic biomarkers of response in a prospective cohort of R/M HNSCC patients (pts) treated with pembrolizumab 200 mg IV Q3W in the INSPIRE study.

Methods: Pts had blood samples (BS) collected at baseline (BL) and on treatment (OT) at cycle 3 (week 9); fresh tumor biopsies (FTB) collected at BL and OT (week 6-9). Analyses included tumor whole exome sequencing and immunophenotyping by flow cytometry of FTB and BS; tumor PD-L1 staining (clone 22C3) using modified proportion score. Response rate (RR) using RECIST 1.1. Median progression-free survival (PFS) and overall survival (OS) estimated by Kaplan-Meier method. Time to progression (TTP) was estimated using cumulative incidence function. Univariable analyses of genomic and immune parameters were conducted to identify response predictors.

Results: Seventeen pts were enrolled: median age 62 years (48-71); smoking history > =10 pack-year (PY)= 11; oral cavity=7, oropharynx=6 (5 HPV+), larynx/hypopharynx=4. Platinum-refractory= 15; > = 2 prior lines of therapy= 4; PD-L1 > = 1%= 9. RR = 3 partial responses (PR), 10 stable disease (SD), 4 progressive disease (PD). Median follow-up was 4.9 months (m)(0.6-19.3); TTP 9.7m (3.5-not-reached (NR)), PFS 4m (2.3-9.5); OS 7.9m (3.4-NR). Pts with PR had >10 PY, PD-L1 >50% and no local recurrence. Pts with PR+SD had less proliferating ki67+, FoxP3+ T-regulatory cells (Tregs) in blood compared to PD pts (p0.05). Seven pts had FTB for analysis (1 PR, 3 SD, 3 PD): patient with PR (HPV+ oropharynx) had less immunosuppressive Tregs via lower expression of CTLA-4 and CD39 in BL tumor and increased proliferating Tregs at paired OT FTB. Tumor somatic coding mutation burden and percent genome copy alteration in FTB at BL (N = 9) did not predict response (PR+SD) but a trend was observed with percent loss of heterozygosity (p0.15).

Conclusions: This preliminary data suggest peripheral and tumor T-regs might play a critical role in R/M HNSCC pts treated with anti-PD1 agents. Dynamic immune-cell changes were more informative than BL genomic markers.

Clinical trial identification: NCT02644369.

Legal entity responsible for the study: Princess Margaret Cancer Centre.

Funding: Merck

Disclosure: A. Spreafico: Consultant and advisory boards: Merck, Bristol-Myers Squibb, Novartis. L.L. Siu: Advisory board: Merck; Funding to institution (Princess Margaret Cancer Centre) to conduct clinical trials: Merck. A. Hansen: Research support: Genentech/Roche, Merck, GlaxoSmithKline, Bristol-Myers Squibb, Novartis, Boston Biomedical, Boehringer-Ingelheim. All other authors have declared no conflicts of interest.

1089P C1GALT1 predicts poor prognosis and is a potential therapeutic target in head and neck cancer

M-C. Lin[1], P-H. Chien[1], H-Y. Wu[2], S-T. Chen[3], H-F. Juan[4], N-Y. Lin[3], P-J. Lou[1], M-C. Huang[3]

[1]Otolaryngology, National Taiwan University Hospital, Taipei, Taiwan, [2]Instrumentation Center, National Taiwan University, Taipei, Taiwan, [3]Graduate Institute of Anatomy and Cell Biology, National Taiwan University, Taipei, Taiwan, [4]Department of Life Science, Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taipei, Taiwan

Background: Head and neck squamous carcinoma (HNSCC) accounts for more than 600,000 cases annually worldwide. Glycosylation is the most common post-translational modification of proteins, and aberrant glycosylation is a hallmark of cancers. Core 1 β1,3-galactosyltransferase (C1GALT1) controls the crucial step in O-glycosylation and promotes malignant behavior in various cancers. However, its role in HNSCC remains unclear.

Methods: Immunohistochemistry was performed to analyze expression of C1GALT1 in 153 HNSCC tumors. Student t-test, Kaplan-Meier analysis, and Cox-regression analyses were used to analyze correlation of C1GALT1 expression with clinicopathological factors and survivals. CRISPR/Cas9 system was used to knock out C1GALT1. MTT assay, transwell migration, and Matrigel invasion assays were carried out to evaluate HNSCC cell viability, migration, and invasion, respectively. Human phospho-RTK array and Western blot analyses were performed to evaluate signaling pathways. ELISA was used to evaluate EGF-EGFR binding affinity. Mass spectrometry was used to identify O-glycopeptides on EGFR. Molecular docking simulation was used for searching C1GALT1 inhibitors. In vivo effects of C1GALT1 and its inhibitor were evaluated in NOD/SCID mice.

Results: C1GALT1 was overexpressed in HNSCC tumors and predicts poor survivals. C1GALT1 overexpression enhanced whereas C1GALT1 knockdown/knockout suppressed cell viability, migration, and invasion in HNSCC cells. Mechanistically, C1GALT1 modulated O-glycosylation of EGFR and enhanced EGF-EGFR binding affinity, leading to increased EGFR signaling and malignant phenotypes. Using mass spectrometry, we identified five O-glycopeptides on EGFR, among which four are within the ligand binding domain. Itraconazole, a C1GALT1 inhibitor, directly bound to C1GALT1 and changed O-glycans on cell surfaces and EGFR. Targeting C1GALT1 with CRISPR/Cas9, shRNA, or itraconazole was able to significantly suppress tumor growth in NOD/SCID mice.

Conclusions: Our findings indicate C1GALT1 as an attractive therapeutic target for HNSCC.

Legal entity responsible for the study: National Taiwan University Hospital.

Funding: Ministry of Science and Technology National Taiwan University Hospital, Hsinchu branch.

Disclosure: All authors have declared no conflicts of interest.

1090P Frequency of PIK3CA mutations in head and neck squamous cell carcinoma (HNSCC) in southern Thailand

P. Thongwatchara[1], P. Thongsuksai[2], T. Dechaphunkul[3], A. Dechaphunkul[1]

[1]Unit of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand, [2]Department of Pathology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand, [3]Otorhinolaryngology Head and Neck Surgery, Songklanagarind Hospital, Songkhla, Thailand

Background: Phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations have been reported in many cancers including HNSCC. The presence of mutations have shown to associate with prognosis and might predict response to phosphoinositide 3-kinase (PI3K) inhibitors. However, the frequency of mutations is various among primary tumor locations, so this might be relevant to distinguish the possibility of treatments and outcomes among HNSCC. In this study, we examined the frequency of PIK3CA mutations in patients with oral cavity and hypopharyngeal carcinoma.

Methods: Ninety-six fresh biopsies consisted of 73 oral cavity and 23 pyriform sinus carcinoma were collected for DNA extraction. DNA samples were first investigated to ascertain a reference mutational points in PIK3CA exons 4, 9 and 20. We subsequently designed two probes labelled with two different fluorescent dyes for the wild-type and mutated alleles. Mutational analysis was further carried out by using allele-specific real time PCR.

Results: We identified mutations in 10% of patients (10 out of 96 HNSCC specimens). Among 10 mutant specimens, there were 5 missense mutations (2 samples in exon 9 (E545K) and 3 samples in exon 20 (H1047R)), and 5 silence mutation in exon 20 (T1025T). None of mutation was found in exon 4. Exon 9 mutation was detected in 2 out of 96 cases and was merely from hypopharyngeal carcinoma. In exon 20, 8 mutations were found (2 hypopharyngeal carcinoma and 6 oral cavity carcinoma). Overall frequency of mutations in three exons were 8% and 17% in oral cavity and hypopharyngeal carcinoma, respectively.

Table: 1090P Frequency of PIK3CA mutations in HNSCC

Location of HNSCC	% PIK3CA mutation			Overall % PIK3CA mutation
	Exon 4	Exon 9	Exon 20	in three exons
Oral cavity carcinoma	0 (0/61)	0 (0/73)	8 (6/73)	8 (6/73)
Hypopharyngeal carcinoma	0 (0/21)	8 (2/23)	8 (2/23)	17 (4/23)
Frequency of mutation				10 (10/96)

Conclusions: Our study showed more frequency of PIK3CA mutations in hypopharyngeal carcinoma than oral cavity carcinoma. These results suggest that its mutation may be more involved in the carcinogenesis, and hypopharynx should be primary site of interest for further studies.

Legal entity responsible for the study: Unit of Medical Oncology, Faculty of Medicine, Prince of Songkla University.

Funding: Faculty of Medicine, Prince of Songkla University.

Disclosure: All authors have declared no conflicts of interest.

1091P Comparison between the 7th and the proposed 8th editions of the UICC staging system for nasopharyngeal carcinoma patients without cervical lymph node metastasis: A retrospective analysis

C. Hu

Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: To evaluate the prognostic value of the proposed 8th Edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system for nasopharyngeal carcinoma (NPC) patients without cervical lymph node metastasis in comparison with the AJCC/ UICC 7th edition.

Methods: This is a retrospective study of 382 newly diagnosed non-metastatic NPC patients without cervical Lymph node metastasis who were treated with intensity-modulated radiotherapy (IMRT). All received elective neck irradiation to levels II, III, VA. Univariate and multivariate analyses were applied to evaluate the prognostic values between adjacent stage categories of the AJCC/ UICC 7th edition and the proposed 8th edition, including overall survival (OS), local relapse-free survival (LRFS), regional relapse-free survival (RRFS), distant metastasis-free survival (DMFS), and disease–free survival (DFS). The Akaike information criterion (AIC) and Harrell's concordance index (c-index) were applied to compare the two prognostic systems with different numbers of stages.

Results: The median follow-up time was 61.1 months, with a range from 1 months to 91 months. The 5-year OS, LRFS, RFFS, DMFS and DFS were 86.9%, 96.7%, 99.1%, 93.3% and 82.6%, respectively. For LRFS and DMFS, the proposed eighth editions had superior prognostic value to the AJCC/ UICC 7th edition ($P = 0.032$ vs. $P = 0.086$ and $P = 0.013$ vs. $P = 0.112$). The 5-year OS and DFS were found to be significant both by the seventh and the proposed 8th editions. The difference between T1 and T3, T1 and T4, T2 and T3 and T2 and T4 by the proposed eighth edition were found to be significant ($P = 0.042$, $P = 0.041$, $P = 0.000$, and $P = 0.000$), however, there was no significant difference between T1 and T3, T2 and T3 by the seventh edition ($P = 0.204$, and $P = 0.215$). In addition, the difference between T1, T2, T3 with T4 were found to be significant in DFS ($P = 0.000$, $P = 0.000$, $P = 0.037$) and there was no significant difference between T1 and T3 ($P = 0.162$) by the seventh edition and there was significantly different between T2 and T4 ($P = 0.026$) by the proposed 8th editions. Multivariate analysis demonstrated that age, T stage of the proposed 8th editions and chemotherapy were independent prognostic factors for OS, LRFS, DMFS and DFS. The AIC value was smaller for the 8th edition compared to the 7th edition staging system. The C-index value was larger for the 8th edition compared to the 7th edition staging system.

Conclusions: IMRT with elective neck irradiation provides excellent local-regional control for NPC patients without cervical lymph node metastasis. The proposed eighth editions had superior prognostic value to the AJCC/ UICC 7th edition for LRFS and DMFS and lead a better distinction between adjacent T stages of nasopharyngeal carcinoma patients for OS and DFS. Overall, the proposed 8th UICC T classification seems to be superior to the 7th UICC T classification for nasopharyngeal carcinoma patients without cervical lymph node metastasis.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1092P Validation of the clinical AJCC/UICC TNM 8th edition for human papillomvirus related oropharyngeal squamous cell carcinoma

S. Deschuymer[1], R. Dok[2], A. Laenen[3], E. Hauben[4], S. Nuyts[1]

[1]Department of Radiation Oncology, University Hospitals Leuven, Leuven, Belgium, [2]Laboratory of Experimental Radiotherapy - Department of Oncology, University of Leuven, Leuven, Belgium, [3]Leuven Biostatistics and Statistical Bioinformatics Centre (L-Biostat), KU Leuven University, Leuven, Belgium, [4]Department of Imaging and Pathology, University Hospitals Leuven, Leuven, Belgium

Background: With the growing interest in treatment de-intensification trials for human papillomavirus positive (HPV+) oropharyngeal squamous cell carcinoma (OPC), accurate patient stratification has become essential for patient selection. The aim of this study was to validate the prognostic ability of the AJCC/UICC TNM 8th edition (8th Ed) for HPV+ OPC.

Methods: Patients with HPV+ OPC treated with curative (chemo)radiotherapy ((C)RT) between 2004 and 2017 were classified according to the TNM 7th edition (7th Ed) and the new clinical TNM 8th Ed. HPV status was determined by p16 immunohistochemistry staining. The 5-year overall survival (5YOS) was estimated using the Kaplan-Meier method and groups were compared using the log-rank test. Harrell's C-index was used as measure of model performance.

Results: A total of 333 OPC were identified of whom 100 were HPV+. The median follow-up was 63.7 months (IQR 30.0;99.9). The 5Y-OS with the 7th Ed were stage I/II 88.9% (CI95% 43.3;98.4), stage III 70.0% (CI95% 22.5;91.8), stage IVa 71.4% (CI95% 57.3;81.6) and stage IVb 29.8% (1.4;71.1) ($p = 0.38$). With the TNM 8th Ed, the 5Y-OS of stage I, II and III were 91.6% (CI95% 76.1;97.2), 55.2% (CI95% 29.2;75.1) and 38.0% (CI95% 8.7;68.2) ($p = 0.006$). On Cox regression analysis, when compared to stage I, OS was significantly lower for stage II ($p = 0.018$, Hazard ratio (HR)= 4.24 (CI95% 1.27;14.13)) and for stage III ($p = 0.004$, HR = 5.40 (CI95% 1.69;17.26)). Nevertheless, there was no significant difference between stage II and III ($p = 0.60$, HR = 1.27 (CI95% 0.51;3.17)). The Harrell's C-index for TNM 8th Ed stage was 0.67.

Conclusions: Although the TNM 8th Ed provides better OS stratification than the 7th Ed for HPV+ OPC following (C)RT, better prognostic models are needed due to the lack of differentiation between stage II and stage III. This study emphasizes the importance of further research in patient selection and personalized treatment for HPV+ OPC.

Legal entity responsible for the study: The ethics committee of the University Hospitals of Leuven.

Funding: Grant from Stand up to Cancer (Kom op tegen kanker), the Flemish cancer society.

Disclosure: S. Deschuymer: Grant: Stand up to Cancer (Kom op tegen kanker), the Flemish cancer society. All other authors have declared no conflicts of interest.

1093P Development of overall survival (OS) and progression free survival (PFS) nomograms for Australian patients with locoregionally advanced oropharyngeal squamous cell carcinoma (LA OPSCC)

K. Xu[1], A. Lo[2], V. Chin[1], C. Gzell[3], C. O'Connor[3], D. Forstner[3], R. Gallagher[1], R. Bova[1], J. Crawford[1], R. Harvey[1], A. Lochhead[4], P. Earls[4], M.R. Qiu[4], E. Hsu[5], G. Bigg-Wither[5], L. Chan[6], H. Bao[6], P. Foltyn[7], H-W. Sim[1], A. Prawira[1]

[1]Medical Oncology, The Kinghorn Cancer Centre, Darlinghurst, Australia, [2]School of Medicine, The University of New South Wales, Sydney, Australia, [3]Radiation Oncology, Genesis Cancer Care, Darlinghurst, Australia, [4]Anatomical Pathology, St Vincent's Pathology, Darlinghurst, Australia, [5]Medical Imaging, St Vincent's Hospital, Darlinghurst, Australia, [6]Nuclear Medicine, St Vincent's Hospital, Darlinghurst, Australia, [7]Oral Health and Dentistry, St Vincent's Hospital, Darlinghurst, Australia

Background: The majority of patients with squamous cell carcinoma of the head and neck present with locally advanced disease. Despite treatment with curative intent, approximately 40% of patients eventually relapse. It is currently difficult to predict those who will relapse at treatment outset. Nomograms can improve prognostic discussions for individual patients and potentially guide future research to individualise treatment. We aim to develop OS and PFS nomograms using retrospective data from patients with LA OPSCC treated in our institution.

Methods: We performed a retrospective analysis of baseline characteristics and outcomes of LA OPSCC patients who underwent curative-intent treatment in our institution from January 2008 to December 2017. Nomograms were constructed to estimate OS and PFS incorporating age, gender, performance status, smoking history, stage, grade, and p16 status. Multivariable Cox models were selected by backward elimination using the Akaike information criterion, and validated internally using bootstrap with 1000 resamples. Nomogram points were assigned proportional to variable effect size.

Results: A total of 417 patients have been identified so far. An initial cohort of 74 patients with complete clinical annotations were analysed. Median follow-up was 24 months, with 9 deaths and 25 events during follow-up. ECOG 0, N stage 0-1, histological grade 1-2 and p16 positive status were favourable predictors in the OS nomogram. Age ≤ 50, male gender, smoking history ≤ 10 pack-years and p16 positive status were favourable predictors in the PFS nomogram. The concordance index for OS was 0.86 (95% CI 0.76 to 0.99) and for PFS was 0.72 (95% CI 0.65 to 0.83). Bias-corrected indices were 0.82 and 0.69, respectively.

Conclusions: We present the first OS and PFS nomograms for Australian patients with LA OPSCC. The nomograms demonstrated clinically useful prediction of OS and PFS in patients with LA OPSCC, relying on four routinely collected variables, with superior concordance to previously reported models. Expansion of the retrospective cohort is ongoing and validation in an external patient cohort is planned.

Legal entity responsible for the study: St Vincent's Hospital, Sydney.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1094P Clinical prognostic factors in patients (pts) with recurrent and/or metastatic (RM) head and neck carcinoma (HNC) treated with cetuximab plus chemotherapy

P. Bossi[1], R. Depenni[2], M. cossu rocca[3], D. Ferrari[4], G. Azzarello[5], M. Alù[6], F. Nolè[3], C. Codecà[4], G. Boscolo[5], M. Piccininni[7], S. Cavalieri[1], G. Pugliese[8], L.F. Licitra[1]

[1]Head and Neck Medical Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Department of Oncology/Hematology, Modena Cancer Center, Modena, Italy, [3]Medical Oncology, Istituto Europeo di Oncologia, Milan, Italy, [4]Oncology, Azienda Ospedaliera San Paolo, Milan, Italy, [5]Oncology Unit, Department of Internal Medical Sciences, Unità Locale Socio Sanitaria 13, Mirano, Italy, [6]Medical Oncology, Arnas Civico, Palermo, Italy, [7]Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Bari, Italy, [8]Oncologia, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy

Background: There is limited information about prognostic factors in RM HNC pts receiving first-line platinum-based chemotherapy and cetuximab. Moreover, we lack survival data in a real-world population, without the selection bias affecting pts enrolled in clinical trials.

Methods: We evaluated all consecutive pts treated from 1/2007 to 12/2016 in 6 Italian Centres. The following baseline prognostic factors were investigated: sex, age, site of disease, tumor grading, HPV status for oropharyngeal cancer, performance status (PS), weight loss in the previous 3 months (less/more than 5%), comorbidities (according to ACE-27), residual tumor at primary site, previous chemotherapy or cetuximab in curative setting, previous radiotherapy, platinum type (cisplatin/carboplatin, CBDCA), chemotherapy schedule (weekly/3-weekly), platinum and cetuximab doublet or with a third drug (i.e. 5FU or paclitaxel).

For each potential predictor variable, Kaplan-Meier curves for OS and PFS were estimated, and a Log-rank test was used to compare survivorship in different levels of the variable. A Cox proportional hazard model was run including only predictors characterized by a significant ($p < 0.05$) Log-rank test.

Results: We analyzed 340 pts, with a median PFS/OS of 5.0/10.6 months. The 1-year and 3-year OS rate for all pts was 44.2% (CI: 39.1-50.0) and 7.8% (CI: 5.1-12.0). Only one out of two pts received a second-line therapy. In univariate analysis lower OS was associated with PS > 0 ($p < 0.001$), residual tumor at primary site ($p < 0.001$) and CBDCA use ($p = 0.012$) while lower PFS was associated with paranasal sinus site ($p = 0.008$), PS > 0 ($p = 0.001$), CBDCA use ($p = 0.035$) and residual tumor at primary site ($p < 0.001$). All these predictors except for platinum type remained significant at multivariate analysis. Pts with clinical response to treatment carried a more favorable prognosis, while progressive disease as best response had a dismal median OS of 5.8 months.

Conclusions: In non-selected RM HNC pts, we obtained a median PFS and OS of 5.0 and 10.6 months, very similar to 5.6 and 10.1 months reported in Extreme trial (Vermorken et al. 2008). At baseline, PS and residual tumor at primary site could be used to define pt prognosis.

Legal entity responsible for the study: Paolo Bossi.

Funding: Has not received any funding.

Disclosure: P. Bossi, D. Ferrari, R. Depenni, G. Azzarello: Advisory board: Merck Serono. L.F. Licitra: Advisory board and research support: Merck Serono. All other authors have declared no conflicts of interest.

1095P Prognostic value of MRI-derived residual retropharyngeal lymph node after intensity-modulated radiotherapy in nasopharyngeal carcinoma and a nomogram for the prediction of it

W-Z. Li[1], H. Liang[1], X. Lv[1], L-R. Ke[2], Y-F. Ye[3], Y-H. Yu[1], W-Z. Qiu[1], G-Y. Liu[1], X-J. Huang[1], K-Y. Liu[1], S-H. Lv[1], X. Guo[1], Y-Q. Xiang[1], W-X. Xia[1]

[1]Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China, [2]Department of Radiology, Sun Yat-sen University Cancer Center, Guangzhou, China, [3]Clinical Trial Design Division, Sun Yat-sen Memorial Hospital, Guangzhou, China

Background: In nasopharyngeal carcinoma (NPC) patients with retropharyngeal lymph node (RLN) metastasis who receive intensity-modulated radiotherapy (IMRT), the incidence of magnetic resonance imaging (MRI)-derived residual retropharyngeal lymph node (RRLN) is not rare and its prognostic value is uncertain. In present study, we aim to investigate the prognostic value of MRI-derived RRLN and sought to develop a nomogram for the prediction of it.

Methods: A total of 922 patients with RLN metastasis without distant metastasis NPC treated with IMRT were enrolled in present study. The Kaplan-Meir survival curves and cox proportional regression model were used to assess the prognostic value of RRLN. The patients were then randomly assigned into the training cohort (n = 645) and the validation cohort (n = 277). Factors significantly associated with RRLN were identified and used to construct nomogram with multivariate logistic regression model. The discrimination and performance of nomogram were evaluated in training cohort and confirmed in validation cohort.

Results: The incidence of RRLN was 28.2%. The 5-year OS, DFS, DMFS, LRRFS of the RRLN group and non-RRLN group were 84.1% vs. 93.2%, 65.1% vs. 87.3%, 71.2% vs. 94.2% and 87.8% vs. 95.6%, respectively (for all rates, $P < 0.05$). Necrosis, extra-nodal neoplastic spread (ENS), minimum axial dimeter (MAD) and the percentage volume of the GTVnx receiving 95% of the prescribed dose (GTVnx V95%) were identified as independent factors associated with RRLN and used to construct the nomogram. The nomogram showed favorable calibration and discrimination in training cohort (AUC, 0.746) and validation cohorts (AUC, 0.738). Patients with high-risk scores had a higher probability of developing RRLN than patients with low-risk scores in training cohort (OR, 5.183, 95% CI 2.845-8.525) and validation cohort (OR, 6.977, 95% CI 3.990-12.200).

Conclusions: MRI-derived RRLN was a negative independent prognostic factor for OS, PFS, DMFS and LRRFS in NPC patients with RLN metastasis who received IMRT. We constructed a nomogram based on clinical and radiological characteristics that predicted an individual's risk of RRLN.

Legal entity responsible for the study: Sun Yat-sen University Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1096P Proteomic comparison based on 18FDG-PET/CT defined metabolic tumor volume in non-metastatic nasopharyngeal carcinoma

C. Chen[1], L. Li[2], Z. Fei[1], J. Wang[2], T. Chen[2]

[1]Radiation Oncology, Fujian Cancer Hospital, Fuzhou, China, [2]Radiation Oncology, Fujian Cancer Hospital, Fujian Medical University, Fuzhou, China

Background: Various PET/CT based metabolic tumor volume (MTV) was found to influence the prognosis of non-metastatic nasopharyngeal carcinoma. The proteomic analysis of primary tumor was compared for ^{18}FDG-PET/CT based MTV in non-metastatic nasopharyngeal carcinoma. We tried to find the potential biomarker related to MTV.

Methods: We respectively analyzed 110 patients with PET/CT confirmed non-metastatic nasopharyngeal carcinoma at our institution. MTV of primary tumors was defined with $SUV_{2.5}$.The ROC curve was portrayed with treatment failure events of patients.With the optimal cut-off point of MTV,another 25 nasopharyngeal carcinoma patients were divided into two groups to compare the primary tumor proteomics.Proteomic analysis was conducted with the combination of iTRAQ and nano-RPLC-MS/MS.We analyzed the previous tumor specimens(97/110) to verify the potential biomarker found by proteomics.

Results: The area under the ROC curve (AUC) was 0.726. And the best cut-off point for MTV was 9.88 ml (≈10 ml). MTV ≤10 ml appeared a favorable disease-free survival (DFS, 93.5% vs 81.3%, P = 0.035). A total of 7913 proteins were identified with proteomics, of which 360 had significant differences. In MTV>10ml group, the expression of 244 proteins was up-regulated and the other 116 was down-regulated. According to GO analysis and clustering, these proteins were mainly localized in organelles (34%), cytoplasm (20%), extracellular matrix (13%), and plasma membrane (10%). They were involved in many biological processes and molecules features. KEGG suggested that these differential proteins participated in metabolism, migration and inflammation-related pathways. The PPI interaction network showed that the core proteins were mainly implicated in protein phosphorylation, signal transduction and cell adhesion. Higher TRIM29 protein expression was found in the MTV>10ml group by immunohistochemistry (x^2=19.041, $P < 0.001$).

Conclusions: With proteomic comparison based on MTV, the differential proteins were closely related to tumor cell growth, migration, metabolism and immunity. Also, patients with MTV ≤10 ml had a favorable DFS. Lower expression of TRIM29 found in this group might be considered as a promising prognostic biomarker.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1097P Prognostic value of metabolic tumor volume in recurrent and/or metastatic head and neck squamous cell carcinoma treated with platinum-based chemotherapy

M. Suzuki[1], N. Takemoto[1], T. Fukuzumi[1], M. Yamamoto[1], S. Otozai[2], T. Yoshii[2], T. Fujii[2], H. Inohara[1]

[1]Otorhinolaryngology/Head and Neck Surgery, Osaka University Graduate School of Medicine, Osaka, Japan, [2]Head and Neck Surgery, Osaka International Cancer Institute, Osaka, Japan

Background: The standard first-line treatment for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is platinum-based chemotherapy, while the predictor of survival has yet to be established, except for tumor human papillomavirus (HPV) status. The present study aimed to evaluate the usefulness of metabolic tumor volume (MTV) measured on FDG-PET/CT in predicting survival of patients with R/M HNSCC after platinum-based chemotherapy.

Methods: Patients with R/M HNSCC treated with platinum-based chemotherapy as first-line treatment following FDG-PET/CT between 2006 and 2017 at Osaka University Medical School Hospital and Osaka International Cancer Institute were eligible. Exclusion criteria were nasopharyngeal carcinoma, >60 days duration between FDG-PET/CT and chemotherapy initiation. FDG-PET/CT data were transferred into the workstation in the DICOM format. A total amount of MTV in the whole body was measured using a SUV-based automated contouring program (PETSTAT Viewer Ver. 2.2), with the SUV threshold being 2.5. Tumor HPV status was determined by p16 immunohistochemistry. The risk of death was assessed by Cox proportional hazard model.

Results: One hundred and four patients met the criteria. The median follow-up duration of surviving patients was 13.1 months (range, 3.2-79.6). The median MTV was 21.9ml (range, 0.0-1118.7). The risk of death increased by 1.03 fold (95% confidence interval, 1.02-1.04; $P < 0.0001$) for every 10-ml increment of MTV, independently of tumor HPV status. The median overall survival was 15.3 months in patients with MTV larger than the median and 9.2 months in patients with MTV equal to or smaller than the median.

Conclusions: MTV is a useful predictor of survival in patients with R/M HNSCC after platinum-based chemotherapy. MTV needs to be considered in allocation for randomized clinical trials.

Legal entity responsible for the study: M. Suzuki.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1098P The prognostic value of early tumor response in metastatic nasopharyngeal carcinoma patients treated with first-line chemotherapy

W-X. Xia, L. Guoying, X. Lv, S-H. Lv, X-J. Huang, W-Z. Qiu, H. Liang, W-Z. Li, K-Y. Liu, Y-H. Yu, Y-Q. Xiang, X. Guo
Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: The prognostic value of the early tumor response to first-line chemotherapy remains unknown in metastatic nasopharyngeal carcinoma (mNPC). The aim of this study was to explore the association between early tumor response (response at 6 weeks) and survival outcomes and to assess the relationship between best (response at 18 weeks) and early tumor response.

Methods: A total of 433 mNPC patients with measurable lesions, who received first line chemotherapy between 2005 and 2016 were enrolled in this study. Response was assessed at completion of 6 weeks and 18 weeks of chemotherapy using RECIST 1.1. To estimate in an unbiased way, the landmark method was used in this study. Log-rank test and Cox regression were used to analyze survival data. The correlation between early tumor response and best tumor response was measured by Kappa agreement, Pearson correlation and receiver operating curves.

Results: The median follow-up time was 54.3 months (IQR: 38.6-79 months). Two hundred and sixty-five patients achieved tumor response at 6 weeks. From the 6-week landmark, patients with tumor response were significantly associated with better OS (hazard ratio, HR = 0.566, $P < 0.001$, median OS: 30.3 versus 21.7 months) and PFS (HR = 0.426, $P < 0.001$, median PFS: 9.2 versus 7.3 months) than the patients without. After adjusting for potential confounders, the early tumor response was an independent prognostic factor associated with OS (HR = 0.539, 95% CI, 0.428 to 0.679, $P < 0.001$) and PFS (HR = 0.467, 95% CI, 0.378 to 0.576, $P < 0.001$), respectively. There was a good correlation between the early and best tumor response (Kappa: 0.82; Pearson: 0.83). The sensitivity, specificity, positive and negative predictive values of early tumor response in predicting best response were 100%, 79%, 88% and 100%.

Conclusions: Early tumor response is an independent prognostic factor in determining survival. The early and best tumor response correlated very well. The data could provide a basis for trial design that addresses alteration of first line chemotherapy intensity. Validation studies are awaited.

Legal entity responsible for the study: Sun Yat-sen University Cancer Center.
Funding: National Natural Science Foundation of China.
Disclosure: All authors have declared no conflicts of interest.

1099P Potential clinical management changes in patients harboring locally advanced squamous-cell carcinoma of head and neck by incorporating pre and post chemoradiotherapy 18.FDG PET/CT: A prospective trial

U.R. Nicolau[1], A.C.M.D. Queiroz[1], T. Felismino[1], E.P.N. Lima[2], V.H.F. Jesus[1], L. Cezana[1], M.S. Alves[1], A.C.A. Pellizzon[1], P.N. Pinto[3], G.M. Porto[3], G.B. Carvalho[4], C.A.L. Pinto[5], V.S.E. Silva[1], A.P. Guimarães[1], T.B. Oliveira[1], M.K. Ikeda[4], T.F. Paiva Jr[1], P.C. Bes[1], L.P. Kowalski[4]
[1]Medical Oncology, A.C. Camargo Cancer Center, São Paulo, Brazil, [2]Nuclear Medicine, A.C. Camargo Cancer Center, São Paulo, Brazil, [3]Medical Radiology, A.C. Camargo Cancer Center, São Paulo, Brazil, [4]Head and Neck Surgery, A.C. Camargo Cancer Center, São Paulo, Brazil, [5]Pathology, A.C. Camargo Cancer Center, São Paulo, Brazil

Background: The utility of performing 18.FDG PET/CT in the tumor staging and as a clinical management tool in the post-12Th-week chemoradiotherapy (CRT) in patients (pts) harboring locally advanced squamous-cell carcinoima of head and neck (LASCCHN) has been established. The aim of this report is to evaluate the impact of incorporating a staging 18.FDG-PET/CT and post CRT, for pts harboring 7Thedition AJCC staged III-IVA/B treated in a single medical centre.

Methods: Patients harboring LASCCHN who underwent induction chemotherapy (IC) with triplet taxane-containing regimen followed by concurrent CRT were prospectively evaluated as part of the A.C. Camargo Cancer Center PET/CT trial. Our pts underwent three 18.FDG-PET/CT. First as a baseline, second after cycle-1 IC and third at 10 to 12 weeks after completion of CRT. Our primary objective was early 18.FDG-PET/CT tumor response assessment after cycle-1 IC, which has been reported elsewhere. Herein we report changes in clinical staging, radiotherapy and surgical management generated by baseline and post-therapy PET-CTs. All pts provided signed consent for trial participation.

Results: Between February 2010 and July 2013, 49 pts (41 oropharynx, 4 hypopharynx and 4 larynx) were recruited. Upstaging in neck lymph nodes were registered in 6 cases (12.2%): N0 to N1 in 2, N1 to N2b in 1, N1 to N2c in 1, N2a to N2c in 1, N2b to N2c in one. One patient harboring unilateral N3 had demonstrated bilateral lymph node disease. Downstaging N1 to N0 was registered in 2 pts. Suspected distant metastatic disease was registered in 2 cases (lung 1, bone 1). Primary occult tumor was identified in 3, and secondary synchronic colorectal tumor was diagnosed in one case. Radiotherapy planning changes were generated by detection of new regional metastatic lymph nodes or identification of primary tumor in 10 patients (20.4%). Post-radiotherapy 18.FDG PET/CT was able to detect residual lymph node disease and residual primary disease in 3 and 1 pts respectively.

Conclusions: These findings confirm the clinical utility of performing pre and post CRT 18.FDG PET/CT in pts harboring LASCCHN.

Clinical trial identification: Brazilian Clinical Trial Registry - ReBEC - RBR-9wwstd.

Legal entity responsible for the study: A.C. Camargo Cancer Center.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1100P Patterns of local failures and suggestions for reduction of clinical target volume for nasopharyngeal carcinoma patients without cervical lymph node metastasis

C. Hu, Y. Li
Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: To investigate the initial irradiated dose of the recurrent site and local failures patterns after Intensity-modulated radiation therapy (IMRT) for nasopharyngeal carcinoma (NPC) patients with retropharyngeal lymph nodes (RLNs) metastasis only, with the aim to demonstrate the adequacy and overall quality of the target volume definitions for further improvement of outcome and therapeutic ratio.

Methods: 382 newly diagnosed non-metastatic NPC patients were retrospectively enrolled, receiving elective neck irradiation to to levels II, III, VA. For patients with local failure, the location and extent of local failures were transferred to the pretreatment planning CT for dosimetric analysis. The dose of radiation received by GTVr (gross tumor volume of recurrence) was calculated and analyzed with dose-volume histogram (DVH). Failures were classified as: "in field" if 95% of GTVr was within the 95% isodose, "marginal" if 20% to 95% of GTVr was within the 95% isodose, or "outside" if less than 20% of GTVr was inside the 95% isodose.

Results: With a median follow-up time of 61.3 months, 12 patients have developed local recurrence (10 cases available). The 5-year OS, LRFS, RRFS, DMFS and DFS were 87.8%, 95.2%, 99.1%, 93.3% and 82.5%, respectively. Dose conformity with IMRT was excellent and the recurrence was mainly within 3 years after the first treatment. The dosimetric analysis showed that 7 failures were classified as "in-field", 2 failures as "marginal" and only 1 failures as "out-field". Most local relapse site located just the same site of primary tumor and most anatomic sites were at low risk of concurrent bilateral tumor invasion.

Conclusions: IMRT with elective neck irradiation provides excellent local control for NPC patients without cervical lymph node metastasis. In-field failures are the main patterns for local recurrence and the radioresistant subvolumes within the GTV are needed to be identified. We proposed suggestions for reduction of target volume during IMRT treatment for NPC patients.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1101P Target delineation and dose prescription for adaptive replanned intensity-modulated radiotherapy in nasopharyngeal carcinoma

X.D. Huan
Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: To investigate the feasibility and benefits of target re-delineation and dose prescription for adaptive replanned radiotherapy in nasopharyngeal carcinoma (NPC) patients who underwent intensity-modulated radiotherapy (IMRT).

Methods: Fifty-four consecutive NPC patients who underwent IMRT were enrolled in this study. The replanning CT (CT-II) for each patient was generated at the 22nd fraction of the IMRT. In Plan-I, GTVnx-I was defined as all detected gross disease. The high-risk clinical target volume (CTV1-I), as subclinical disease consisting of a 1-cm margin surrounding the GTVnx-I. The low-risk clinical target volume (CTV2), as a 0.5- to 1.0-cm margin surrounding the CTV1-I. In Plan-II, the GTVnx-II, as all detected gross disease detected after 22 fractions. CTV1-II maintained the extent of the originally irradiated CTV1-I, including the area in which the tumor disappeared/dissolved after 22 fractions. The CTV2 was not delineated. The doses prescribed were as follows: Plan-I: PGTVnx/rpn/nd 53-54 Gy/25 F; PCTV1/nd 47.5-48 Gy/25 F; PCTV2 45 Gy/25 F; and Plan-II: PGTVnx/rpn/nd: 15-15.5 Gy/7 F; PCTV1/nd 13.5 Gy/7 F. The parameters were compared. Clinical outcomes and toxicities were evaluated.

Results: The median reductions in the GTVnx, GTVnd-R, bilateral parotids and bilateral submandibular glands were 25.07%, 38.17%, 23.43% (left), 21.12% (right), 23.37% (left) and 23.00% (right) ($P < 0.05$), respectively; bilateral RPLN and GTVnd-L

exhibited median reductions of 22.50% (left), 25.00% (right), and 32.80% ($P > 0.05$), respectively. The average V95% of PGTVnx reached nearly 100% in the two plans. Plan-II significantly reduced the Dmean% in the optic chiasma, thyroid gland, hypopharynx, spinal cord, brain stem, pituitary, oropharynx and oral cavity compared with Plan-A ($P < 0.05$). Recurrence did not occur in the regression area, and the acute reactions were mild. The 3-year OS/LRFFS/DMFS rates were 93.3%/90.5%/91.4%, respectively.

Conclusions: Adaptive replanned IMRT in NPC provided a new perspective for target re-delineation and dose prescription. The results of this study showed significant dosimetric and clinical benefits without recurrence and reducing survival.

Legal entity responsible for the study: Sun Yat-sen University Cancer Center.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1102P Significance of pre-treatment F-18 FDG PET/CT parameters in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy

Y. Huang[1], C. Chen[2], Y. Li[1], X. Qiu[1], T. Chen[1]

[1]Radiation Oncology, Fujian Cancer Hospital, Fujian Medical Univercity, Fuzhou, China, [2]Radiation Oncology, Fujian Cancer Hospital, Fuzhou, China

Background: The aim of this study was to assess the prognostic significance of parameters derived from pretreatmentF-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) for patients with nasopharyngeal carcinoma (NPC) received intensity-modulated radiation therapy (IMRT). Furthermore, the functional information provided by PET/CT may offer the feasibility of biological conformality in tumor target delineation and dose planning.

Methods: We retrospectively reviewed 82 NPC patients who underwent pretreatment F-18 FDG PET/CT and received IMRT between 2010 and 2013. Maximum standardized uptake value (SUV_{max}) and metabolic tumor volume (MTV) of the primary tumor were measured by F-18 FDG PET/CT. MTV might be viewed as a collection of absolute SUV values equal to or greater than a certain threshold on each axial image of PET/CT. The ROC curve was used to determine the appropriate cut-off point of SUV_{max} and MTV. The prognostic significance of MTV, SUV_{max} was assessed in the study. Meanwhile, the paper studies the relation between SUV_{max}, MTV, and primary tumor volume (PTV). Receiver operating characteristic (ROC) analysis was used to determine the optimal MTV cut-off value.

Results: Positive correlations between PTV and MTV, SUV_{max} and MTV were found. PTV, SUV_{max}, and MTV were significant predictors of survival. The 3-year progression-free survival (PFS) for $SUV_{max} \leq 8.20$ and $SUV_{max} > 8.20$ were 91.1% and 73.0% ($p = 0.027$). With furthermore analysis, patients having tumor with lower MTV had higher 3-year PFS than patients having tumor with higher MTV. The percentage of the $MTV_{5.0}$ in PTV was 14.66±15.75% (95%CI,11.20-18.13).

Conclusions: Our study indicated that PET/CT-derived parameters, SUV_{max} and MTV, are very important in assessing prognosis and making radiotherapy planning. Patients having tumor with lower MTV had higher 3-year PFS than patients having tumor with higher MTV. It is necessary to give a more aggressive treatment for patients with higher MTV. The $MTV_{5.0}$ might be an appropriate quantitative definition of hypoxic sub-volumes for radiotherapy boost to improve the therapeutic effect.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1103P Sentinel lymph node biopsy for clinically N0 oral squamous cell carcinoma

H. Goda, K-I. Nakashiro

Oral and Maxillofacial Surgery, Ehime University Graduate School of Medicine, Ehime, Japan

Background: Despite advances in early detection, diagnosis, and treatment of oral squamous cell carcinoma (OSCC), the survival for patients with early stage OSCC remains at 80% for the past 30 years. Nodal status is still the most significant prognostic factor of OSCC. Therefore, early detection of the cervical lymph nodes metastasis is expected to further improve survival. Sentinel lymph node biopsy (SLNB) is a widely accepted procedure in various human malignancies. In clinically N0 (cN0) OSCC cases, SLNB has received considerable attention for its role in deciding whether to perform neck dissection. In this study, we assessed the efficiency of SLNB for cN0 OSCC in a single-institution experience.

Methods: A total of 135 patients with cN0 OSCC underwent SLNB between 2001 and 2016, of which 128 were clinically T1 and T2. The primary site was tongue, gingiva, oral floor, buccal mucosa, and lip in 49%, 36%, 7%, 6%, and 1%, respectively. The location of sentinel lymph node (SLN) was determined by radioisotope (RI) method with preoperative lymphoscintigraphy and intraoperative use of a handheld gamma probe and/or dye method and evaluated by histopathological examination and genetic analysis.

Results: SLNB was performed with RI method (90%) or dye method (10%). SLNs were successfully identified with RI method (100%) and dye method (70%). The average number of SLN/case was 1.9 with RI method and 2.3 with dye method. The rate of SLN identified side was 85% in ipsilateral, 9% in bilateral, and 6% in contralateral. Twenty two of 135 patients (16%) had metastasis-positive SLN. Thirteen patients with negative SLN developed the latent neck lymph node metastasis. The sensitivity, specificity, and accuracy was 62.9% (22/35), 100% (100/100), and 90.4% (122/135), respectively. Three-year overall survival rate for SLNB-negative patients was 95.6% (108/113).

Conclusions: SLNB is a minimally invasive and highly reliable method staging the cN0 for patients with OSCC. Patients with negative SLNB showed more excellent neck control rate and the SLNB provides more accurate staging than elective neck dissection or wait and see.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1104P An insight on head and neck cancer management in China

Y. Xiaoshi[1], D. Weiyi[2]

[1]Department of Epidemiology, China Medical University, Shenyang, China, [2]Head and Neck Cancer Center, Stomatology Hospital of China Medical University, Shenyang, China

Background: As no Chinese data has evaluated the oncologists' strategy for treatment and management of the head and neck cancer (HNC), this survey investigated Chinese oncologists' treatment strategy in HNC.

Methods: This survey was conducted during October 2017 to January 2018 in 100 randomly selected tertiary Chinese hospitals from 21 cities. The plan was to include 300 non-randomly selected Chinese oncologists to know their responses on HNC. The investigating stages included: development of a questionnaire after consulting 9 experts in HNC; execution of a pre-test by 40 oncologists from 5 cities; reliability and validity evaluation followed by finalisation of the questionnaire; and conduct of formal investigation with oncologists. Results for all evaluations were presented as percentages.

Results: Of the 296 questionnaires received, 272 were considered valid. Among valid respondents, 65.1% oncologists reported nasopharyngeal carcinoma as the most common HNC, followed by laryngeal/hypopharyngeal (22.1%) carcinoma. 71.3% oncologists acknowledged having a multidisciplinary team for HNC treatment in their hospitals. Prescribed regimens for recurrent/metastatic HNC included taxane + platinum (TP), taxane-cisplatin-5fluorouracil (TFP), PF, TF and others (45.2%, 27.9%, 21%, 2.2% and 3.7%). Oncologists (77.6%) add target therapy to chemotherapy as the first line therapy in recurrent/metastatic cancer. For locally advanced HNC, anti-EGFR would be preferred by 84.2% oncologists. 39.0% oncologists reported considering inclusion of targeted therapy at combined radical radiotherapy and chemotherapy stage. HPV was believed to be associated with HNC prognosis by 72.0% oncologists; 1.9% oncologists disagreed and 26.1% were unsure. HPV testing rate was 67.3%. The reasons for not testing HPV were immature technical conditions (41.2%), no impact on treatment (40.8%), no consent by patients (25.0%) and low HPV incidence in Chinese HNC patients (18.01%).

Conclusions: In conclusion, oncologists in China have not fully followed international guidelines of HNC which might be due to practical considerations. These findings will provide future education for HNC management.

Legal entity responsible for the study: China Medical University

Funding: Merck Serono Co. Ltd, Beijing, China.

Disclosure: All authors have declared no conflicts of interest.

1105P Real-world outcomes and costs in patients with recurrent or metastatic squamous cell carcinoma of the head and neck

A. Lafuma[1], F-E. Cotté[2], C. Le Tourneau[3], C. Emery[1], A-F. Gaudin[2], E. Torreton[1], J. Gourmelen[4], J. Bonastre[5]

[1]Health Economy, Cemka-Eval, Bourg-la-Reine, France, [2]Health Economics and Outcome Research, Bristol-Myers Squibb, Rueil-Malmaison, France, [3]Medical Oncology, Institut Curie, Paris, France, [4]UMS 011, UVSQ, INSERM, Villejuif, France, [5]CESP, Gustave Roussy, Villejuif, France

Background: Overall survival (OS) of patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) is extremely poor. New therapeutic options emerge but need to establish their economic value. The objective was to describe OS and costs in French R/M SCCHN patients.

Methods: The EGB, a random representative sample (1/97th) of the French national healthcare system claims database was used. All adult patients with a diagnosis of SCCHN with a first R/M between Jan 2009 and Dec 2014 were selected. Data were analyzed from the index date (first chemotherapy) until patients' death or Dec 2015 (minimum follow-up of 12 months). Two periods were distinguished: 'chemotherapy treatment' (CT) and 'end-of-life' (EoL) (from last CT to death). OS was estimated using the Kaplan-Meier method. Costs included all hospitalizations for SCCHN, consultations, medical devices, biology and imaging procedures, supportive and palliative

care, transportation, patients' out of pocket expenses and indirect cost (daily allowances for sick leaves and disability pensions).

Results: Among 267 patients identified, 85% were men, 44% had metastases at the index date and mean age was 62.0 years (±9.9). Most common tumor locations were oropharynx (29%), oral cavity (12%), larynx (10%) and hypopharynx (10%) but 39% of the patient had multiple locations. Median OS was 9.3 months in overall population with no significant difference between recurrent or metastatic patients (10.5 vs. 8.3 months, p = 0.092). The median OS ranged from 8.3 months for tumors located in the oro/hypopharynx to 10.9 months for those in the oral cavity. The average cost per patient was €48,069 breakdown into €31,136 [95CI: 27,935–34,336] for hospitalizations and €16,933 [14,866–19,000] for outpatient care. During CT period (209 days on average), main cost drivers were CT acquisition and administration (€13,755), home care (€2454), transportation (€1954) and physician fees (€1214). During EoL period (125 days), palliative care (€3548), home care (€977), nursing care (€711) and physician fees (€618) were the main cost drivers.

Conclusions: This analysis of real-world data confirms the poor prognosis in patients with R/M SCCHN and provides cost data for future economic evaluations.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: A. Lafuma, C. Le Tourneau, C. Emery, E. Torreton, J. Bonastre: Consultancy: BMS. F-E. Cotté, A-F. Gaudin: Employee: BMS. All other authors have declared no conflicts of interest.

1106P Treatment patterns in elderly patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC): Results from an EORTC led survey

S. Oosting[1], I. Desideri[2], D. Staelens[3], C. Caballero[3], S. Tribius[4], C. Simon[5], S. Singer[6], V. Gregoire[7], C. Fortpied[3], A. Luciani[8]

[1]Medical Oncology, University Hospital Groningen (UMCG), Groningen, Netherlands, [2]Radiation Oncology, Università di Firenze, Dipartimento di Patologia e Oncologia Sperimentali, Florence, Italy, [3]EORTC - European Organisation for Research and Treatment of Cancer, Brussels, Belgium, [4]Radiation Oncology, Asklepios Klinik St. Georg, Hamburg, Germany, [5]Otolaryngology/Head and Neck Surgery, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, [6]Institute of Medical Biostatistics, Division of Epidemiology and Health Services Research, University Medical Center Mainz, Mainz, Germany, [7]Radiation Oncology, Leon Berard Cancer Center, Lyon, France, [8]Medical Oncology, Azienda Ospedaliera S. Paolo, Milan, Italy

Background: An increase in the number of elderly patients diagnosed with head and neck cancer is expected, but there is no consensus on what is the optimal treatment for patients >70 years with locally advanced disease. Geriatric assessment (GA) is recommended but not validated for guiding treatment decisions. We hypothesized that significant heterogeneity will exist across institutions in patterns of care delivered to elderly patients with LA-HNSCC and in the use of GA and assessment of quality of life (QoL).

Methods: Members of the EORTC, the European Head and Neck Society and national groups in Europe were asked to complete a questionnaire about treatment delivered and use of GA and QoL assessment in elderly patients with LA-HNSCC.

Results: Investigators from 111 centers replied, including 90 (81.1%) academic centers, 16 (14.4%) community hospitals and 5 (4.5%) private clinics. Large differences in treatment patterns were found. For instance, for oropharyngeal carcinoma, one third of the centers indicate that they treat <5% of elderly patients with chemoradiation, while 18 centers (16.2%) treat >40% of elderly patients with chemoradiation. More than half of the centers hardly or never use cetuximab in elderly patients with hypopharyngeal carcinoma, while one in five centers treat >20% of the elderly patients with cetuximab. Furthermore, 3 centers (2.7%) treat <5% of elderly patients with oral cavity cancer with surgery and postoperative radiotherapy, while 73 centers (65.7%) offer this to at least 40% of their elderly patients. Fourteen centers (12.6%) routinely perform GA while 43 centers (38.7%) never do, and 39 centers (35.1%) sometimes do. QoL is assessed on a routine basis in one fifth of the centers.

Conclusions: Large differences exist across institutions in the patterns of care delivered to elderly patients with LA-HNSCC. Prospective studies are required in this population to learn how to use GA, how to improve QoL and ultimately improve treatment outcome. For that, consensus on standard of care is essential.

Legal entity responsible for the study: EORTC.

Funding: Has not received any funding.

Disclosure: S. Oosting: Research grants (paid to institution): Pfizer, Novartis, Celldex. All other authors have declared no conflicts of interest.

1107P The importance of comorbidity assessment in patients with oral squamous cell carcinoma (OSCC): Could the adult comorbidity evaluation – 27 (ACE-27) provide an additional information?

U.M. Jariod Ferrer[1], S. Blanco Sanfrutos[2], M.A. Gavin Clavero[1], T. Uson Bouthelier[1], B. Nadal Cristobal[1], I. Moral Saez[1], I. Pajares Bernad[3], A.I. Cisneros Gimeno[4], J. Martinez Trufero[3]

[1]Oral and Maxillofacial Surgery, Hospital Miguel Servet, Zaragoza, Spain, [2]Oral and Maxillofacial Surgery, Hospital Can Misses Ibiza, Ibiza, Spain, [3]Medical Oncology Department, Hospital Miguel Servet, Zaragoza, Spain, [4]Anatomy Department, University of Zaragoza, Zaragoza, Spain

Background: Disease stage is the most powerful prognostic factor in OSCC but is not accurate enough to identify highest risk patients. Other patient-related conditions as comorbidity add relevant prognostic value. We show the importance of the comorbidity assessment in contrast to other historic prognosis factors.

Methods: Retrospective review of patients with resectable OSCC from 2011 to 2014. Baseline pretreatment comorbidity data were collected according to ACE–27. Clinical, pathological, presurgical blood samples and treatment data were collected. Kaplan-Meier and Cox proportional hazards modeling were used to determine associations with OS (Overall Survival), DSS (Disease-Specific Survival) and DFS (Disease-Free Survival).

Results: Among 215 patients, median age was 67 years (range 32-96). Median follow-up was 31 months (1– 78). 74% suffered at least one previous comorbid condition. 3-year OS, DSS and DFS were 68%, 77% and 65%, respectively. The multivariable model is showed in the table. Suffering a severe comorbidity had the highest prognostic value, greater than present a locally advanced OSCC [HR = 6.24; 95%CI=2.08-18.67p< 0.001].

Table: 1107P Multivariable model

Variable	HR	95%CI	p
Low comorbidity	2.61	[0.95-7.21]	0.006
Moderate comorbidity	3.17	[1.24-8.11]	0.02
Severe comorbidity	6.24	[2.08-18.67]	<0.001
Haemoglobin < 13.6 g/dL	1.92	[1.04-3.55]	0.04
Stage II	2.57	[0.87-7.58]	0.009
Stage III-IV	4.10	[1.15-14.67]	0.03
N0. Watchful waiting	2.82	[0.98 – 8.12]	0.05
Therapeutic neck disection	2.57	[1- 6.60]	0.05
PLR (platelets to lymphocytes ratio) >66	3.98	[0.88-17.93]	0.07
Age > 80	2.88	[1.28-6.46]	0.01

Conclusions: We described the account of comorbidity assessment as a prognosis factor of resectable OSCC. We provide the importance of additional clinical and easily accessible information to tumor stage, capable of discriminating prognostic risk factors in resectable OSCC.

Legal entity responsible for the study: The Clinical Research Ethics Committee of Aragón (CEIC-A).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1108P Can concomitant diseases predict the compliance with cisplatin plus RT in patients with LA SCCHN? An exploratory endpoint analysis of the COMPLY trial

J. Dunst[1], G. Hildebrandt[2], M. Becker-Schiebe[3], T. Kuhnt[4], F. Weykamp[5], F. Martucci[6], D. Vordermark[7], M. Pless[8], D. Hofmann[9], V. Bühler[10], S.I. Rothschild[11]

[1]Klinik für Strahlentherapie, Universitätsklinikum Schleswig-Holstein, Kiel, Germany, [2]Radiooncology, Universitätsklinikum Rostock, Rostock, Germany, [3]Radiooncology, Klinikum Braunschweig, Braunschweig, Germany, [4]Radiooncology, Universitätsklinikum Leipzig, Leipzig, Germany, [5]Strahlentherapie, Universitätsklinikum Heidelberg, Heidelberg, Germany, [6]Radiooncology, IOSI - Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland, [7]Radiooncology, Universitätsklinikum Halle/Saale, Halle/Saale, Germany, [8]Radiooncology, Kantonsspital Winterthur, Winterthur, Switzerland, [9]Medical Affairs Oncology, Merck Serono GmbH, Darmstadt, Germany, [10]Medical Affairs Oncology, Merck (Schweiz) AG, Zug, Switzerland, [11]Radiooncology, Universitätsspital Basel, Basel, Switzerland

Background: International guidelines recommend the use of high-dose platinum chemoradiotherapy (CRT) (3 x 100 mg/m^2, q3w) for the treatment of LA SCCHN. The clinical benefit of CRT decreases with lower cumulative dosage. Dose reductions to ≤ 200 mg/m^2 lead to a significantly lowered OS. Predictive factors would help to select patients who are suitable for an optimal cumulative dose of cisplatin.

Methods: The COMPLY trial included patients with LA SCCHN from Germany and Switzerland. Eligible patients were treated in 2013/2014. The planned target dose of cisplatin had to be > 200 mg/m^2. Compliance was defined as an administration of > 200 mg/m^2 cisplatin. R/M SCCHN, nasopharyngeal carcinomas, adjuvant treatment or participation in other clinical trials were excluded. The exploratory objective was to identify a predictive score for therapy compliance with platinum-based CRT. A multiple logistic regression analysis was performed to identify independent explanatory variables associated with compliance with cisplatin. Only independent variables with a p-value <0.15 in the univariate analysis were considered for multiple logistic regression analysis.

Results: 184 patients in 9 sites were included. Median age was 61.0 years, 82.6% were male, 167 patients (90.8%) were ECOG 0-1. A significant difference in treatment compliance with cisplatin was shown for patients with concomitant musculoskeletal/connective tissue disorders (odds ratio for absence of disease vs. presence: 9.43; 95% CI: 1.20, 74.02; p = 0.03) and respiratory, thoracic and mediastinal disorders (odds ratio for absence of disease vs. presence: 6.59; 95% CI: 1.47, 29.48; p = 0.01) by system organ class. The probability of treatment compliance with cisplatin, being an estimate from a scoring system developed for the study, was 43.4% in subjects with absence of both disorders while the treatment compliance was 8.9% in subjects who presented with either one of the disorders and 1.2% in subjects with both disorders.

Conclusions: These exploratory results indicate that subjects without musculoskeletal/connective tissue and respiratory, thoracic and mediastinal disorders as concomitant diseases were more likely to have received cisplatin >200 mg/m^2.

Editorial acknowledgement: The Medical Affairs Oncology Department of Merck Serono GmbH, Darmstadt, Germany assisted in the writing of this abstract.

Legal entity responsible for the study: Merck Serono GmbH, Darmstadt, Germany.

Funding: Merck Serono GmbH, Darmstadt, Germany.

Disclosure: J. Dunst: Honoraria: Merck KGaA. D. Vordermark: Advisor: Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Merck KGaA; Honoraria as speaker: Roche, AstraZeneca, Merck KGaA, Lilly, Ferring. M. Pless: Advisory boards honoraria: Merck, D. Hofmann: Employee and stock ownership: Merck Serono GmbH. V. Bühler: Employee: Merck (Schweiz) AG. S.I. Rothschild: Advisory boards honoraria (to Institution): Merck; Research funding: Merck. All other authors have declared no conflicts of interest.

1109P Comparison of acute hematologic and renal toxicities in two chemotherapy schedules of cisplatin for epithelial cell carcinoma of head and neck

A. Ameri[1], S. Norouzi[1], A. Sourati[1], K. Novin[2], S. Azghandi[3]

[1]Jorjani Cancer Center, Imam Hossein Hospital, Teheran, Iran, [2]Radiation Oncology Department, Shohada Haftetir Hospital, Teheran, Iran, [3]Radiation Oncology Department, Shohada Tajrish Hospital, Teheran, Iran

Background: Standard approach for treatment of locally advanced head and neck carcinoma is concurrent chemoradiation with cisplatin 100mg/m^2 every three week. However, prescribing cisplatin at this dose is associated with increased toxicity that can interrupt and compromise treatment results. Many centers use alternative schedules of weekly cisplatin at doses of 30-40 mg/m^2 per week.

Methods: In this study, 77 patients with head and neck cancer were randomized in a phase II clinical trial to compare toxicity for two cisplatin schedules, 100mg/m^2 three weekly and 40mg/m^2 weekly.

Results: The incidence of grade 3-4 hematologic events was not significantly different between the two groups, but the mean level of glomerular filtration rate in the three weekly group was significantly higher than the weekly group. There was no significant difference between the two groups in terms of mean overall treatment time and mean dose of cisplatin. Cisplatin cumulative dose $\geq$ 200mg/m^2 was higher in the weekly group, but no significant difference was observed. The main reason for treatment interruption was neutropenia for the three-weekly group, but in the weekly group, it was renal dysfunction for chemotherapy delay, and thrombocytopenia for radiotherapy break.

Conclusions: Weekly prescribing cisplatin can lead to higher cumulative doses, which may improve treatment outcomes. The incidence of grade 3-4 hematologic events was not significantly different between the two groups; However, the weekly schedule was associated with a higher drop in GFR, requiring further investigation.

Clinical trial identification: IRCT20180223038829N.

Legal entity responsible for the study: Shahid Beheshti University of Medical Science.

Funding: Research and Development Center of Shahid Beheshti University of Medical Science.

Disclosure: All authors have declared no conflicts of interest.

1110P Patient reports of mouth symptoms after radiotherapy treatment for head and neck cancer: An international survey

C. Curtis[1], A. Nicotera[2], C. Griseri[2], H. Roddam[3]

[1]The Swallows Head and Neck Cancer Support Group, Blackpool, UK, [2]Allied Health Research Unit, University of Central Lancashire, Preston, UK, [3]Health Sciences, University of Central Lancashire, Preston, UK

Background: People with head and neck cancer frequently have symptoms that are caused by their disease or by their treatments, which may significantly impact on their quality of life living with and beyond cancer. This international research survey captured a self-rating report by people who have had radiotherapy (RT) treatment for head and neck cancer about their experience of oral symptoms, including Dry Mouth (Xerostomia).

Methods: This survey was designed by patients, and then submitted for ethical approvals in collaboration with a healthcare researcher. The international survey was open to anyone over 18 who has had treatment for head and neck cancer, whether or not they currently have symptoms of Dry Mouth. The electronic survey was only in English and the ethical permissions granted that patients who wished to take part could request assistance if needed; due to illness, fatigue, confidence in accessing the internet, or English literacy. Participant recruitment was supported through a wide range of networks including healthcare practitioners, charities and patient support groups. The average time to complete the 18-item survey was under 10 minutes; including both multiple choice and open questions. The statistical analysis reflected correlations between the participant demographics and self-report of symptoms. An interpretive analysis of free text responses highlighted patient values and priorities.

Results: Over 100 individuals responded, from across UK, US, Canada, Australia, India and mainland Europe. The analysis demonstrates patterns between the patient demographics, types of radiotherapy treatments, time since treatment, and current symptoms. This is the first time that this original dataset will be presented. The findings also generated insights into the self-reported impact of these symptoms on patients' quality of life.

Conclusions: This study comprises important evidence of patients' experiences and symptoms following RT treatment. The cross-sectional dataset also indicates the global view of recent and current RT treatment approaches. Future collaborative research by healthcare researchers, patient groups and relevant pharma is imperative. This research will be presented by a Patient Advocate.

Legal entity responsible for the study: University of Central Lancashire.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1111P Risk factors for aspiration pneumonia during concurrent chemoradiotherapy or bio-radiotherapy for head and neck cancer

H. Shirasu[1], T. Yokota[1], K. Fushiki[1], H. Inoue[1], M. Shibata[1], M. Furuta[1], T. Kawakami[1], S. Kawai[2], S. Hamauchi[1], A. Todaka[1], T. Tsushima[1], N. Machida[1], K. Yamazaki[1], A. Fukutomi[1], Y. Onozawa[1], H. Yasui[1]

[1]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [2]Division of Medical Oncology, Shizuoka Cancer Center, Shizuoka, Japan

Background: Aspiration pneumonia (AP) is one of the most important side effects in chemoradiotherapy (CRT) and bio-radiotherapy (BRT) for patients (pts) with head and neck cancer (HNC). AP is involved in on-cancer related mortality in HNC pts. However, the relation between AP during CRT or BRT and treatment outcomes in HNC pts has not been identified. The aims of this study were to assess the influence of AP on treatment outcomes, and to identify clinical risk factors for AP during definitive CRT or BRT for HNC pts.

Methods: We retrospectively assessed the data of pts with locally advanced HNC who received definitive CRT or BRT at Shizuoka Cancer Center (August 2006 to December 2016). AP was defined as a clinical condition that met all the following criteria: (i) pts with both subjective and objective symptoms of pneumonia; (ii) the presence of aspiration was suspected clinically (choking or delayed swallowing) or by endoscopy or video-fluorography exams; (iii) no evidence of micro-organisms that cause atypical pneumonia.

Results: Of 374 HNC pts who received CRT or BRT, 95 (25.4%) developed AP during treatment. The study cohort of 374 pts had the following features: median age 65 years (range: 19-83); male/female, 322/52; performance status 0/1/2/3, 196/109/14/3; number of metastatic sites 1/2/3/4, 98/60/27/4; primary site larynx/nasopharynx/nasal-sinus/oropharynx/oral-cavity/ear-canal, 57/48/132/21/101/14/1; T-classification 1/2/3/4a/4b, 32/136/86/92/28; N-classification (UICC 7th) 0/1/2a/2b/2c/3, 76/54/19/134/75/16; induction chemotherapy -/+, 273/101; chemotherapy regimen cisplatin/carboplatin/cetuximab, 278/64/32. AP was significantly associated with treatment response of CRT or BRT (multivariate-adjusted odds ratio for complete response 0.55, p < 0.029). Multivariate analyses identified four independent factors for AP, including poor oral hygiene, high N-classification, hypoalbuminemia before treatment, and inpatient treatment.

Conclusions: AP during CRT or BRT has a detrimental effect on treatment response in HNC pts. Careful attention should be paid to AP in HNC pts with these risk factors receiving CRT or BRT.

Legal entity responsible for the study: H. Shirasu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1112P Nutritional support dependence after curative chemoradiotherapy in head and neck cancer: A supplementary analysis of a phase II trial (JCOG0706S1)

Y. Imamura[1], N. Kiyota[1], T. Akimoto[2], G. Ogawa[3], J. Eba[3], S. Minami[4], Y. Hasegawa[5], S. Iwae[6], N. Monden[7], K. Matsuura[8], H. Fujii[9], Y. Onozawa[10], A. Homma[11], R. Hayashi[12], M. Tahara[13]

[1]Medical Oncology/Hematology, Kobe University Hospital, Kobe, Japan, [2]Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [3]Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital East, Tokyo, Japan, [4]Otolaryngology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan, [5]Head and Neck Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, [6]Head and Neck Surgery, Hyogo Cancer Center, Akashi, Japan, [7]Head and Neck Surgery, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [8]Head and Neck Surgery, Miyagi Cancer Center, Natori, Japan, [9]Clinical Oncology, Jichi Medical University, Shimotsuke, Japan, [10]Clinical Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [11]Otolaryngology-Head and Neck Surgery, Hokkaido University, Sapporo, Japan, [12]Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Japan, [13]Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: Curative chemoradiotherapy (CRT) for locally advanced head and neck cancer (LA-HNC) causes severe acute and late adverse reactions, including nutritional support dependence. The aim of this supplementary analysis of a previous single-arm phase II study of CRT with S-1 plus cisplatin for unresectable LA-HNC (JCOG0706) which demonstrated promising efficacy (Cancer Sci.2015;106:726) was to explore risk factors of laryngo-esophageal dysfunction-free survival (LEDFS) and nutritional support dependence over 12 months (NSD12M).

Methods: The study population comprised 45 patients (pts) in the JCOG0706. Risk factors of LEDFS and NSD12M were analyzed using Cox regression models and logistic regression models, respectively, with consideration to the pts' laboratory data just before CRT. Radiation fields were reviewed to analyze the relationship between the extent of irradiated fields and functional outcomes.

Results: Proportions of alive without nutritional support at registration and 2, 6, 12, and 24 months after registration were 82.2%, 35.6%, 68.9%, 77.8%, and 64.4%. All six pts who required nutritional support at 12 months remained tube feeding-dependent thereafter. With a median follow-up period of 3.5 years of all pts, 3-year LEDFS was 48.9%. For LEDFS, the hazard ratio was 0.42 in pts with nutritional support at registration (vs. without nutritional support; 95% confidence interval [CI] 0.17-1.04). For NSD12M, odds ratio was 6.78 in pts with hemoglobin less than the median value of 13.4 g/dL (vs. higher than or equal to the median; 95% CI 1.24-36.85); and was 6.00 in pts with albumin less than the median value of 3.9 g/dL (vs. higher than or equal to the median; 95% CI 1.11-32.54). Primary sites in disease-free pts with NSD12M were the oropharynx (N = 2) or hypopharynx (N = 1), and all their pharyngeal constriction muscles were irradiated with a curative dose of 70 Gy/35 fr.

Conclusions: Functional outcomes were affected by severe dysphasia requiring nutritional support before CRT, and lower pretreatment values of hemoglobin and albumin. These risk factors should therefore be taken into consideration in planning treatment strategy for pts with LA-HNC.

Clinical trial identification: UMIN000001272.

Legal entity responsible for the study: JCOG.

Funding: National Cancer Center Research and Development Fund (23-A-16, 23-A-21, 25-B-2 and 26-A-4); Grants-in-Aid for Cancer Research (18-19, 20S-3,20S-6) from Ministry of Health, Labour and Welfare of Japan.

Disclosure: All authors have declared no conflicts of interest.

1113P The retrospective analysis of nephrotoxicity for cisplatin dose of CRT compared 100 mg/m2 to 80 mg/m2 for head and neck cancer (HNC) patients

T. Oguri[1], K. Nakano[1], N. Fukuda[1], K. Kawaguchi[1], T. Urasaki[1], M. Nishizawa[1], M. Yunokawa[1], M. Ono[1], S. Taira[1], J. Tomomatsu[1], T. Toshiyasu[2], H. Mitani[3], S. Takahashi[4]

[1]Department of Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [2]Department of Radiation Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [3]Head and Neck Surgery, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [4]Department of Medical Oncology, Cancer Institute Hospital of JFCR, Tokyo, Japan

Background: Concurrent chemoradiotherapy (CRT) with single agent cisplatin for patients with head and neck cancers (HNC) have been used as the standard treatment for a long time. Although recommended dose of cisplatin is 100mg/m2, we sometimes reduced cisplatin dose to 80mg/m2 depends on general condition in real world setting. It remains unclear whether the efficacy and the safety, especially in nephrotoxicity, for CRT of HNC patients with cisplatin dose 100mg/m2 or 80mg/m2 are different.

Methods: We reviewed medical records of NHC patients who received CRT in our institute retrospectively. The primary objectives of this study were to evaluate the nephrotoxicity and the rate of patients treated with cumulative dose of cisplatin 200mg/m2 or more.

Results: During January 2014 to October 2017, 261 HNC patients who received CRT were treated. The starting dose of cisplatin were 80mg/m2 in 118 patients vs 100mg/m2 in 143 patients, respectively. There were more patients over 70 years who received cisplatin in 80mg/m2 than 100mg/m2 (27.1% vs 4.2%, $p < 0.001$). The mean Creatinine Clearance (Ccr) obtained using the Cockcroft-Gaut at baseline was significantly lower in 80mg/m2 than 100mg/m2 (87.82 vs 97.28, $p = 0.0022$). There were no significantly differences in patient's other characteristics as follows gender, performance states, pathology. The incidence of Grade 2 or higher elevation in creatinine was 2 (1.7%) in 80mg/m2 group and 4 (2.8%) in 100mg/m2 group, respectively ($p = 0.554$). The rate of change in CCR showed no difference between both groups (-5.73% in 80mg/m2 vs -7.63% in 100mg/m2, $p = 0.2927$), either. The rate of cumulative dose of cisplatin ≧200mg/m2 was significantly higher in 100mg/m2 than 80mg/m2 (97.2% vs 72.0%, $p < 0.001$). 2-year PFS rate was not significantly different between 80 mg/m2and 100 mg/m2 in oropharynx (89.3% vs 88.2%, $p = 0.7760$) and in hypopharynx/ larynx (70.28% vs 80.92%, $p = 0.4740$), respectively.

Conclusions: Cisplatin dose of CRT for HNC patients in 100mg/m2was feasible without increasing the nephrotoxicity and the rate of cumulative dose of cisplatin ≧ 200mg/m2was higher compared to 80mg/m2.

Legal entity responsible for the study: Tomoyo Oguri.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1114P Comparison of treatment outcomes and tolerability of patients with recurrent (R) nasopharyngeal carcinoma (NPC) and metastatic disease at diagnosis (M1): A retrospective analysis

C. Sookthon[1], P. Pattaranutaporn[2], C. Jiarpinitnun[2], N. Ngamphaiboon[3]

[1]Medicine, Ramathibodi Hospital, Bangkok, Thailand, [2]Radiology, Ramathibodi Hospital, Bangkok, Thailand, [3]Medicine, Division of Medical Oncology, Ramathibodi Hospital, Bangkok, Thailand

Background: In current clinical trials and practice, patients with R and M1 NPC are considered the same entity and typically received similar systemic treatments. However, natural history, treatment outcomes and tolerability of systemic chemotherapy between both groups remains unknown.

Methods: R and M1 NPC patients were identified. Patient characteristics, treatment modalities, tolerability, and survival outcome were retrospectively abstracted. Tolerability of chemotherapy was defined by dose reduction, hospitalization, delayed, and/or termination of chemotherapy.

Results: A total of 144 NPC patients (R = 98, M1=46) were analyzed. In R patients, locoregional recurrence and distant metastasis were observed in 30% and 66%, respectively. In R group, median time to recurrence was 16.6 months. Median OS of M1 patients was not difference from R group (12.3 vs 11.8 months; $p = 0.09$). However, patients with M1 had shorter OS when compared with locoregional group (12.3 vs 26.7 months; $p = 0.01$). Patients who received doublet had longer OS than single agent chemotherapy in both groups. There was no different in OS between 1st line cisplatin- and carboplatin-based chemotherapy in R group (34.2 vs 19.3 months; $p = 0.15$), but significant difference in M1 patients (14.7 vs 12.3 months; $p = 0.05$). Tolerability to systemic chemotherapy were comparable among R and M1 NPC patients.

Table: 1114P

Characteristic	Metastasis at diagnosis N = 46 (%)	Recurrence N = 98(%)	P-value
Baseline Patient Characteristics			
-Median age (range)	56(29-75)	50(19-79)	0.17
-male	34 (73.9)	75 (76.5)	0.73
-smoker	21(45.7)	42(42.9)	0.84
ECOG 0-1 >2	41 (89.1) 3 (6.5)	95 (96.9) 2 (2.0)	0.18
chemotherapy			
1st line	33 (71.7)	66(67.3)	0.60
2nd line	15 (32.6)	28 (28.6)	0.62
>=3rd line	7 (15.2)	11 (11.2)	0.50
doublet single	32(69.6) 0	53(54.1) 11 (11.2)	0.01
cisplatin carboplatin	22(47.8) 10(21.7)	12(12.2) 41(41.8)	<0.01

Conclusions: There was no different in tolerability and survival of R and M1 NPC patients. Physicians should expect similar outcomes of R and M1 NPC patients who received systemic chemotherapy.

Legal entity responsible for the study: Ramathibodi Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1115P Impact of the multidisciplinary approach on the survival of squamous head and neck cancer in our institution

M.J. Martínez-Ortiz[1], Á. Martínez-Ortiz[2], G. Marín-Zafra[1], P. Cerezuela-Fuentes[1], J. Balsalobre[1], J.A. Díaz-Manzano[3], J. Trujillo-Santos[4], M.T. García-García[1]

[1]Medical Oncology, Hospital Universitario Santa Lucia, Cartagena, Spain, [2]Radiotherapy and Radiology, Hospital Universitario Santa Lucia, Cartagena, Spain, [3]ORL, HCUV Arrixaca, Murcia, Spain, [4]Internal Medicine, Hospital Universitario Santa Lucia, Cartagena, Spain

Background: Our hospital has about 650 beds. Since 2008, the multidisciplinary tumours team (MDT) evaluates once a week, all new cases of head and neck cancer, approximately 75/year. The main objective is to ascertain the 2-year survival of patients with squamous cell cancer of the head and neck (HNSCC) treated by a MDT and without an MDT, determining whether there are statistically significant differences.

Methods: Observational retrospective study of two cohorts, which aims to analyse the survival in the cohort by an MDT (C1, those from 01/01/2005 to 12/31/2008) with respect to the cohort without an MDT (C2, 01/01/2009 to 12/31/2012). We included all patients with an initial diagnosis of HNSCC at our centre. With access to the Pathological Anatomy database, the records of the MDT, the medical history, we collected the primary endpoint (survival at 2 years) and characteristics related to the patient, tumour, treatment and tracking (date and cause of death). Definitive sample consists of 408 patients, 200 in pre-MDT cohort and 208 in post-MDT cohort. A descriptive analysis is given of the demographic, clinical and epidemiological characteristics of the sample and a survival analysis with rates calculated using the Kaplan Meier method. The log-rank test was used to assess the differences in survival between cohorts, and a Cox proportional-hazards regression model was used to perform the univariate and multivariate survival analysis.

Results: Our population presents age (mean) 64.2y (SD 12.4), male 82.6%, ECOG<2 89%, 32.1% laryngeal location, tumour stage IVA 31.6%. Treatment with surgery (S) 43.4%. From our comparative analysis we want to highlight (C1 vs C2) 2-years OS was 59.5% and 70.2% ($p = 0.042$). After univariate and multivariate survival analysis, MDT is an independent variable of better prognosis in terms of overall survival in our study (HR 0.696).

Conclusions: The population served in our area presents demographic and clinical and epidemiological characteristics similar to those of other series published in our country. There is a statistically significant improvement in the survival of patients treated by MDT, this approach being an independent variable of better prognosis in terms of overall survival in our study.

Legal entity responsible for the study: M. J. Martínez-Ortiz.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1125P Prophylactic versus reactive nutritional supplement in local advanced nasopharyngeal carcinoma patients receiving radical chemo-radiotherapy

Y-Y. Chen, S. Huang, X. Chen, Q. Hu

Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou, China

Background: The aim of this study was to investigate the effect of prophylactic versus reactive nutritional supplement on nutritional status and treatment tolerance in local advanced nasopharyngeal carcinoma (NPC) patients receiving neoadjuvant chemotherapy (NACT) and concurrent chemoradiotherapy (CCRT).

Methods: NPC patients were randomly assigned to prophylactic nutritional intervention group (A) or the control group (B). Patients in group A were supported with enteral nutrition supplement except daily diet from the beginning of radiotherapy (RT). Nutritional intervention aimed to reach 30 kcal/kg/d. Group B was treated with conventional diet guidance at first, appropriate nutritional intervention will be given when serious malnutrition (PG-SGA≥4) appeared. Weight and nutritional questionnaires (NRS 2002, PG-SGA) were collected at the baseline, before, during and after CCRT.

Results: From October 2016 to May 2018, 114 patients from our cancer center were randomly assigned to the group A and B (58 vs 56). The completion rates of NACT and RT were 88.6% and 100%. 80.7% of patients completed CCRT (A vs B = 90% vs 71%, P = 0.013, 95%IC=0.038-0.326). Grade 3/4 mucositis and grade 2/3 skin reaction were observed in 26.3% and 23.7% of patients. Though more serious radiation reactions were observed in group B, no statistical difference between group A and B (22.4% vs 30.4% and 21% vs 27%, $P > 0.05$). All patients experienced weight loss during the NACT and CCRT. Comparing to baseline, the rate of weight loss ≥5% and≥10% before, during, after RT and 1 month after RT were 3.5%, 28.9%, 29.8%, 64.7% and 0, 4.4%, 18.4%, 31%. The overall incidence of PG-SGA≥4 and ≥9 were32.6%, 39%, 95.9%, 100%, 78.7% and 2.3%, 10.5%, 50%, 72.3%, 14.8%, respectively. But the repeated measures showed that the difference of weight loss and PG-SGA scores between two groups were not significant ($P > 0.05$).

Conclusions: Malnutrition risk was gradually increased during the treatment of NPC.Prophylactic nutritional intervention can improve the tolerance of concurrent chemotherapy, but it has no advantage in weight loss and scores of short-term nutritional assessments.

Clinical trial identification: NCT02948699.

Legal entity responsible for the study: Zhejiang Cancer Hospital.

Funding: Nutricia.

Disclosure: All authors have declared no conflicts of interest.

1116TiP A randomized phase III study to evaluate the value of the omission of prophylactic neck dissection for stage I/II tongue cancer (RESPOND: JCOG1601)

N. Hanai[1], T. Asakage[2], N. Kiyota[3], A. Homma[4], N. Monden[5], H. Fukushima[6], T. Fujii[7], T. Ogawa[8], K. Tanaka[9], J. Mizusawa[10], J. Eba[11], R. Hayashi[12]

[1]Head and Neck Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, [2]Department of Head and Neck Surgery, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan, [3]Medical Oncology/Hematology, Kobe University Hospital, Kobe, Japan, [4]Otolaryngology-Head and Neck Surgery, Hokkaido University, Sapporo, Japan, [5]Head and Neck Surgery, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [6]Department of Otolaryngology-Head and Neck Surgery, Cancer Institute Hospital, Tokyo, Japan, [7]Department of Otolaryngology, Osaka International Cancer Institute, Osaka, Japan, [8]Department of Otorhinolaryngology, Head and Neck Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan, [9]1 JCOG Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan, [10]JCOG Data Center/ Operations Office, National Cancer Center, Tokyo, Japan, [11]JCOG Data Center, National Cancer Center, Tokyo, Japan, [12]Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Japan

Background: The standard local treatment for early-stage tongue cancer with no clinical lymph node metastases is partial glossectomy. However, whether or not prophylactic neck dissection (ND) should be performed has been controversial. In 2015, D'Cruz et al. reported that prophylactic ND contributes to the improvement of overall survival (OS) for clinical T1-2N0 tongue cancer regardless of the depth of invasion (DOI). However, considering the occult lymph node metastasis of 30% and disadvantages associated with prophylactic ND such as cosmetic issues and complications including accessory and facial nerve paralysis, partial glossectomy alone can still be regarded as a treatment option for patients (pts) carefully selected by DOI, provided there is appropriate follow-up with full use of computed tomography (CT) and other diagnostic imaging modalities to detect recurrence early enough to conduct salvage surgery.

Trial design: We have commenced a phase III randomized controlled trial to confirm the non-inferiority of glossectomy alone compared to glossectomy with prophylactic ND (standard arm) in terms of OS. Histologically proven stage I/II tongue cancer with DOI 3-10 mm by enhanced magnetic resonance imaging is eligible. The selection based on the DOI is a novel aspect of this study. We set the key inclusion criterion of DOI as 3-10 mm since prophylactic ND is unnecessary for pts with DOI < 3 mm according to the data from D'Cruz et al, and pts with DOI > 10 mm are classified as T3 according to the 8th TNM classification. The primary endpoint is OS. The secondary endpoints include relapse-free survival (RFS), local-RFS, proportion of non-resectable recurrence, proportion of neck lymph node recurrence, and adverse events. We assumed a 5-year OS of 85% in the standard arm and set the non-inferiority margin at 7.5%. The sample size was set at 440 pts, with a one-sided α of 5%, power of 70%, an accrual period of 5 years, and a follow-up period of 5 years. For follow-up observation, CT is essential at 3, 6, 12, 18, and 24 months postoperatively and then annually thereafter. Enrollment launched November, 2017 and five pts were enrolled as of April 2018.

Clinical trial identification: UMIN000030098.

Legal entity responsible for the study: National Cancer Center.

Funding: The grant for practical research for innovative cancer control from the Japan Agency for Medical Research and Development (AMED) (JP18ck0106438) and the National Cancer Center Research and Development Fund (29-A-3).

Disclosure: N. Hanai: Grants (during the conduct of the study): MHLW Japan, AMED; Honoraria: ONO, Bristol-Meyers Squibb, Merck Serono. T. Asakage, H. Fukushima, T. Fujii, T. Ogawa, K. Tanaka, J. Mizusawa, J. Eba, R. Hayashi: Grants (during the conduct of the study): MHLW Japan, AMED. N. Kiyota: Grants (during the conduct of the study), MHLW Japan, AMED; Grants (outside the submitted work): ONO, AstraZeneca, Pfizer; Honoraria: ONO, Bristol-Meyers Squibb, Merck Serono, Eisai, Bayer. A. Homma: Grants (during the conduct of the study): MHLW Japan and AMED; Honoraria: ONO. N. Monden: Grants (during the conduct of the study): MHLW Japan and AMED; Honoraria: Merck Serono.

1117TiP IMvoke010: Randomized phase III study of atezolizumab (atezo) as adjuvant monotherapy after definitive therapy of squamous cell carcinoma of the head and neck (SCCHN)

R. Haddad[1], D.J. Wong[2], Y. Guo[3], J. Fayette[4], E.E.W. Cohen[5], M. Kowgier[6], A. Sandler[7], C. Matheny[8], F. Kabbinavar[9], D. Raben[10]

[1]Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [2]Medicine, Hematology/Oncology, University of California Los Angeles, Los Angeles, CA, USA, [3]Department of Clinical Chinese Medicine, Tongji University East Hospital, Shanghai, China, [4]ENT, Lung, Sarcomas and GIST, Centre Léon Bérard, Lyon, France, [5]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA, [6]Biostatistics, F. Hoffmann-La Roche, Ltd, Mississauga, ON, Canada, [7]Product Development - Oncology, Genentech Inc. - Roche - USA, South San Francisco, CA, USA, [8]Product Development - Oncology, Genentech, Inc, South San Francisco, CA, USA, [9]PDO, Genentech, Inc, San Francisco, CA, USA, [10]Radiation Oncology, University of Colorado, Denver, CO, USA

Background: Locally advanced SCCHN is associated with a high risk for local recurrence and distant metastases. Treatment includes a combination of surgery, radiation therapy and chemotherapy to optimize the chances for long-term disease control and improved survival. After definitive local therapy, patients (pts) are monitored for local recurrence and/or distant metastases as standard of care. No effective systemic adjuvant treatment has been identified. Atezo is an anti–programmed death-ligand 1 (PD-L1) monoclonal antibody that prevents PD-L1 from binding to its receptors PD-1 and B7.1, thereby restoring anti-tumor immunity. Efficacy results from a cohort of pts with recurrent/metastatic SCCHN in the Phase I PCD4989g study suggest that atezo offers a potential clinical benefit. The objective of IMvoke010 (NCT03452137) is to evaluate the efficacy and safety of adjuvant atezo in pts with locally advanced SCCHN who are at high risk for disease recurrence or progression following definitive curative therapy.

Trial design: IMvoke010 is a global, double-blind, placebo-controlled, randomized Phase III trial enrolling pts who have completed definitive local/regional therapy for Stage III human papillomavirus (HPV)-positive oropharyngeal carcinoma or Stage IVA or IVB HPV-negative SCCHN involving the oral cavity, oropharynx, larynx or hypopharynx and are at high risk for disease recurrence or progression. Approximately 400 pts will be randomized 1:1 to receive placebo or atezo 1200 mg Q3W for up to a year ($\leq$16 cycles) or until unacceptable toxicity, disease recurrence or progression. Pts with nasopharyngeal carcinoma, metastatic disease, or progressive disease during or at completion of definitive local therapy will be excluded. Stratification factors include HPV status, response to definitive local therapy and whether primary surgery was performed as part of definitive therapy. Primary endpoints are independent review facility-assessed event-free survival (EFS) and overall survival. Key secondary endpoints include investigator-assessed EFS, safety, and patient reported outcomes. Exploratory biomarkers will also be assessed.

Clinical trial identification: NCT03452137.

Editorial acknowledgement: Medical writing assistance for this presentation was provided by Steffen Biechele, PhD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd.

Legal entity responsible for the study: F. Hoffmann-La Roche, Ltd.

Funding: F. Hoffmann-La Roche, Ltd.

Disclosure: R. Haddad: Consultant: BMS, Merck, Genentech, Pfizer, Loxo, AstraZeneca; Research support: Genentech, Pfizer, Merck, BMS, AstraZeneca. D.J. Wong: Consultant: Bristol-Myers Squibb, Genentech; Research funding: Bristol-Myers Squibb, Genentech, Merck, Kura, Armo Biosciences, AstraZeneca. J. Fayette: Honoraria: BMS, AstraZeneca, MSD, Innate Pharma, Merck. A. Sandler: Personal fees (during the conduct of the study): Genentech/Roche; Personal fees and other (outside the submitted work): Genentech/Roche, C. Matheny: Personal fees (during the conduct of the study): Genentech/Roche; Personal fees and non-financial support (outside the submitted work): Genentech/Roche, other from Roche; Patent Stanford pending. F. Kabbinavar: Employment and stocks: Genentech. D. Raben: Consultant: Genentech, Merck, AstraZeneca; Advisory board: Genentech, Merck, Nanobiotix. All other authors have declared no conflicts of interest.

1118TiP A phase I/II dose escalation study of the CDK4/6 inhibitor, palbociclib in combination with cetuximab and intensity modulated radiation therapy (IMRT) for locally advanced squamous cell carcinoma of the head and neck (SCCHN)

N. Ngamphaiboon[1], S. Lukerak[1], C. Jiarpinitnun[2], A. Jinawath[3], N. Jinawath[4], J. Juengsamarn[1], L. Arsa[3], J. Konmun[5], N. Kongsuphon[5], N. Sankaseam[1], E. Sirachainan[1], P. Witoonpanich[2], A. Kositwattanarerk[2], P. Pattaranutaporn[2]

[1]Medicine, Ramathibodi Hospital, Bangkok, Thailand, [2]Radiology, Ramathibodi Hospital, Bangkok, Thailand, [3]Pathology, Ramathibodi Hospital, Bangkok, Thailand, [4]Traslational Medicine, Ramathibodi Hospital, Bangkok, Thailand, [5]Pharmacy, Ramathibodi Hospital, Bangkok, Thailand

Background: Alterations in CDK4-cyclin D-retinoblastoma (Rb) pathway may lead to carcinogenesis in many cancers. Human Papilloma Virus (HPV) plays a major role in SCCHN carcinogenesis. It induces many alterations in the CDK4-Cyclin D-Rb and apoptotic pathways such as up-regulation of p16, loss of Rb and p53 functions. Loss of p16 expression is known as a poor prognostic marker in SCCHN for survival. A novel therapy for p16/HPV-negative SCCHN is clearly an unmet medical need. Palbococlib is an orally active, highly selective inhibitor of the CDK4/6 with ability to block Rb phosphorylation. In a phase I study of palbociclib and cetuximab in refractory recurrent/metastatic SCCHN, the maximum tolerated dose (MTD) was not reached. In addition, palbociclib showed a radiosensitization property in a preclinical study. Thus, addition of palbociclib to cetuximab and IMRT provides a strong rationale to improve an efficacy for treatment of locally advanced SCCHN, especially in p16/HPV-negative tumor.

Trial design: This is a dose escalation phase I/II study designed to determine the MTD and toxicity of palbociclib, cetuximab, and IMRT for locally advanced SCCHN, using a classical 3 + 3 design. The study included locally advanced SCCHN of oral cavity, oropharynx, larynx, and hypopharynx. Nasopharyngeal carcinoma and other SCCHNs were excluded. Palbociclib has been escalated in 3 dose levels (DLs), starting from 75 mg, and escalated to 100 and 125 mg PO daily for 21 days on and 7 days off for 2 cycles. In all DLs, cetuximab was given at 400 mg/m^2 IV on day -7 and then 250 mg/m^2 IV weekly for 7 weeks. IMRT was delivered 5 days on and 2 days off with a total dose of 70 Gy for 33 fractions. At the MTD or RP2D, we will accrue up to 15 locally advanced p16-negative SCCHN patients to allow for definitive evaluation of tolerability, correlative endpoints and preliminary efficacy. Potential biomarkers involving the CDK4-cyclin D-Rb pathway alterations and HPV status will be explored. To date, a total of 8 patients were accrued in the study. The latest patient was accrued to the DL3 cohort, which is the last dose level.

Clinical trial identification: NCT03024489.

Legal entity responsible for the study: Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Funding: Pfizer.

Disclosure: N. Ngamphaiboon: Research funding: Pfizer, MSD; Advisory board: Roche, MSD, Amgen; Lecture honorarium: Roche, AstraZeneca, Eli Lilly, Eisai, Amgen. N. Jinawath: Advisory Board: Amgen. All other authors have declared no conflicts of interest.

1119TiP Randomized phase II multicenter study comparing modified PFE regimen with modified TPEx regimen in recurrent or metastatic squamous cell carcinoma of the head and neck: TEMPER study

M. Shimokawa[1], M. Suzuki[2], M. Sugasawa[3], K. Shiga[4], T. Satoh[5], H. Inohara[6]

[1]Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Japan, [2]Department of Otorhinolaryngology for Head and Neck Surgery, Osaka University Graduate School of Medicine, Suita, Japan, [3]Department of Head and Neck Surgery, Saitama Medical University International Medical Center, Hidaka, Japan, [4]Department of Head and Neck Surgery, Iwate Medical University School of Medicine, Morioka, Japan, [5]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan, [6]Department of Otorhinolaryngology for Head and Neck Surgery, Osaka University, Osaka, Japan

Background: Recurrent or metastatic squamous cell carcinoma of the head and neck have a poor prognosis. The PFE (Platinum, 5-FU and Cetuximab) regimen is established as the first-line standard therapy in the world, as per a Phase III study conducted in Europe. A phase II study conducted in China suggested that lower dose of cisplatin and 5-FU achieve similar outcome than PFE in an Asian population with an acceptable toxicity profile. In a phase II study, TPEx (Docetaxel, Platinum and Cetuximab) regimen showed favorable overall survival and response rate when indirectly compared to the PFE regimen. Administration of the TPEx regimen in Asian population is likely to be more toxic than in Caucasian patients. Therefore, we considered to compare the modified TPEx regimen and the modified PFE regimen to assess the efficacy and safety of this regimen.

Trial design: TEMPER is open-label, randomized, a multicenter phase II study comparing modified TPEx regimen vs. modified PFE regimen as the first-line treatment with recurrent or metastatic squamous cell carcinoma of the head and neck. Patients will be allocated randomly (1:1) to the two treatment groups with dynamic allocation method. Treatment will be stratified by ECOG PS, p16-positive oropharynx carcinoma and history of chemotherapy. The primary endpoint is progression-free survival. Secondary endpoints are response rate, adverse events and overall survival. A median progression-free survival of 6.0 months is assumed for the modified PFE, and 148 events are deemed necessary to detect a hazard ratio of 0.71 in modified TPEx, with 80% power and a two-sided significance level of 20%. The target sample size is set at 180 patients (90 patients in both groups), allowing for dropouts. Clinical trial information: UMIN000025436. This study is supported by Merck KGaA.

Legal entity responsible for the study: Clinical Research Support Center Kyushu.

Funding: Clinical Research Support Center Kyushu.

Disclosure: M. Shimokawa: Consulting: Sysmex, T. Satoh: Honoraria: Chugai Pharma, Merck Serono, Bristol-Myers Squibb, Takeda, Yakult Honsha, Lilly, Bayer Yakuhin, Ono Pharmaceutical, Merck; Consulting or advisory role: Bayer Yakuhin, Lilly, Ono Pharmaceutical, Takara Bio, Merck Serono; Research funding: Yakult Honsha, Chugai Pharma, Ono Pharmaceutical, Sanofi, Lilly, Daiichi Sankyo, Merck, Merck Serono, Gilead Sciences, Dainihon Sumitomo. H. Inohara: Consulting or advisory role: Merck; Speakers' bureau: Merck, Ono, Eisai, Meiji, TaihoM; Travel expenses: MSD, Nippon Kayaku. All other authors have declared no conflicts of interest.

1120TiP Randomized phase III study in EBV positive locally advanced nasopharyngeal carcinoma treated with concurrent chemo-radiotherapy with or without anti-viral drug

K. Alsaleh[1], A. Elbasmi[2], A. Hussein[1], F. Alshaflan[3], M. El-Sherify[1]

[1]Radiation Oncology Department, Kuwait Cancer Control Centre Al Sabah Hospital, Shuwaikh, Kuwait, [2]Cancer Registry Department, Kuwait Cancer Control Centre Al Sabah Hospital, Shuwaikh, Kuwait, [3]Virology Department, Kuwait Cancer Control Centre Al Sabah Hospital, Shuwaikh, Kuwait

Background: Nasopharyngeal is relatively prevalent in South East Asia and mainland China, northern Africa and Alaska. For advanced disease, there is a greater than 50% risk of recurrence after radiotherapy (RT) alone, and approx. half of all recurrences are distant failures. A meta-analysis of 6 randomized trials showed that addition of chemotherapy (CT) to RT significantly improved disease-free/ progression-free survival rates by 34% to 40% respectively. Epstein-Barr virus (EBV) has yielded significant insight into pathogenesis of NPC. It is undifferentiated form of NPC that shows most consistent worldwide association with EBV suggesting that targeted approaches should be considered for preventive and therapeutic intervention. The prognostic value of pre-treatment EBV DNA viral load for non-endemic areas proved in retrospective study conducted in Italy, disease free survival (DFS) and over all survival (OS) were significantly longer in patients with pre-treatment negative EBV DNA than in positive patients. Antiviral drugs have been used to inhibit EBV replication and target viral DNA polymerase Aim of this study is to define the efficacy of adding anti-viral treatment to eliminate PCR-DNA EBV in patients with NPC. It will also be correlated with the response rate (RR), local control, DFS, and OS.

Trial design: Patients and Methods: All patients with diagnosis of nasopharyngeal squamous cell carcinoma, . Patients should have positive PCR-DNA EBV. Patients will receive concurrent chemoradiotherapy which consisted of Cisplatin 40 mg/m2 weekly or 100mg/m2 every 3 weeks with IMRT 70Gy/35 fractions. Randomization to antiviral therapy acyclovir tablets 800 mg/day during the whole course of treatment Or Placebo. We aim to enroll 100 patients for study with 2:1 randomization. Follow up with PCR-DNA EBV will be done mid-treatment and immediately after treatment then with usual follow up of the NPC cases.

Legal entity responsible for the study: Radiation Oncology Department, Kuwait Cancer Control Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1121TiP KEYNOTE-412: Phase III study of pembrolizumab plus chemoradiation vs chemoradiation alone for locally advanced head and neck squamous cell carcinoma (HNSCC)

J-P. Machiels[1], L. Licitra[2], Y.G. Tao[3], C-J. Yen[4], D. Rischin[5], J.N. Waldron[6], B.A. Burtness[7], V. Gregoire[1], S.S. Agarwala[8], J. Yorio[9], J-P. Delord[10], S. Aksoy[11], S. Ikeda[12], R-L. Hong[13], J.Y. Ge[14], H. Brown[14], B. Bidadi[14], L.L. Siu[6]

[1]Oncology, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [2]Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, University of Milan, Milan, Italy, [3]Oncology, Gustave Roussy, Villejuif, France, [4]Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, [5]Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia, [6]Medical Oncology and Hematology, UHN Princess Margaret Cancer Centre, Toronto, ON, Canada, [7]Medicine, Yale University School of Medicine, New Haven, CT, USA, [8]Oncology, St. Luke's Cancer Center, Bethlehem, PA, USA, [9]Oncology, Texas Oncology–Austin Central, Austin, TX, USA, [10]Oncology, Institut Claudius Régaud, Toulouse, France, [11]Oncology, Hacettepe University, Ankara, Turkey, [12]Oncology, Medical Hospital, Tokyo Medical and Dental University, Tokyo, Japan, [13]Oncology, National Taiwan University Hospital, Taipei, Taiwan, [14]Medical Oncology, Merck & Co, Inc, Kenilworth, NJ, USA

Background: Preclinical data suggest improved tumor growth control and survival when radiation therapy (RT) is combined with a PD-1 inhibitor. Pembrolizumab is effective for treatment of recurrent/metastatic HNSCC, and initial results from a phase 1b study suggest that pembrolizumab plus chemoradiation therapy (CRT) is tolerable in patients with locally advanced (LA) HNSCC. KEYNOTE-412 (NCT03040999) is a phase 3, randomized, placebo-controlled, double-blind trial to determine efficacy and safety of pembrolizumab plus CRT and as maintenance therapy vs placebo plus CRT in LA-HNSCC.

Trial design: Eligibility criteria are age ≥18 years; newly diagnosed, treatment-naive, oropharyngeal p16–positive (any T4 or N3), oropharyngeal p16–negative (any T3-T4 or N2a-N3), or larynx/hypopharynx/oral cavity (any T3-T4 or N2a-N3) SCC; evaluable tumor burden (RECIST v1.1); and ECOG performance status 0/1. Patients will be randomly assigned (1:1) to receive pembrolizumab 200 mg every 3 weeks plus cisplatin-based CRT or placebo plus cisplatin-based CRT. Treatment will be stratified by RT regimen (accelerated RT [56-70 Gy, 6 fractions/week for 6 weeks] or standard RT [56-70 Gy, 5 fractions/week for 7 weeks]), tumor site/p16 status (oropharynx p16 positive vs p16 negative or larynx/hypopharynx/oral cavity), and disease stage (III vs IV). Priming dose of pembrolizumab or placebo will be given 1 week before CRT, followed by 2 doses during CRT, and an additional 14 doses after CRT, for a total of 17 pembrolizumab or placebo infusions. Response will be assessed by MRI and CT 12 weeks after CRT, every 3 months for 3 years, then every 6 months for years 4 and 5. Treatment will be discontinued at time of centrally confirmed disease progression, unacceptable toxicity, or patient/physician decision to withdraw. Patients will be evaluated to determine necessity of neck dissection 12 weeks after completion of CRT. Primary end point is event-free survival and secondary end points are overall survival, safety, and patient-reported outcomes. Biomarkers will be an exploratory end point. Recruitment is ongoing in 21 countries and will continue until ∼780 patients are enrolled.

Clinical trial identification: NCT03040999, trial initiation date: 2/2/17.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Matthew Grzywacz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co, Inc, Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co, Inc.

Funding: Merck & Co, Inc.

Disclosure: J.-P. Machiels: Consultant: Boehringer Ingelheim, Pfizer, Merck, Debiopharm Group, Nanobiotix, Innate Pharma; Research funding: Novartis, Sanofi, Bayer, Janssen. L. Licitra: Consultant: Eisai, Amgen, Boehringer Ingelheim, Debiopharm Group, AstraZeneca, Novartis, Bayer, Merck, Merck Serono, Roche, Bristol-Myers Squibb; Research funding: Eisai, Amgen, Merck Serono, Boehringer Ingelheim, AstraZeneca, Novartis, Roche, Merck. D. Rischin: Research funding: Genentech/Roche, Merck, Amgen, Regeneron, BMS. B.A. Burtness: Consultant: Merck, MedImmune, Boehringer Ingelheim, Amgen, Bayer, Debiopharm Group, VentiRx, AstraZeneca; Research funding: Merck, Advaxis. S. Aksoy: Honararia: Novartis, Roche, Merck, Abdi Ibrahim AS, Astellas Oncology; Consultant: Pfizer, Abdi Ibrahim AS. J.Y. Ge, H. Brown, B. Bidadi: Employment and stock: Merck. L.L. Siu: Consultant: Merck, AstraZeneca, MorphoSys, Symphogen; Research funding: Bristol-Myers Squibb, Genentech/Roche, GlaxoSmithKline, Merck, Novartis, Pfizer, Medimmune, AstraZeneca, Boehringer Ingelheim, Bayer, Amgen, Syhphogen, Astellas Pharma. All other authors have declared no conflicts of interest.

1122TiP Pembrolizumab in patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC): The phase II KEYNOTE-629 study

L.F. Licitra[1], L.L. Siu[2], E.E.W. Cohen[3], P. Zhang[4], B. Gumuscu[4], R. Swaby[4], K. Harrington[5]

[1]Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, University of Milan, Milan, Italy, [2]Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [3]Department of Translational Science, University of California San Diego Health, Moores Cancer Center, La Jolla, CA, USA, [4]Medical Oncology, Merck & Co, Inc, Kenilworth, NJ, USA, [5]Head and Neck/Skin Units, The Institute of Cancer Research, London, UK

Background: There are no approved treatments or standard of care for recurrent or metastatic cSCC. Effectiveness of common therapies for cSCC is limited. Regimens effective for SCC of the head and neck (HNSCC) may also be effective for cSCC. Pembrolizumab is a programmed death 1 (PD-1) inhibitor that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Evidence of pembrolizumab efficacy and safety has been shown in patients with recurrent or metastatic HNSCC in the phase 1b KEYNOTE-012 study. The single-arm, open-label phase 2 KEYNOTE-629 trial will be conducted to evaluate the efficacy and tolerability of pembrolizumab in patients with previously treated recurrent or metastatic cSCC (NCT03284424).

Trial design: Patients will be given pembrolizumab 200 mg every 3 weeks by intravenous infusion, continued for 35 doses (∼2 years) or until disease progression, unacceptable toxicity, intercurrent illness, nonadherence, or investigator or patient decision to withdraw. Radiographic imaging will be performed every 6 weeks for year 1 and every 9 weeks thereafter. Adverse events will be monitored and graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Key inclusion criteria are age ≥18 years; histologically confirmed cSCC as the primary site of malignancy; metastatic disease or locally recurrent disease not curable by surgery or radiation; measurable disease per RECIST v1.1; and Eastern Cooperative Oncology Group performance status 0/1. There is no requirement for prior chemotherapy or biological systemic treatment for incurably recurrent/metastatic disease. Primary end point is objective response rate per RECIST v1.1 assessed by blinded independent central review. Secondary end points are duration of response, disease control rate (complete or partial response or stable disease for ≥12 weeks), progression-free survival per RECIST v1.1, overall survival, safety, and tolerability. Pharmacokinetics, biomarkers, and health-related quality of life will be evaluated as exploratory end points. Recruitment is ongoing in 10 countries and will continue until 100 patients are enrolled.

Clinical trial identification: NCT03284424. Trial initiated September 15, 2017.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Matthew Grzywacz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co, Inc, Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co, Inc.

Funding: Merck & Co, Inc.

Disclosure: L.F. Licitra: Consultant: Eisai, Amgen, Boehringer Ingelheim, Debiopharm Gropu, AstraZeneca, Sobi, Novartis, Bayer, Merck, Merck Serono, Roche, BMS; Research funding: Eisai, Amgen, Merck Serono, Boehringer Ingelheim, AstraZeneca, Novartis, Roche, Merck. L.L. Siu: Consultant: Merck, AstraZeneca/Medimmune, MorphoSys, Symphogen; Research funding: BMS, Genentech/Roche, GlaxoSmithKline, Merck, Novartis, Pfizer, Medimmune, AstraZeneca, Boehringer Ingelheim, Bayer, Amgen, Symphogen, Astellas. E.E.W. Cohen: Consultant: Merck, BMS, AstraZeneca, Human Longevity, Inc, Pfizer, EMD Serono. P. Zhang:

Employment and travel: Merck, B. Gumuscu, R. Swaby: Employment and stock: Merck. K. Harrington: Honoraria, Consultant, Speakers Bureau: Amgen, AstraZeneca, Merck, Merck Sharp & Dohme, Pfizer, BMS; Research funding: AstraZeneca, Merck; Travel: Merck Sharp & Dohme.

1123TiP A randomized phase II study of cisplatin plus radiotherapy versus durvalumab plus radiotherapy followed by adjuvant durvalumab versus durvalumab plus radiotherapy followed by adjuvant tremelimumab and durvalumab in intermediate risk, HPV-positive, locoregionally advanced oropharyngeal squamous cell cancer (LA-OSCC) (Canadian Cancer Trials Group HN.9)

A. Spreafico[1], K. Sultanem[2], B. Chen[3], S.V. Bratman[4], J. Ringash[4], A.V. Louie[5], A. McNiven[4], K. Whelan[3], J. Hilton[6], J. Yoo[7], J-P. Machiels[8], L.F. Licitra[9], S. Oosting[10], J.N. Waldron[11], L.L. Siu[11], W.R. Parulekar[12]

[1]Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, ON, Canada, [2]Radiation Oncology, The Jewish General Hospital, Montreal, Montreal, QC, Canada, [3]HN, Canadian Cancer Trial Group, Kingston, ON Canada, Kingston, ON, Canada, [4]Radiation Oncology, Princess Margaret Cancer Center, Toronto, ON, Canada, [5]Radiation Oncology, London Health Science Centre, London, ON, Canada, [6]Medical Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, ON, Canada, [7]Surgical Oncology, London Health Science Centre, London, ON, Canada, [8]Oncology, Cliniques Universitaires St. Luc, Brussels, Belgium, [9]Head and Neck Medical Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [10]Medical Oncology, University Hospital Groningen (UMCG), Groningen, Netherlands, [11]Medical Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [12]Oncology and Medicine, Canadian Cancer Trial Group, Kingston, ON Canada, Kingston, ON, Canada

Background: Definitive cisplatin-based chemoradiotherapy (CRT) in patients (pts) with locoregionally advanced head and neck SCC is associated with acute and long-term toxicities. Immune checkpoint inhibitors, such as anti-PD1/L1 and anti-CTLA4 antibodies, are actively being investigated in this disease setting. HN.9 evaluates a chemosparing approach in pts with HPV+ intermediate risk LA-OSCC (defined by AJCC 8th edition as: T1-2N1 smokers; T3N0-N1 smokers and T1-3N2 any smoking history).

Trial design: CCTG HN.9 is a non-comparative, randomized phase II study in intermediate risk HPV+ LA-OSCC. Pts will be randomized at a 1:1:1 ratio to: CRT (arm A); immunoradiotherapy (IRT) with durvalumab (durva) followed by durva maintenance (Arm B); IRT followed by durva and tremelimumab (treme) maintenance (Arm C). Treatment schedule: 70 Gy/35 over 7 weeks (RT) + cisplatin 100mg/m2 d1, 22, 43 (Arm A); RT + durva 1500 mg d-7, 22 (IRT) followed by Q4W for 6 doses (Arm B); IRT followed by durva Q4W for 6 doses + treme Q4W for 4 doses (Arm C). Key eligibility criteria: intermediate risk HPV+ LA-OSCC; adequate organ function; no autoimmune disorders; no immunosuppressive therapy. Pts will be stratified by smoking status, age, ECOG PS and TNM classification. The primary objective is to estimate the efficacy of the 3 treatment arms in terms of event-free survival (EFS). Secondary objectives: overall survival; locoregional control; distant metastasis-free survival; quality of life and swallowing assessments; economic evaluation. Correlative studies include: immunophenotyping, radiomic, ctDNA, microbiome analyses. The planned sample size is 240 pts over 2.5 years with 3 years follow-up. Assuming the new treatment will improve 3-years EFS from 83 to 91%, with one-sided type I error of 0.1, 80 pts/arm, the study will have 80% of power to reject the null hypothesis (3-year EFS rate is 83% or lower). Study activation: April 2018.

Clinical trial identification: NCT03410615.

Editorial acknowledgement: Supported by AstraZeneca.

Legal entity responsible for the study: Canadian Cancer Trial Group.

Funding: AstraZeneca.

Disclosure: A. Spreafico: Advisory Board: Novartis, BMS, Merck; Research support (to institution): AstraZeneca/MedImmune. K. Sultanem, S.V. Bratman, J. Hilton, J.N. Waldron: Research support (to institution): AstraZeneca/MedImmune. J-P. Machiels: Advisory board member: MSD (uncompensated), Debio, Nanobiotix, Innate. S. Oosting: Research grants (to institution): Novartis, Pfizer, Celldex. L.L. Siu: Consultant: AstraZeneca/MedImmune; Research support (to UHN): AstraZeneca/MedImmune. W.R. Parulekar: Advisory board fees: Pfizer. All other authors have declared no conflicts of interest.

1124TiP Randomized, phase II study of ficlatuzumab with or without cetuximab in patients (pts) with cetuximab-resistant, recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)

J.E. Bauman

Medicine, University of Arizona Cancer Center, Tucson, AZ, USA

Background: Cetuximab, an anti-EGFR monoclonal antibody (mAb), is approved for R/M HNSCC but only a minority benefits. c-Met and EGFR signaling converge at the PI3K/Akt and MAPK nodes. Preclinical evidence shows that c-Met can drive tumor-intrinsic resistance to EGFR inhibition. Ficlatuzumab is an IgG1 mAb against HGF, the sole ligand for cMet. We recently completed a phase Ib study evaluating ficlatuzumab and cetuximab in pts with cetuximab-resistant, R/M HNSCC (Bauman JE et al, ASCO 2017). Twelve pts were treated; 11 were platinum-refractory. Grade 3 adverse events included edema, hypoalbuminemia, infection, and thromboembolism. No DLTs were seen. Median progression-free survival (PFS) at the recommended phase II dose (RP2D) was 6.0 mos (90% CI = 2 mos – not reached). Confirmed overall response rate (ORR) was 17% (90% CI = 0-28%). Clinical benefit rate was 67%. Serum Veristrat, a proteomic classifier predictive of differential treatment benefit from anti-EGFR therapy, did not correlate with PFS. We designed a randomized phase II trial evaluating ficlatuzumab with or without cetuximab in patients with cetuximab-resistant, R/M HNSCC. The combination arm follows the hypothesis that continued anti-EGFR blockade may overcome reciprocal compensation between the EGFR and cMet pathways.

Trial design: This is a multicenter phase II trial with a randomized, non-comparative, 2-arm design (Arm A: ficlatuzumab and Arm B: ficlatuzumab + cetuximab) in pts with R/M HNSCC after failure of cetuximab. Key eligibility criteria include: R/M HNSCC; cetuximab resistance (recurrence during or within 6 mos of cetuximab-radiation or palliative cetuximab); ECOG 0-1; mandatory baseline research biopsy. The primary objective is to assess the efficacy of ficlatuzumab, with or without cetuximab, as measured by PFS. To test the hypothesis that either regimen improves historical PFS from 2 months to 3.33 months requires 66 eligible patients. Key secondary endpoints are ORR and survival. Biomarkers to be correlated with efficacy include tumor HGF/cMet dimers, phosphoproteins, and immunoscores and serum Veristrat. Two of 66 patients have enrolled.

Legal entity responsible for the study: University of Arizona Cancer Center.

Funding: University of Arizona Cancer Center; Aveo.

Disclosure: The author has declared no conflicts of interest.

1126TiP Nivolumab and ipilimumab in combination with radiotherapy in patients with locally advanced head and neck cancer

J.M. Johnson[1], V. Bar Ad[2], E. Lorber[1], A. Luginbuhl[3], J.M. Curry[3], D. Cognetti[3], S. Keith[4], R. Axelrod[1], R. Zinner[1], U. Rodeck[5], L.A. Harshyne[6], A. Argiris[7]

[1]Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA, USA, [2]Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA, USA, [3]Department of Otolaryngology, Thomas Jefferson University, Philadelphia, PA, USA, [4]Department of Pharmacology & Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA, USA, [5]Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA, USA, [6]Department of Neurosurgery, Thomas Jefferson University, Philadelphia, PA, USA, [7]Medical Oncology, Hygeia Hospital, Athens, Greece

Background: Definitive treatment of locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) often incorporates concurrent chemoradiotherapy. Platinum agents have been the backbone of systemic therapy in combined modality approaches. However, the addition of cisplatin to radiotherapy (RT) results in a modest survival benefit and is associated with multiple acute and late toxicities. The study of alternative approaches is warranted. Nivolumab (nivo), a fully human anti-programmed cell death-1 (PD-1) monoclonal antibody (mAb), has demonstrated a survival advantage when compared with standard treatment in patients with platinum-refractory recurrent or metastatic SCCHN. Combination of nivo with the CTLA-4 directed mAb ipilimumab (ipi) has yielded improvements in antitumor activity in melanoma and is under investigation in multiple other solid tumor types including SCCHN. Similarly, the combination of RT and immunotherapy leads to synergistic effects in the laboratory and has promise in early phase clinical trials. This clinical trial combines immunotherapy and RT to build upon these observations.

Trial design: This is a single arm pilot trial that enrolls previously untreated patients with LA SCCHN who are candidates for curative intent, including stage IVA-B tumors of the oral cavity, oropharynx, hypopharynx, and larynx. HPV+ oropharyngeal tumors must be staged as T4, or N2c or N3 by AJCC 7th edition. Nivo and ipi are initiated 2 weeks prior to the beginning of RT. Nivo 3 mg/kg is administered every 2 weeks IV for a total of 17 doses and ipi 1 mg/kg is administered every 6 weeks for a total of 6 doses. RT (using IMRT) is prescribed as 2 Gy/fraction/day to a total dose of 70 Gy. The primary objective is the safety of the combination of nivo and ipi with RT with a focus on in-field toxicities (mucositis, dermatitis, edema, bleeding) with secondary endpoints of 1-year PFS, ORR, and OS. Exploratory correlative studies include tumor PD-L1 expression, tumor immune bias via the Th1/Th2 ratio, and exosome quantity and composition. The sample size is 24 patients following a two-stage design with 12 patients enrolled in the first stage and 12 more in the expansion cohort. Enrollment began in May 2017 and is ongoing.

Clinical trial identification: NCT03162731.

Legal entity responsible for the study: Thomas Jefferson University - Sidney Kimmel Cancer Center.

Funding: Bristol Myers Squibb.

Disclosure: J.M. Johnson: Pharmaceutical-sponsored investigator-initiated clinical trials funds: Bristol-Myers Squibb, AstraZeneca, Merck; Consultative services: Foundation Medicine. A. Luginbuhl, D. Cognetti, A. Argiris: Pharmaceutical sponsored investigator-initiated clinical trials funds: Bristol-Myers Squibb. J.M. Curry: Pharmaceutical-sponsored investigator-initiated clinical trials funds: AstraZeneca. All other authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii400–viii441, 2018
doi:10.1093/annonc/mdy288

IMMUNOTHERAPY OF CANCER

1127O A personal neoantigen vaccine, NEO-PV-01, with anti-PD1 induces broad de novo anti-tumor immunity in patients with metastatic melanoma, NSCLC, and bladder cancer

P.A. Ott[1], R. Govindan[2], A. Naing[3], T.W. Friedlander[4], K. Margolin[5], J.J. Lin[6], N. Bhardwaj[7], M.D. Hellman[8], L. Srinivasan[9], J. Greshock[9], M. Moles[9], R.B. Gaynor[9], M.J. Goldstein[9], S. Hu-Lieskovan[10]

[1]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [2]Internal Medicine, Division of Oncology, Washington University in St. Louis, St. Louis, MO, USA, [3]Division of Oncology, MD Anderson Cancer Center, Houston, TX, USA, [4]Department of Medicine, UCSF, San Francisco, CA, USA, [5]Medical Oncology, City of Hope National Medical Center, Duarte, CA, USA, [6]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA, [7]Department of Medicine, Mt. Sinai School of Medicine, New York, NY, USA, [8]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [9]Research & Development, Neon Therapeutics, Inc., Cambridge, MA, USA, [10]Medical Oncology, UCLA/JCCC, Los Angeles, CA, USA

1128O Pre-specified interim analysis of a randomized phase IIb trial of trastuzumab + nelipeptimut-S (NeuVax) vs trastuzumab for the prevention of recurrence demonstrates benefit in triple negative (HER2 low-expressing) breast cancer patients

D.F. Hale[1], E.A. Mittendorf[2], T.A. Brown[1], G.T. Clifton[1], T.J. Vreeland[2], J. Myers[1], K. Peace[1], D. Jackson[1], J. Greene[1], J. Holmes[3], G.E. Peoples[4]

[1]General Surgery, San Antonio Military Medical Center, Fort Sam Houston, TX, USA, [2]Surgical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [3]Medical Oncology, Naval Medical Center San Diego, San Diego, CA, USA, [4]Metis Foundation, CVDP, San Antonio, TX, USA

1129O Stage 2 enrollment complete: Sitravatinib in combination with nivolumab in NSCLC patients progressing on prior checkpoint inhibitor therapy

T.A. Leal[1], A.I. Spira[2], C. Blakely[3], K. He[4], D. Berz[5], D. Richards[6], J. Uyeki[7], A. Savage[8], T. Roque[9], E. Massarelli[10], R.M. Jotte[11], I. Chen[12], J. Christensen[13], P. Olson[13], V. Tassell[14], L. Horn[15]

[1]Medical Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA, [2]Virginia Cancer Specialists, Fairfax, VA, USA, [3]Thoracic Medical Oncology, University of California San Francisco, San Francisco, CA, USA, [4]Research, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA, [5]Research, Beverly Hills Cancer Center, Beverly Hill, CA, USA, [6]Research, Texas Oncology P.A., Houston, TX, USA, [7]Research, Texas Oncology - Austin Midtown, Austin, TX, USA, [8]Research, Hematology Oncology Associates - Barnett Office, Medford, MA, USA, [9]Research, USO, Sherman, TX, USA, [10]Medical Oncology, City of Hope, Duarte, CA, USA, [11]Medical Oncology / Hematology, Rocky Mountain Cancer Centers, Denver, CO, USA, [12]Clinical Development, Mir, San Diego, CA, USA, [13]Translational Research, Mirati Therapeutics, Inc., San Diego, CA, USA, [14]Clinical Development, Mirati Therapeutics, Inc., San Diego, CA, USA, [15]Research, Vanderbilt Ingram Cancer Center, Nashville, TN, USA

1130O **Responses and durability of clinical benefit in renal cell carcinoma treated with pegilodecakin in combination with anti-PD-1 inhibitors**

N.M. Tannir[1], A. Naing[2], K.P. Papadopoulos[3], D.J. Wong[4], W.M. Korn[5], R. Aljumaily[6], K.A. Autio[7], S. Pant[2], T.M. Bauer[8], A. Drakaki[4], N. Daver[9], A. Hung[10], M. Oft[11], J. Leveque[12]

[1]Genitourinary Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [2]Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA, [3]Clinical Research, START Center for Cancer Care, San Antonio, TX, USA, [4]Medicine, University of California Los Angeles (UCLA), Los Angeles, CA, USA, [5]Medicine, University of California San Francisco (UCSF), San Francisco, CA, USA, [6]Hematology/Oncology, OUHSC, Oklahoma City, OK, USA, [7]Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [8]Medical Oncology, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [9]Leukemia, MD Anderson Cancer Center, Houston, TX, USA, [10]Biostatistics, ARMO BioSciences, Redwood City, CA, USA, [11]Pre-Clinical and Clinical Development, ARMO BioSciences, Redwood City, CA, USA, [12]Scientific Affairs, ARMO BioSciences, Redwood City, CA, USA

1131PD **Preliminary results of phase I/II study of SENL-B19 chimeric antigen receptor T cell therapy in pediatric and adult patients with relapsed/refractory acute lymphoblastic leukemia (r/r-ALL)**

F. Ma[1], J. Li[2], J. Ren[3], X. Zhang[3], F. Wang[3], X. Guo[3], J. Zhang[3], D. Wang[4], Q. Liu[5], J. Luo[3]

[1]Pediatrics, The Second Hospital of Hebei Medical University, Shijiazhuang, China, [2]R&D, Hebei Senlang Biotech. Co Ltd, Shijiazhuang, China, [3]Hematology, The Second Hospital of Hebei Medical University, Shijiazhuang, China, [4]Hematology, Harrison International Peace Hospital, Hengshui, China, [5]Hematology, The First Hospital of Hebei Medical University, Shijiazhuang, China

1132PD **Clinical efficacy of T-cell therapy after short-term BRAF-inhibitor induction in checkpoint inhibitor resistant metastatic melanoma patients**

T.H. Borch[1], R. Andersen[1], M.A.H. Rana[1], P. Kongsted[1], M. Pedersen[1], M. Nielsen[1], J.W. Kjeldsen[1], A. Kverneland[1], C.L. Lorentzen[1]Ø., Met[1], M. Donia[2], I.M. Svane[1]

[1]Center for Cancer Immunotherapy and Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [2]Center for Cancer Immune Therapy and Department of Oncology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark

1133PD **A phase IIa trial to assess the safety and efficacy of BL-8040 and pembrolizumab in patients with metastatic pancreatic adenocarcinoma (PDAC)**

M. Hidalgo[1], R. Epelbaum[2], B.M. Wolpin[3], S.M. Stemmer[4], R. Geva[5], T. Golan[6], E. Borazanci[7], M. Borad[8], K.S. Pedersen[9], J.O. Park[10], R. Ramirez[11], A. Peled[12], T.M. Lustig[13], O. Bohana Kashtan[14], O. Rosenfeld[13], E. Sorani[14], K. Schlienger[15], A. Vainstein Haras[13], D.D. Von Hoff[7]

[1]Division of Hematology Oncology, Beth Israel Deaconess Med. Center, Boston, MA, USA, [2]Oncology, Rambam Health Care Center, Haifa, Israel, [3]Gastrointestinal Cancer Center, Dana Farber Cancer Institute, Boston, MA, USA, [4]Oncology, Rabin Medical Center Davidoff Cancer Centre, Beilinson Campus, Petah Tikva, Israel, [5]Oncology, Tel Aviv Sourasky Medical Center-(Ichilov), Tel Aviv, Israel, [6]Oncology, Chaim Sheba Medical Center, Ramat Gan, Israel, [7]Oncology, Honor Health/TGen, Scottsdale, AZ, USA, [8]Oncology, Mayo Clinic Cancer Center, Scottsdale, AZ, USA, [9]Oncology, Washington University School of Medicine, St Louis, MO, USA, [10]Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [11]Oncology, Ochsner Medical Centre, Jefferson, LA, USA, [12]Goldyne Savad Institute of Gene Therapy, Hebrew University of Jerusalem, Jerusalem, Israel, [13]Clinical, BioLineRx Ltd, Modi'in, Israel, [14]Research and Development, BioLineRx Ltd, Modi'in, Israel, [15]Early Development Oncology, Merck & Co, Rahway, NJ, USA

1134PD **A phase Ia/IIb trial of the CXCR4 inhibitor X4P-001 and nivolumab for advanced renal cell carcinoma (RCC) that is unresponsive to nivolumab monotherapy**

T.K. Choueiri[1], M.B. Atkins[2], T.L. Rose[3], R.S. Alter[4], E. Tsiroyannis[5], K. Niland[5], Y. Wang[5], S. Parasuraman[5], L. Gan[5], D.F. McDermott[6]

[1]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [2]Medical Oncology, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA, [3]Hematology and Oncology, University of North Carolina School of Medicine, Chapel Hill, NC, USA, [4]Internal Medicine, The John Theurer Cancer Center, Hackensack, NJ, USA, [5]Oncology, X4 Pharmaceuticals, Cambridge, MA, USA, [6]Heme/Onc, Beth Israel Deaconess Med. Center, Boston, MA, USA

1135PD **Characterization of the immune tumor microenvironment (TME) to inform personalized medicine with immuno-oncology (IO) combinations**

J.J. Luke[1], R. Edwards[2], C. Hedvat[2], D. Pandya[2], S. Ely[2], R. Meier[2], D. McDonald[2], C.T. Harbison[2], V. Baxi[2], G. Lee[2], P. Szabo[2], T. Garcia[3], R. Bao[3], T.P. Reilly[2], E. Jaffee[4], F.S. Hodi[5]

[1]Department of Medicine, The University of Chicago Medical Center, Chicago, IL, USA, [2]Immuno-Oncology, Bristol-Myers Squibb, Princeton, NJ, USA, [3]Center for Research Informatics, The University of Chicago Medical Center, Chicago, IL, USA, [4]Department of Medical Oncology, The Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy, Baltimore, MD, USA, [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

1136PD **Discrepancy of tumor neoantigen burden between primary lesions and matched metastases in lung cancer**

T. Jiang, C. Zhou

Medical Oncology, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China

1137PD **Identification of adenosine pathway genes associated with response to therapy with the adenosine receptor antagonist CPI-444**

S. Willingham[1], A.N. Hotson[1], G. Laport[2], L. Kwei[2], L. Fong[3], M. Sznol[4], J. Powderly[5], R. Miller[6]

[1]Translational Research, Corvus Pharmaceuticals, Burlingame, CA, USA, [2]Clinical Research, Corvus Pharmaceuticals, Burlingame, CA, USA, [3]Oncology, University of California, San Francisco, San Francisco, CA, USA, [4]Medical Oncology, Yale University School of Medicine Medical Oncology, New Haven, CT, USA, [5]Carolina Biooncology Cancer Therapy, Huntersville, NC, USA, [6]Corvus Pharmaceuticals, Burlingame, CA, USA

1138PD **First in human study with GSK3359609 [GSK609], inducible T cell co-stimulator (ICOS) receptor agonist in patients [Pts] with advanced, solid tumors: Preliminary results from INDUCE-1**

A. Hansen[1], T.M. Bauer[2], V. Moreno[3], M. Maio[4], S. Groenland[5], J. Martin-Liberal[6], H. Gan[7], D. Rischin[8], M. Millward[9], A.J. Olszanski[10], D.C. Cho[11], E. Paul[12], M. Ballas[13], C. Ellis[13], H. Zhou[14], S. Yadavilli[13], J. Sadik Shaik[15], E.V. Schmidt[16], A. Hoos[13], E. Angevin[17]

[1]Division of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, ON, Canada, [2]Oncology, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [3]Medical Oncology-Start Madrid-FJD, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [4]Division of Medical Oncology and Immunotherapy, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy, [5]Medical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands, [6]Oncology, Vall dHebron Institute of Oncology (VHIO) - Cellex Center, Barcelona, Spain, [7]Cancer Clinical Trial Centre, (Austin Health) Austin Hospital, Melbourne, Australia, [8]Department of Medical Oncology, Peter MacCallum Cancer Centre, and the University of Melbourne, Melbourne, Australia, [9]Linear Cancer Research, Sir Charles Gairdner Hospital, Nedlands, Australia, [10]Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [11]Department of Medicine, New York University Langone Medical Center, New York, NY, USA, [12]Oncology, R&D, GlaxoSmithKline, Research Triangle Park, NC, USA, [13]Oncology, R&D, GlaxoSmithKline, Collegeville, PA, USA, [14]QSci, Clinical Statistics, GlaxoSmithKline, Collegeville, PA, USA, [15]Clinical Pharmacology, GlaxoSmithKline, Collegeville, PA, USA, [16]Early Oncology, Clinical Development, Merck & Co Inc, North Wales, PA, USA, [17]Drug Development Department, Département d'Innovation Thérapeutique et des Essais Précoces, Gustave Roussy Institut de Cancérologie, Villejuif, France

1139PD **Novel small-molecule RORγ agonist immuno-oncology agent LYC-55716: Safety and efficacy in a phase IIA open-label, multicenter trial**

J. Wang[1], S.V. Liu[2], H.E. Uronis[3], C. Wu[4], D. Mahalingam[5], A. Spira[6], L. Carter[7], X. Hu[7], G. Weems[8], H.J. Wilkins[8], L.R. Duska[9], K. Kelly[10]

[1]Drug Development Unit, Sarah Cannon Research Institute at Florida Cancer Specialists, Sarasota, FL, USA, [2]Department of Medicine, Georgetown University Medical Center, Washington, DC, USA, [3]Department of Medicine, Duke University Medical Center, Durham, NC, USA, [4]Department of Hematology and Medical Oncology, Emory University, Atlanta, GA, USA, [5]Department of Medicine, Northwestern University, Chicago, IL, USA, [6]Medical Oncology, Virginia Cancer Specialists Research Institute, Fairfax, VA, USA, [7]Biology, Lycera Corp., Ann Arbor, MI, USA, [8]Clinical Development, Lycera Corp., Plymouth Meeting, PA, USA, [9]Department of Obstetrics and Gynecology, University of Virginia Health System, Charlottesville, VA, USA, [10]Hematology Oncology, University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA

1140PD **Phase I study of KN035, a novel fusion Anti-PD-L1 antibody administered subcutaneously in patients with advanced solid tumors in the USA**

K.P. Papadopoulos[1], W. Harb[2], N. Lu[3], X. Ma[4], Y. He[3], L. Yuan[4], M. Fu[5], Y. Lin[6], W. Xu[7], X. Wang[8], P. Wang[9], T. Xu[10], R. Dong[4], J. Gong[11]

[1]Clinical Research Department, South Texas Accelerated Research Therapeutics (START), San Antonio, TX, USA, [2]Horizon Oncology Research, LLC., Horizon BioAdvance, Lafayette, IN, USA, [3]Clinical Operation Department, 3D Medicines Co., Ltd., Beijing, China, [4]Medical Affairs Department, 3D Medicines Co., Ltd., Shanghai, China, [5]Clinical Operation Department, 3D Medicines Co., Ltd., Potomac, MD, USA, [6]Preclinical Research Department, 3D Medicines Co., Ltd., Shanghai, China, [7]Research & Development, 3D Medicines Co., Ltd., Beijing, China, [8]Department of Early Discovery, Suzhou Alphamab Co., Ltd., Suzhou, China, [9]Department of Pharmacology, Suzhou Alphamab Co., Ltd., Suzhou, China, [10]Suzhou Alphamab Co., Ltd., Suzhou, China, [11]3D Medicines Co., Ltd., Shanghai, China

1141PD **Association between immune-related adverse events and efficacy in patients treated with anti-PD-(L)1**

M. Kfoury[1], A-L. Voisin[2], M. Najean[3], S. Champiat[1], S. Laghouati[2], J-M. Michot[1], C. Robert[4], C. Mateus[4], L. Albiges[5], B. Besse[5], C. Massard[1], M. Texier[3], O. Lambotte[6], A. Marabelle[1]

[1]Drug Development Department, Institut Gustave Roussy, Villejuif, France, [2]Pharmacovigilance Unit, Institut Gustave Roussy, Villejuif, France, [3]Department of Biostatistics and Epidemiology, Institut Gustave Roussy, Villejuif, France, [4]Department of Dermatology, Institut Gustave Roussy, Villejuif, France, [5]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France, [6]Department of Internal Medicine and Clinical Immunology, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

1142PD Efficacy of immune checkpoint inhibitors in lung sarcomatoid carcinoma: Data from a French multicentric cohort

C. Domblides[1], I. Monnet[2], J. Mazieres[3], F. Barlesi[4], V. Gounant[5], S. Baldacci[6], B. Mennecier[7], A.C. Toffart[8], C. Audigier Valette[9], L. Doucet[10], E. Giroux-Leprieur[11], F. Guisier[12], O. Molinier[13], M. Perol[14], E. Pichon[15], G. Robinet[16], D. Templement Grangerat[17], A-M. Ruppert[1], M. Wislez[1]

[1]Pneumology, APHP, CancerEst, Tenon University Hospital, Paris, France, [2]Pneumology, CH Intercommunal de Créteil, Créteil, France, [3]Thoracic Oncology, Hospital Larrey, Toulouse, France, [4]Oncology Department, Aix-Marseille University - Faculté de Médecine Nord, Marseille, France, [5]Pneumology, Hopital Bichat Claude Bernard, Paris, France, [6]Haut de France, Hopital Calmette, CHRU Lille, Lille, France, [7]Pathologie Respiratoire, C.H.U. Strasbourg-Nouvel Hopital Civil, Strasbourg, France, [8]Pneumology, CHU de Grenoble, La Tronche, France, [9]Pneumology, Hospital Sainte Musse, Toulon, France, [10]Oncology, Hôpital St. Louis, Paris, France, [11]Pneumology, Hopital Ambroise Pare, Boulogne-Billancourt, France, [12]Pneumology, CHU Hôpitaux de Rouen-Charles Nicolle, Rouen, France, [13]Pneumology, Centre Hospitalier Du Mans, Le Mans, France, [14]Pneumology, Centre Léon Bérard, Lyon, France, [15]Pneumology, CHRU Bretonneau, Tours, France, [16]Pneumology, C.H.U. Brest - Hôpital Morvan, Brest, France, [17]Pneumology, Le Centre Hospitalier Annecy Genevois, Metz-Tessy, France

1143P Responses and durability of clinical benefit in pancreatic ductal adenocarcinoma (PDAC) patients treated with pegilodecakin (AM0010) in combination with 5-FU/LV and oxaliplatin (FOLFOX)

J.R. Hecht[1], A. Naing[2], G.S. Falchook[3], M.R. Patel[4], R. Aljumaily[5], D.J. Wong[6], K.A. Autio[7], Z.A. Wainberg[6], M. Javle[8], J. Bendell[9], S. Pant[10], A. Hung[11], M. Oft[12], J. Leveque[13], K.P. Papadopoulos[14]

[1]Clinical Medicine, David Geffen School of Medicine at UCLA, Santa Monica, CA, USA, [2]Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Drug Development, Sarah Cannon Research Institute at HealthONE, Denver, CO, USA, [4]Clinical Trials/Drug Development, Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL, USA, [5]Medicine, Division of Hematology/Oncology, Oklahoma University, Oklahoma City, OK, USA, [6]Medicine, Division of Hematology/Oncology, David Geffen School of Medicine at UCLA, Santa Monica, CA, USA, [7]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [8]Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [9]GI Oncology Research, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [10]Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA, [11]Biostatistics, ARMO BioSciences, Redwood City, CA, USA, [12]Pre-Clinical and Clinical Development, ARMO BioSciences, Redwood City, CA, USA, [13]Scientific Affiars, ARMO BioSciences, Redwood City, CA, USA, [14]Clinical Research, START Center for Cancer Care, San Antonio, TX, USA

Background: Therapeutic options for second line metastatic pancreatic ductal adenocarcinoma (PDAC) are limited with FOLFOX or FOLFIRI having mOS of 5-6 months. PDAC has low tumor mutational burden and tumor infiltrating CD8+ T cells are rare, which may explain why immune-oncology approaches to date have been less than promising. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also up-regulates IFNγ and the expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden and promotes immunosurveillance by expanding effector memory T cells (Mumm et al. 2010, 2011). Finally, pegilodecakin reduces tumor inflammatory processes such as angiogenesis and and metastatic dissemination (Oft 2017), the off-target auto-immune side effects of immunotherapy and the inflammatory-related side effects of some chemotherapies, including FOLFOX-induced peripheral neuropathy (Krukowski JNeurosci 2016).

Methods: In a 353 patient phase 1/1b dose escalation and expansion study conducted in the US from 2013 to 2017, 21 heavily pretreated metastatic PDAC subjects received pegilodecakin in combination with FOLFOX. Responses were assessed by irRC. CD8 T cell activity was determined by IHC and TCR clonality in the blood.

Results:

Table: 1143P

Pegilodecakin Regimen	N E (ITT)[2]	Prior Therapies Median (Range)	ORR (%)	CR (%)	DCR (%)	mPFS (mos)	mOS (mos)[3]	One-Year OS (%)	Two-Year OS (%)
Plus FOLFOX[1]	19 (21)	2 (1-5)	15.8	10.5	73.7	2.6	10.2	42.9	28.6

[1]Pegilodecakin 5.0 μg/kg + FOLFOX;

[2]E (evaluable - baseline tumor assessment + >1 post-baseline assessments, and no major protocol deviations); ITT (intent to treat); All treated/safety population: n = 25; 25 pts were treated with pegilodecakin (5 ug/kg) in combination with FOLFOX. 21 out of 25 pts progressed on prior gemcitabine containing regimen and did not receive prior platinum containing therapy.

[3]Subjects with OS > 8 mos had 75-250 CD8+ T cells/mm^2 in the retreatment tumor and had a clonal expansion of new T cell clones in the blood. Data cut on 05.01.18; Median follow-up 26.4 months (22.0-32.0 months).

Grade 3/4 TrAEs included thromobocytopenia (56%), anemia (44%), neutropenia (36%), leukopenia (12%) and fatigue (12%). Grade 1/2 neuropathy was observed in 16% of patients but no grade 3/4 neuropathy.

Conclusions: Pegilodecakin in combination with FOLFOX is well-tolerated in patients with metastatic PDAC, and has a reduced incidence of FOLFOX related neuropathy. Immune activation and overall survival are encouraging in this advanced PDAC population.

Clinical trial identification: NCT02009449.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: A. Hung, M. Oft, J. Leveque: Employee: ARMO BioSciences. All other authors have declared no conflicts of interest.

1144P Responses and durability of clinical benefit in non-small cell lung cancer treated with pegilodecakin in combination with anti-PD-1 inhibitors

E.B. Garon[1], D.J. Wong[1], J.G. Schneider[2], R. Aljumaily[3], W.M. Korn[4], M.R. Patel[5], K.A. Autio[6], K.P. Papadopoulos[7], A. Naing[8], N. Gabrail[9], P.N. Munster[10], J. Goldman[1], A. Hung[11], M. Oft[12], J. Leveque[13], D.R. Spigel[14]

[1]Medicine, Division of Hematology/Oncology, University of California Los Angeles (UCLA), Los Angeles, CA, USA, [2]Hematology/Oncology, Winthrop University Hospital, Mineola, NY, USA, [3]Oncology, OUHSC, Oklahoma City, OK, USA, [4]Medicine, Gastroenterology and Medical Oncology, University of California San Francisco (UCSF), San Francisco, CA, USA, [5]Oncology, Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL, USA, [6]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [7]Clinical Research, START Center for Cancer Care, San Antonio, TX, USA, [8]Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA, [9]Gabrail Cancer Center, Canton, OH, USA, [10]Medicine, University of California San Francisco (UCSF), San Francisco, CA, USA, [11]Biostatistics, ARMO BioSciences, Redwood City, CA, USA, [12]Pre-Clinical and Clinical Development, ARMO BioSciences, Redwood City, CA, USA, [13]Scientific Affairs, ARMO BioSciences, Redwood City, CA, USA, [14]Medical Oncology, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

Background: Responses in NSCLC to agents targeting the PD-1/PD-L1 axis are correlated with PD-L1 expression by immunohistochemistry (IHC), tumor mutational burden (TMB), interferon associated mRNA Expression Profile (GEP) and the absence of liver metastases. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also up-regulates IFNγ and the expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden and promotes immunosurveillance by expanding effector memory T cells (Mumm et al. 2010, 2011). Finally, pegilodecakin reduces tumor inflammatory processes such as angiogenesis and and metastatic dissemination (Oft 2017), the off-target auto-immune side effects of immunotherapy and the inflammatory-related side effects of some chemotherapies.

Methods: In a 353 patient phase 1/1b dose escalation and expansion study, 34 pre-treated NSCLC subjects received pegilodecakin with pembrolizumab or nivolumab. Responses were assessed by irRC. PD-L1 was tested with the 22C3 IHC assay, TMB by whole exome sequencing and pre-treatment GEP by Nanostring.

Results:

Conclusions: Pegilodecakin when added to anti-PD-1 therapy in advanced NSCLC patients was associated with response rates and durability of benefit greater than has been seen with anti-PD-1 alone. Responses were seen in settings in which anti-PD-1 therapy has demonstrated limited benefit, such as absent PD-L1 expression, low TMB and/or the presence of liver metastasis. These preliminary findings support further studies of pegilodecakin with anti-PD-1 therapies.

Clinical trial identification: NCT02009449.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: A. Hung, M. Oft, J. Leveque: Employee: ARMO BioSciences. All other authors have declared no conflicts of interest.

1145P Responses and durability of clinical benefit in triple negative breast cancer patients treated with pegilodecakin monotherapy or in combination with platinum plus taxane-based chemotherapy

A. Naing[1], K.A. Autio[2], G.S. Falchook[3], F. Meric-Bernstam[1], J.K. Litton[4], N.K. Ibrahim[4], A. Hung[5], M. Oft[6], J. Leveque[7], M.R. Patel[8]

[1]Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA, [2]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3]Drug Development, Sarah Cannon Research Institute, Denver, CO, USA, [4]Breast Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA, [5]Biostatistics, ARMO BioSciences, Redwood City, CA, USA, [6]Pre-Clinical and Clinical Development, ARMO BioSciences, Redwood City, CA, USA, [7]Scientific Affairs, ARMO BioSciences, Redwood City, CA, USA, [8]Oncology, Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL, USA

Background: Late line, triple negative breast cancer (TNBC) is an unmet need. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also up-regulates IFNγ and the expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden and promotes immunosurveillance by expanding effector memory T cells (Mumm et al. 2010, 2011). Finally, pegilodecakin reduces tumor inflammatory processes such as angiogenesis and and metastatic dissemination (Oft 2017), the off-target auto-immune side effects of immunotherapy and the inflammatory-related side effects of some chemotherapies.

Table: 1144P

Pegilodecakin[1]	N	Prior Therapies	ORR	DCR	mPFS	mOS	irAE[11]	irAE[11]
Regimen	E (ITT)[10]	Median (Range)	%	%	mos	mos	All Grades (%)	Grades 3 & 4 (%)
Plus Pembrolizumab[2]	5 (5)	2 (0-5)	40.0	100	11.0	32.2		
Plus Nivolumab[3]	22 (29)	2 (0-5)	41.0	82.0	7.4	NR		
Pooled Plus Anti-PD-1[4]	27 (34)	2 (0-5)	41.0	85.0	8.9	NR	14.7	5.9
Sub-Populations	N							
PD-L1 High[5]	5		80.0	100	10.7	NR		
PD-L1 Low[6]	3		67.0	91.6	8.9	NR		
PD-L1 Negative[7]	12		33.0	67.0	5.7	NR		
TMB High[8]	2		50.0	50.0	7.2	14.0		
TMB Low[9]	8		63.0	100	10.3	NR		
Liver Mets	8		63.0	75.0	9.8	12.3		

[1]10-20μg/kg QD SC;
[2]2mg/kg, q3wk IV;
[3]3mg/kg, q2wk IV;
[4]pembrolizumab and nivolumab cohorts combined;
[5]PD-L1 >50%;
[6]PD-L1 1%-49%;
[7]PD-L1 <1%;
[8]TMB High (tumor mutational burden high) >243 mut/exome;
[9]TMB Low (tumor mutational burden low) <243 mut/exome;
[10]E (evaluable - baseline tumor assessment + >1 post-baseline assessments, and no major protocol deviations); ITT (intent to treat);
[11]irAE - Immune-Related Adverse Events (e.g. pneumonitis, adrenal insufficiency, thyroiditis, hypothyroiditis, hypophysitis, mucositis/stomatis, colitis, hepatitis, cholangitis, polyarthritis, myasthenia gravis, optic neuritis); Data cut on 05.01.18; Median follow-up for pembrolizumab cohort 37.3 months (35.9-39.1 months); Median follow-up for nivolumab cohort 23.2 months (9.1-32.0 months)

Methods: In a 353 patient phase 1/1b dose escalation and expansion study conducted in the US from 2013 to 2017, 18 heavily pretreated TNBC subjects received pegilodecakin alone (N = 8) or in combination with platinum and taxane-based chemotherapy (N = 8) or platinum and gemcitabine chemotherapy (N = 10). Responses were assessed by irRC.

Results: G3/4 TrAEs in monotherapy are anemia (38%), thrombocytopenia (38%) and fatigue (25%); and in the platinum/taxane combo: anemia (75%), neutropenia (75%), thrombocytopenia (75%), leukopenia (50%), and febrile neutropenia (25%); in carbo/gem combo: thrombocytopenia (60%), fatigue (30%) and anemia (20%).

Table: 1145P

Pegilodecakin	N	Prior Therapies	ORR	DCR	mPFS	mOS
Regimen	E (ITT)[5]	Median (Range)	%	%	mos	mos
Monotherapy[1]	4 (8)	5 (3-8)	-	25.0	2.0	5.3
Plus Chemotherapy 1[2]	7 (8)	4 (2-5)	28.6	71.4	3.9	11.2
Plus Chemotherapy 2[3]	9 (10)	3 (1-5)	-	55.6	3.3	6.8
Pooled Plus Chemotherapy[4]	16 (18)	4 (1-5)	12.5	62.5	3.7	8.0

[1]20μg/kg QD SC;
[2]Pegilodecakin 10 μg/kg + Carboplatin + Paclitaxel or Pegilodecakin 2.5 or 10 μg/kg + Carboplatin + Docetaxel or Pegilodecakin 10 μg/kg + Cisplatin + Paclitaxel or Cisplatin + Docetaxel;
[3]Pegilodecakin 5.0 or 10 μg/kg + Carboplatin + Gemcitabine;
[4]Chemotherapy cohorts 1 & 2 combined;
[5]E (evaluable - baseline tumor assessment + >1 post-baseline assessments, and no major protocol deviations); ITT (intent to treat); Data cut on 05.01.18.

Conclusions: Pegilodecakin in combination with platinum and taxane-based chemotherapy in advanced TNBC was associated with objective responses and durable clinical benefit as measured by disease control and overall survival. These preliminary findings support further studies of pegilodecakin in combination with standard of care chemotherapy in both later and earlier stages patients with TNBC.

Clinical trial identification: NCT02009449.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: A. Hung, M. Oft, J. Leveque: Employee: ARMO BioSciences. All other authors have declared no conflicts of interest.

1146P Durability of clinical benefit in metastatic epithelial ovarian cancer patients treated with pegilodecakin monotherapy or in combination with platinum plus taxane-based chemotherapy

K.A. Autio[1], A. Naing[2], A. Hung[3], M. Oft[4], J. Leveque[5], G.S. Falchook[6]

[1]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA, [3]Biostatistics, ARMO BioSciences, Redwood City, CA, USA, [4]Pre-Clinical and Clinical Development, ARMO BioSciences, Redwood City, CA, USA, [5]Scientific Affairs, ARMO BioSciences, Redwood City, CA, USA, [6]Drug Development, Sarah Cannon Research Institute at HealthONE, Denver, CO, USA

Background: Checkpoint inhibition as monotherapy has limited success in advanced metastatic epithelial ovarian cancer (epOC) and strategies to increase immunogenicity are needed. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also up-regulates IFNγ and expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden (eg, epOC) and promotes immunosurveillance by expanding effector memory T cells (Mumm et al 2010, 2011). Pegilodecakin reduces tumor inflammatory processes such as angiogenesis and metastatic dissemination (Oft 2017), the off-target autoimmune side effects of immunotherapy and the inflammatory-related side effects of some chemotherapies. Preclinical data suggest synergy of pegilodecakin in reducing tumor volume when combined with platinum/taxane based chemotherapy.

Methods: In a 353 pt phase 1/1b dose escalation and expansion study conducted in the US (2013-2017), 12 platinum-refractory, heavily pretreated epOC pts received daily pegilodecakin alone (N = 9) or in combination with platinum/taxane-based chemotherapy (N = 3). Responses were assessed by irRC.

Results: In monotherapy 4 (44%) had a PFS of more than 3.5 months and a survival of more than 14.7 months. No IRAEs were seen. G3/4 TrAEs in monotherapy: anemia (33%), fatigue (33%), thrombocytopenia (22%); in platinum/taxane combo: anemia (33%), diarrhea (33%), neutropenia (33%), thrombocytopenia (33%).

Table: 1146P

Pegilodecakin	N	Prior Therapies	ORR	DCR	mPFS	mOS
Regimen	E (ITT)[3]	Median (Range)	%	%	mos	mos
Monotherapy[1]	9 (9)	5 (4-11)	-	66.7	2.4	13.8
Plus Chemotherapy[2]	3 (3)	2 (1-7)	-	66.7	5.2	10.7

[1]1.0 or 20 μg/kg;
[2]Pegilodecakin 10 μg/kg + Carboplatin + Paclitaxel or Pegilodecakin 10 μg/kg + Cisplatin + Paclitaxel or Pegilodecakin 2.5 μg/kg + Carboplatin + Docetaxel;
[3]E (evaluable - baseline tumor assessment + >1 post-baseline assessments, and no major protocol deviations); ITT (intent to treat); Data cut on 05.01.18.

Conclusions: Pegilodecakin alone demonstrated durable disease control with manageable toxicity in a proportion of treatment refractory epOC pts. Preliminary findings in a small subset of epOC pts who received pegilodecakin in combination with platinum plus taxane-based chemotherapy yielded promising results.

Clinical trial identification: NCT02009449.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: A. Hung, M. Oft, J. Leveque: Employee: ARMO BioSciences. All other authors have declared no conflicts of interest.

1147P Preliminary results from a phase I study of GBR 1302, a bispecific antibody T-cell engager, in HER2 positive cancers

M. Wermke[1], J. Alt[2], J. Kauh[3], J. Back[4], Y. Salhi[5], V. Reddy[6], M. Barve[7], S. Ochsenreither[8]

[1]University Hospital Carl-Gustav-Carus, Dresden, Germany, [2]University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany, [3]Clinical Sciences, Glenmark Pharmaceuticals, Inc, Mahwah, NJ, USA, [4]Drug Discovery, Glenmark Pharmaceuticals SA, La Chaux-de-Fonds, Switzerland, [5]Biometrics, Glenmark Pharmaceuticals, Inc, Mahwah, NJ, USA, [6]Biologics Research, Glenmark Pharmaceuticals, Inc, Mahwah, NJ, USA, [7]Oncology, Mary Crowley Cancer Research, Dallas, TX, USA, [8]Charité Comprehensive Cancer Center, Charité University of Medicine, Berlin, Germany

Background: GBR 1302 is a HER2xCD3 bispecific antibody engineered to direct T-cells to HER2expressing tumor cells. This ongoing firstinhuman study (NCT02829372) in subjects with HER2positive cancers aims to evaluate the safety, tolerability, and preliminary efficacy of GBR 1302.

Methods: Adults with HER2-positive (immunohistochemistry 2+ or 3+) solid tumors with no available standard treatment receive GBR 1302 on Day 1 and Day 15 in 28-day treatment cycles at escalating dose levels, starting at 1 ng/kg. The primary endpoint includes determination of the maximum tolerable dose and safety profile of GBR 1302. Secondary and exploratory endpoints include pharmacodynamic (PD) testing for modulation of cellular and cytokine biomarkers.

Results: To date, 19 evaluable subjects for dose limiting toxicity (DLT) have been treated up to a dose of 750 ng/kg; dose escalation is ongoing. Grade (G) 1 to 2 infusion related reaction (IRR)/cytokine release syndrome (CRS) is the most comment treatment emergent adverse event that has been observed in subjects treated at doses ≥100 ng/kg. The majority of subjects were managed with conservative treatment. 2 subjects experienced DLT events: one asymptomatic subject (100 ng/kg) was noted to have reduced left ventricular ejection fraction on routine echocardiogram at 4 weeks, which resolved spontaneously after treatment discontinuation; the second subject (500 ng/kg) experienced G4 IRR/CRS which required ICU care but resolved within 36 hours. Beginning at 30 ng/kg, CD3, CD4, and CD8 positive T-cell populations decreased within 6 hours of administration and recovered to levels at or above baseline by 48 hours. Dose-proportional, transient increases in cytokines (IL-2, IL-6, IL-10, IFN-γ, TNF-α), which peaked at 6 hours and began to normalize within 48 hours, were observed. No subjects have documented radiological response, but 2 subjects (HER2 3+ gastroesophageal adenocarcinoma and HER2 2+ breast adenocarcinoma) have prolonged disease stabilization lasting ≥4 months.

Conclusions: The combination of clinical findings and PD changes suggests T-cell activation with higher dosages of GBR 1302. Dose escalation is continuing and updated results will be presented.

Clinical trial identification: NCT02829372.

Editorial acknowledgement: Editorial assistance provided by Ashley Skorusa, PhD of Prescott Medical Communications Group (Chicago, IL) and funded by Glenmark Pharmaceuticals S.A., Switzerland.

Legal entity responsible for the study: Glenmark Pharmaceuticals, SA.

Funding: Glenmark Pharmaceuticals, SA.

Disclosure: M. Wermke: Honoraria: BMS, Novartis, Roche, Bayer, Glenmark, AstraZeneca; Travel reimbursements: AstraZeneca, BMS, MSD, Novartis, Glenmark; Research funding: Novartis, Pfizer. J. Kauh, Y. Salhi, V. Reddy: Employee: Glenmark

Pharmaceuticals, Inc. J. Back: Employee: Glenmark Pharmaceuticals, SA. S. Ochsenreither: Payment for scientific advice: Glenmark. All other authors have declared no conflicts of interest.

1148P A phase Ia study of a personalized TSA-CTL (tumor specific antigen-induced cytotoxic T lymphocytes) therapy in metastatic melanoma

B. Li, S. Qiu

GenoImmune Therapeutics, BGI-Shenzhen, Shenzhen, China

Background: Neoantigens are derived from tumor specific mutations and presented by MHC on cancer cells. The set of neoantigens likely bypass immune tolerance and less likely induce autoimmunity because they are absent from normal cells. Targeting multiple neoantigens may significantly enhance the clinical efficacy of anti-tumor treatment with less toxicity. We present the proof-of-concept clinical application of personalized neoantigens induced T cell therapy.

Methods: This open-label phase Ia clinical trial is designed to test the safety and objective response of the tumor specific antigen-induced cytotoxic T lymphocytes (TSA-CTL). This study will enroll 9 advanced melanoma patients. Participants should have measurable metastases with at least one lesion that is resectable or tumor biopsies for DNA and RNA extraction. For each patient, we generate autologous TSA-CTLs based on neoantigens which identified through machine learning approaches with exome sequencing. Patients will receive 6 doses of TSA-CTL infusion. Toxicity (endpoint 1) will be defined by Common Terminology Criteria for Adverse Events v5.0, and objective response (endpoint 2) will be determined by the Response Evaluation Criteria in Solid Tumors.

Results: Seven patients have been enrolled so far and three of them have completed 3 cycles of TSA-CTL infusion. The fifth patient display pruritus grade 1. No other related adverse events just after the treatment were observed. We detected neoantigen-specific CD8+ T cells in peripheral blood through pMHC tetramer and found that neoantigen-specific CD8+ T cell increased after the TSA-CTL infusions for the third patient and the fifth patient. After three cycles of TSA-CTL infusion, the third and the fourth patient was assessed as SD with three metastasis' regression and PR, respectively. Further treatment and analyses are ongoing.

Conclusions: No major direct side effects are observed. Although with very limited trial subjects, a few patients did show favorable responses. Our study highlights the promise of personalized cell therapy for tumor-specific T cells and provide guidance for the future development. Clinical trial information: NCT02959905.

Clinical trial identification: NCT02959905; Release date: November 9, 2016.

Legal entity responsible for the study: BGI-Shenzhen.

Funding: BGI-Shenzhen.

Disclosure: B. Li, S. Qiu: Employee: BGI Tech Solutions (Hong Kong Co. Ltd)

1149P Safety, tolerability, and pharmacokinetics of the OX40 agonist ABBV-368 in patients with advanced solid tumors

A. Spira[1], K. Chung[2], A. Patnaik[3], A.W. Tolcher[4], M.E. Blaney[5], A. Parikh[5], A. Reddy[5], W. Henner[5], M. McDevitt[5], D. Afar[5], J. Powderly[6]

[1]Research Institute, Virginia Cancer Specialists, Fairfax, VA, USA, [2]Hematology/Oncology, Greenville Health System, Greenville, SC, USA, [3]Clinical Research, South Texas Accelerated Research Therapeutics (START), San Antonio, TX, USA, [4]Clinical Research, South Texas Accelerated Research Therapeutics (START); NEXT OncologyTM, San Antonio, TX, USA, [5]Oncology, AbbVie Inc., Redwood City, CA, USA, [6]Medical Oncology, Carolina BioOncology Institute, Huntersville, NC, USA

Background: ABBV-368 is a novel humanized IgG1 agonist monoclonal antibody specific for human OX40, a TNF receptor superfamily member expressed on activated and memory T-cell subsets, as well as T regulatory cells. The proposed ABBV-368 therapeutic mechanism of action includes activation of T effector cells and inhibition of the suppressive capacity of T regulatory cells. This ongoing first-in-human, phase 1, two-part study (NCT03071757) is investigating the safety, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and preliminary antitumor activity of ABBV-368 in patients (pts) with advanced solid tumors.

Methods: Eligible pts include adults (≥18 years) with advanced or metastatic solid tumors. ABBV-368 was administered intravenously in a 3 + 3 dose-escalation design at doses ranging from 0.01 to 3.0 mg/kg every 2 weeks (4 cohorts). PK was assessed in cycle 1 and cycle 3. OX40 receptor saturation, Ki67 proliferation marker expression in peripheral blood immune cell subsets, and additional PD biomarkers were evaluated.

Results: As of Feb 12, 2018, 38 pts with advanced or metastatic tumors were enrolled in dose-escalation cohorts. Median age was 65 years (range, 38–78). No dose-limiting toxicities were reported during dose escalation. Overall, 15 (39.5%) pts reported grade (Gr) ≥3 treatment-emergent adverse events (TEAEs). Three (7.9%) pts reported Gr ≥ 3 TEAEs related to ABBV-368. Two investigator-reported immune-related AEs were documented, including hypothyroidism; neither were serious. ABBV-368 PK was approximately dose-proportional from 0.1- to 3-mg/kg doses during cycle 1, with dose-dependent target saturation. Initial antitumor activity has been observed. Updated safety, PK, PD, and efficacy data will be reported.

Conclusions: ABBV-368 was well tolerated; a maximum tolerated dose was not reached. Antitumor activity was observed at doses predicted to be biologically active. Further evaluation of ABBV-368 is ongoing in pts with advanced solid tumors.

Clinical trial identification: NCT03071757.

Editorial acknowledgement: Medical writing support was provided by Mary L. Smith, PhD, CMPP, from TRM Oncology, Atlanta, GA, and funded by AbbVie.

Legal entity responsible for the study: AbbVie Inc.

Funding: AbbVie Inc.

Disclosure: A. Spira: Consultant and Institutional research support: AbbVie. A. Patnaik: Research grants to institution: Merck & Co., Inc. LG; Advisory board member: Merck & Co., Inc., AstraZeneca, AbbVie, Pfizer, Genentech/Roche; Research grant: Bristol-Myers Squibb. A.W. Tolcher: Consultant: AbbVie. M.E. Blaney, A. Parikh, A. Reddy, W. Henner, M. McDevitt, D. Afar: Employee and may own stock: AbbVie. J. Powderly: Employee and leadership role: Carolina BioOncology Institute PLLC; Stock/ownership: Iovance, Juno, Bluebird Bio, Kite Pharma, ZioPharm; Speaker bureau: Genentech, Bristol-Myers Squibb, Merck; Research funding: AstraZeneca, Genentech, Clovis, Corvus, Incyte, AbbVie, Bristol-Myers Squibb, MacroGenics; Patent or intellectual property: Founder of BioCytics, developing T-cell immunotherapies. All other authors have declared no conflicts of interest.

1150P Recombinant humanized anti-PD-1 monoclonal antibody (JS001) in patients with refractory/metastatic nasopharyngeal carcinoma: Preliminary results of an open-label phase II clinical study

R. Xu[1], F.H. Wang[2], F.J. Feng[3], Q. Li[4], N. Xu[5], X.C. Hu[6], W.J. Liao[7], Y. Jiang[8], X. Lin[9], Q.Y. Zhang[10], X.L. Yuan[11], H.X. Huang[12], Y. Chen[13], G.H. Dai[14], J.H. Shi[15], L. Shen[16], C. Ren[17], H. Wu[18], H. Feng[18], S. Yao[18]

[1]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China, [2]Medical Oncology, Sun Yat-sen University Cancer Center, Guang Zhou, China, [3]Medical Oncology, Jiangsu Cancer Hospital, Nan Jing, China, [4]Medical Oncology, Cancer Center of Shanghai First People's Hospital, Shanghai, China, [5]Medical Oncology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China, [6]Medical Oncology, Tumor Hospital Affiliated to Fudan University, Shang Hai, China, [7]Medical Oncology, Cancer Center of NanFang Hospital, GuangZhou, China, [8]Medical Oncology, The Affiliated Tumor Hospital of Shantou University Medical College, Shan Tou, China, [9]Medical Oncology, Fujian Medical University Union Hospital, Fuzhou, China, [10]Medical Oncology, The Affiliated Tumor Hospital of Harbin Medical University, Ha Er Bin, China, [11]Oncology, Wuhan Tongji Hospital, Wu Han, China, [12]Medical Oncology, Liuzhou Worker's Hospital, Liu Zhou, China, [13]Medical Oncology, Cancer Center of West China Hospital of Sichuan University, Chengdu, China, [14]Medical Oncology, Beijing 301 Hospital, BeiJing, China, [15]Medical Oncology, Linyi Tumour Hospital, Lin Yi, China, [16]Beijing Cancer Hospital, Beijing, China, [17]Medical Oncology, Sun Yat-sen University; Cancer Center, GuangZhou, China, [18]Clinical Medicine, Shanghai Junshi Biosciences Co., Shanghai, China

Background: Patients with metastatic nasopharyngeal cancer (NPC) who experienced disease progression after standard therapy have limited treatment options. NPC is closely associated with Epstein–Barr Virus (EBV) infection and has been reported to have high levels of PD-L1 expression and tumor infiltrating lymphocytes, favoring immune-therapy potential in treating NPC. JS001, a humanized recombinant IgG4 antibody against PD-1, selectively blocks the interactions of PD-1 with its ligands PD-L1 and PD-L2, and promotes antigen specific T cell activation. Phase I studies of JS001 in subjects with heavily pretreated solid tumors had demonstrated an acceptable safety profile in doses up to 10 mg/kg Q2W.

Methods: Refractory/metastatic NPC Patients received JS001 3 mg/kg Q2W until disease progression or unacceptable toxicity. All patients with measurable disease were assessed for clinical response every 8 weeks. Tumor PD-L1 expression (SP142) and plasma EBV DNA levelwere monitored for correlation with clinical response.

Results: Between Dec 22th 2016 and May 4th 2018, 139 NPC pts were enrolled into the study. The median age was 46 years, 84% male (n = 117), with average 3.4 lines of prior systemic therapies. By Nov 15th 2017, treatment related AEs occurred in 84% patients, which were mostly grade 1 or 2, including fever (18.2%), hypothyroidism (18.2%), proteinuria (10.9%), fatigue (9.1%), TBIL increase (9.1%), leukopenia (9.1%) and anemia (7.3%). Grade ≥ 3 treatment related AEs occurred in 14.5% patients. Out of 52 evaluable pts by Jan 2018, 16 partial responses (30.8% ORR) and 16 stable diseases (61.5% DCR) were observed. PD-L1+ pts had slightly higher ORR 38.5% and 65.4% DCR. Interestingly, an average drop of 47-fold plasma EBV DNA copy number was observed in responding pts, which typically proceeded the radiographic identification of clinical benefits.

Conclusions: PD-1 mAb JS001 has demonstrated encouraging clinical activity in heavily pretreated NPC pts and a manageable safety profile. A change in plasma EBV DNA copy number might serve as a prognosis marker for NPC upon immunotherapy.

Clinical trial identification: NCT02915432.

Legal entity responsible for the study: Shanghai Junshi Biosciences Co.

Funding: Shanghai Junshi Biosciences Co.

Disclosure: H. Wu, H. Feng, S. Yao: Employee: Shanghai Junshi Biosciences Co. All other authors have declared no conflicts of interest.

1151P Cemiplimab, a human monoclonal anti-PD-1, in patients (pts) with advanced or metastatic hepatocellular carcinoma (HCC): Data from an expansion cohort in a phase I study

M.J. Pishvaian[1], G.J. Weiss[2], G.S. Falchook[3], N. Yee[4], M. Gil-Martin[5], S. Shahda[6], V. Moreno[7], I. Brana[8], M. Crittenden[9], S. Formenti[10], R. Al-Rajabi[11], K.P. Papadopoulos[12], E. Stankevich[13], M. Feng[13], J. Li[14], M. Mathias[15], G. Kroog[15], I. Lowy[15], M.G. Fury[15]

[1]*Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington DC, USA,* [2]*Department of Internal Medicine, University of Arizona College of Medicine, Phoenix, AZ, USA,* [3]*Drug Development, Sarah Cannon Research Institute at HealthONE, Denver, CO, USA,* [4]*Hematology/Oncology, Penn State Cancer Institute, Hershey, PA, USA,* [5]*Institut Català d'Oncologia, L'Hospitalet de Llobregat, Spain,* [6]*Indiana University School of Medicine, Indiana University Melvin Bren Simon Cancer Center, Indianapolis, IN, USA,* [7]*START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain,* [8]*Department of Medical Oncology, Vall D'Hebron Institute of Oncology, Barcelona, Spain,* [9]*Earle A. Chiles Research Institute, Robert W. Franz Cancer Center, Providence Portland Medical Center and The Oregon Clinic, Portland, OR, USA,* [10]*Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, USA,* [11]*Department of Internal Medicine, Division of Hematology/Oncology, University of Kansas Cancer Center, Kansas City, KS, USA,* [12]*Clinical Research, START, San Antonio, TX, USA,* [13]*Clinical Sciences, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA,* [14]*Biostatistics & Data Management, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA,* [15]*Clinical Sciences, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA*

Background: For pts with unresectable HCC, systemic therapy options are limited. Sorafenib is approved in the US and Europe for HCC treatment. For pts who progress on sorafenib, regorafenib and nivolumab are approved as second-line therapy. Cemiplimab (REGN2810) has demonstrated encouraging efficacy and safety profile in a Phase 1 dose escalation study in pts with advanced malignancies (NCT02383212). We present results of the Phase 1 HCC expansion cohort.

Methods: HCC pts who were not candidates for surgery and had progressed on, could not tolerate, or refused first-line systemic therapy received cemiplimab 3 mg/kg Q2W for up to 48 weeks. The main objectives were to evaluate the safety, tolerability, and antitumour activity of cemiplimab.

Results: As of 1 Sept, 2017, 26 pts were enrolled (25 M/1 F), median (range) age was 65 (40–78) years; 24 pts (92.3%) had $\geq$1 prior systemic therapy; ECOG performance status was 1 in 19 pts (73.1%), 0 in 6 (23.1%) and missing in 1. Median duration of follow-up was 7.2 (range: 1.8–15.5) months. By investigator assessment, 5 pts (19.2%) had partial response, 14 (53.8%) had stable disease, 6 (23.1%) had progressive disease and 1 was not evaluable. Median progression-free survival was 3.7 months (95% CI: 2.3–9.1). Five pts (19.2%) completed the planned 48-week treatment, and 21 (80.8%) discontinued prematurely, mainly due to disease progression (65.4%). Three of the 5 pts who completed planned treatment remained without disease progression at the last response assessment. The most common treatment-emergent adverse events (TEAEs) of any grade were fatigue (26.9%), decreased appetite, increased aspartate aminotransferase (AST), abdominal pain, pruritus, and dyspnoea (each 23.1%). Grade $\geq$3 TEAEs occurring in $\geq$ 2 pts were hyponatraemia (3 pts), autoimmune hepatitis (2 pts) and increased AST (2 pts). Two pts (7.7%) had a TEAE resulting in death: 1 with pulmonary embolism that was considered unrelated to treatment and another with hepatic failure considered possibly related to treatment.

Conclusions: Cemiplimab demonstrated evidence of antitumour activity in pts with advanced or metastatic HCC. The safety profile is comparable with that of other anti-PD-1 inhibitors.

Clinical trial identification: NCT02383212.

Editorial acknowledgement: Medical writing support under the direction of the authors was provided by Emmanuel Ogunnowo, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc. and Sanofi according to Good Publication Practice guidelines (http://annals.org/aim/article/2424869/good-publication-practice-communicating-company-sponsored-medical-research-gpp3).

Legal entity responsible for the study: Regeneron Pharmaceutical Inc., and Sanofi.

Funding: Regeneron Pharmaceutical Inc. and Sanofi.

Disclosure: G.J. Weiss: Personal fees and ownership interest: Circulogene; Ownership interest: Angiex; Personal fees: Paradigm, Igynta, Pfizer, Merck, Idea Pharma, GLG Council, Novartis; Travel/lodging fees: Cambridge Healthtech Institute, Tesaro, and Nantworks; Patent PCT/US2011/020612 issued. G.S. Falchook: Funding for trial for submitted work. N. Yee: Research, travel, accommodation and expenses: Daiichi Sankyo, Foundation Medicine and Caris Life Sciences. S. Shahda: Advisory board fees: Ipsen and Bayer; Research grants: Incyte and Apexian. M. Crittenden: Research funding: Jounce and Nanobiotix. R. Al-Rajabi: Grants: Regeneron Pharmaceuticals, Inc. E. Stankevich: Shareholder and employee: Regeneron Pharmaceuticals, Inc., Shareholder: Celgene, Bristol-Myers Squibb, and Merck. M. Feng: Shareholder and employee: Regeneron Pharmaceuticals, Inc., Shareholder: Bayer. J. Li, M. Mathias, G. Kroog: Shareholder and employee: Regeneron Pharmaceuticals, Inc. I. Lowy: Shareholder and employee, fees for travel and accommodation expenses, leadership: Regeneron Pharmaceuticals, Inc. M.G. Fury: Shareholder, employee, holds patents, royalties, other intellectual property: Regeneron Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

1152P Safety and clinical activity of MEDI0562, a humanized OX40 agonist monoclonal antibody, in adult patients with advanced solid tumors

B. Glisson[1], R. Leidner[2], R.L. Ferris[3], J. Powderly[4], N.A. Rizvi[5], B. Keam[6], R. Schneider[7], S. Goel[8], J.P. Ohr[9], Y. Zheng[10], S. Eck[11], M. Gribbin[12], D.M. Townsley[12], V. Chiou[12], S.P. Patel[13]

[1]*Thoracic Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA,* [2]*Medical Oncology, Providence Cancer Center Oncology and Hematology Care Clinic Eastside Portland, Portland, OR, USA,* [3]*Immunology, University of Pittsburgh Cancer Center, Pittsburgh, PA, USA,* [4]*Carolina BioOncology Institute, Huntersville, NC, USA,* [5]*Hematology/Oncology, Columbia University Medical Center, New York, NY, USA,* [6]*Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea,* [7]*Oncology, Mary Crowley Cancer Research - Medical City, Dallas, TX, USA,* [8]*Medical Oncology, Montefiore Medical Center (East campus) - Medical Park at Eastchester Albert Einstein Cancer Center, Bronx, NY, USA,* [9]*Medical Oncology/Hematology, UPMC Hillman Cancer Center, Pittsburgh, PA, USA,* [10]*Clinical Pharmacology and Dmpk, MedImmune, Gaithersburg, MD, USA,* [11]*Translational Sciences, MedImmune, Gaithersburg, MD, USA,* [12]*Oncology, MedImmune, Gaithersburg, MD, USA,* [13]*Hematology/Oncology, UC San Diego Moores Cancer Center, La Jolla, CA, USA*

Background: MEDI0562, a humanized IgG4 OX40 monoclonal antibody, demonstrated a manageable safety profile and pharmacologic activity in preliminary analyses of the Phase 1 study (NCT02318394) in pts with advanced solid tumors.[1] Here we present updated safety data and clinical activity for pts treated during the dose-escalation phase.

Methods: Pts were treated with one of 6 escalating doses of MEDI0562 (0.03, 0.1, 0.3, 1.0, 3.0, and 10 mg/kg) every 2 weeks (Q2W) until confirmed disease progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks with immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).

Results: A total of 55 pts received MEDI0562 across 6 dose cohorts (3 + 3 design), with a maximum administered dose of 10 mg/kg Q2W and no DLTs observed. Median duration of exposure was 10 (2 to 48) weeks. Adverse events (AEs) and treatment-related AEs (trAEs) were reported in 96% and 67% of pts, respectively; the most common trAEs were fatigue (31%) and infusion-related reaction (15%). Gr 3 trAEs occurred in 16% of pts with the most common being pyrexia (4%); 53% of pts had trAEs of Gr1 or 2, with no apparent dose relation. There were no trAEs leading to discontinuation or Gr 4 or 5 trAEs. Of 50 response evaluable pts, 2 pts (sq cell carcinoma of the larynx – 0.03 mg/kg Q2W and bladder cancer – 3 mg/kg Q2W) had irPR at the first tumor assessment, with an overall survival of 13.8 and 10.2+ mos, respectively. Stable disease was seen in 22 (44%) pts with SD in 20 pts lasting >3 mos. Serum exposure of MEDI0562 increased approximately dose proportionally. Posttreatment antidrug antibody (ADA) was detected in 26 (51%) of 55 pts. ADA exhibited variable impact on PK exposure at all doses below 3 mg/kg. A 1.5 to 3.0-fold increase in mean peaks of the percentage of peripheral Ki67+ CD4+ and Ki67+ CD8 +memory T cells was observed across ascending dose levels.

Conclusions: MEDI0562 was generally well tolerated in adult pts with advanced solid tumors and exhibited clinical and pharmacological activity. Based on the ADA data, a suggested MEDI0562 Phase 2 dose of $\geq$ 3 mg/kg Q2W was selected. 1. Glisson et al Ann Oncol ESMO 2016.

Clinical trial identification: NCT02318394.

Legal entity responsible for the study: MedImmune.

Funding: MedImmune, the global biologics R&D arm of AstraZeneca.

Disclosure: B. Glisson: Research funding to institution: Pfizer, Inc. R. Leidner: Institutional research funding: MedImmune, BMS, and Ignyta; Honoraria: AstraZeneca; Advisory board: Regeneron and Merck. R.L. Ferris: Advisory board: Amgen, AstraZeneca/MedImmune, Bristol-Myers Squibb, EMD Serono, PPD, Lilly, Merck, Pfizer, Tesaro; Clinical trial research funding: AstraZeneca/MedImmune, Bristol-Myers Squibb, Merck; Research funding: Tesaro, VentiRx Pharmaceuticals. J. Powderly: Clinical trial funding: AstraZeneca, Curis, Corvus, InCyte, AbbVie, BMS, MacroGenics, Top Alliance BioSciences. N.A. Rizvi: Consulting/Advisory board: AstraZeneca, Abbvie, BMS, Eli Lilly, Merck, Merck KGaA, Novartis, Pfizer, Regeneron, Roche; Board of directors member and shareholder: ARMO BioSciences; Co-founder and shareholder: Gritstone Oncology; Scientific advisory board member: Neogenomics. Y. Zheng, S. Eck, D.M. Townsley: Employee: MedImmune, AstraZeneca. S.P. Patel: Consulting, institutional research support: AstraZeneca/MedImmune. All other authors have declared no conflicts of interest.

1153P Autologous dendritic-cell vaccine based on cancer-testis antigens "CaTeVac" in the treatment of soft tissue sarcoma

N. Pipia[1], I.A. Baldueva[1], T.L. Nekhaeva[1], A.V. Novik[1], A.B. Danilova[1], N.A. Avdonkina[1], S.A. Protsenko[2], Y.I. Komarov[2], D.V. Girdyuk[1], A.P. Oganesyan[2], A.M. Belyaev[3]

[1]*Oncoimmunology, N.N. Petrov Research Institute of Oncology, St. Petersburg, Russian Federation,* [2]*Chemotherapy and Innovative Technology, N.N. Petrov Research Institute of Oncology, St. Petersburg, Russian Federation,* [3]*N.N. Petrov Research Institute of Oncology, St. Petersburg, Russian Federation*

Background: Recent advances in the cancer immunotherapy provide an opportunity to develop the therapeutic autologous dendritic cell vaccine for metastatic forms of soft tissues sarcomas (STS). Previous studies showed the possibility of developing delayed

effects from this treatment. The aim of this study is to compare efficacy of the 2nd line therapy of STS patients with or without CaTeVac therapy during the whole systemic treatment.

Methods: Seventy-four patients (pts.) were included since 2008 to 2017. All patients had stage III inoperable or stage IV STS and received 2nd line of systemic therapy. Group 1 received CaTeVac as adjuvant therapy or maintenance therapy after the 1st or 2nd line of systemic therapy or as monotherapy after at least 1 line of chemotherapy. Group 2 never received CaTeVac during treatment course. Patients in the groups were comparable by histologic types and previous treatment. Overall survival (OS) from the start of the 2nd line of therapy to death was assessed as efficacy measure.

Results: Median OS of patients in group 1 was 24,4 mo (741 days, 95% CI, 509-973), versus 14.2 mo (431 days, 95% CI, 56-806) in group 2 (Log-Rank $p = 0.019$, Breslow $p = 0.03$). Relative risk of death (exp(B)) in group 1 was 0,358 (95% CI 0.171-0.751) in the Cox regression and was independent from and comparable to the treatment effect (exp(B) 0.254 (95% CI 0.133-0.484), $p = 0.000011$. Sex and age showed no impact on survival ($p > 0.05$).

Conclusions: CaTeVac shows impact on overall survival and should be assessed in randomized clinical trials with OS endpoints.

Legal entity responsible for the study: N.N. Petrov Research Institute of Oncology.

Funding: Ministry of Health Russian Federation.

Disclosure: All authors have declared no conflicts of interest.

1154P A phase I study of MEDI1873, a novel GITR agonist, in advanced solid tumors

C.S. Denlinger[1], J.R. Infante[2], R. Aljumaily[3], A. Naing[4], A. Chintakuntlawar[5], N.A. Rizvi[6], H. Ross[7], M. Gordon[8], R. Kumar[9], M. Ma[9], L. Yan[10], P. Vicini[11], N. Standifer[10], J. Cann[9], A. Perera[11], N. Durham[9], S. Krishnan[9], A. Balmanoukian[12]

[1]Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [2]Cancer Center, Sarah Cannon Research Institute, Nashville, TN, USA, [3]Oncology, Oklahoma University Medical Center, Oklahoma City, OK, USA, [4]Oncology, MD Anderson Cancer Center, Houston, TX, USA, [5]Internal Medicine, Mayo Clinic, Rochester, MN, USA, [6]College of Physicians and Surgeons, Columbia University Medical Center, New York, NY, USA, [7]Oncology, Mayo Clinic, Scottsdale, AZ, USA, [8]Medical Oncology, HonorHealth Research Institute, Scottsdale, AZ, USA, [9]Medical Oncology, MedImmune, Gaithersburg, MD, USA, [10]Medical Oncology, MedImmune, South San Francisco, CA, USA, [11]Medical Oncology, MedImmune, Cambridge, UK, [12]Medical Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA

Background: MEDI1873 is a novel GITR-ligand/IgG1 agonist fusion protein that binds the co-stimulatory glucocorticoid-induced TNF receptor family-related protein (GITR) on $CD4^+$ and $CD8^+$ effector T cells and regulatory T cells. This Phase 1 study evaluated safety, maximum tolerated dose (MTD), pharmacokinetics (PK), immunogenicity, immunomodulatory effects and preliminary antitumor activity in pts with advanced solid tumors.

Methods: MEDI1873 was administered IV Q2W. During dose escalation (DE), it was evaluated in 2 single pt cohorts (1.5 and 3 mg), followed by 3 + 3 DE in 6 cohorts (7.5, 25, 75, 250, 500 and 750 mg). Pts with NSCLC, HNSCC or CRC receiving 75 or 250 mg were evaluated in pharmacodynamic (PD) cohorts using biopsies pretreatment and at day 29. All pts had flow cytometric assessment of lymphocytes pre- and on-treatment up to day 43. Antitumor response was assessed using RECIST v 1.1.

Results: As of 1 March 2018, 40 pts were dosed in the DE (28) and PD (12) cohorts. An MTD was not reached (maximum administered dose was 750 mg). Three DLTs occurred: Grade 3 worsening tumor pain at 250 mg, Grade 3 nausea and vomiting at 500 mg and Grade 3 non-STEMI at 750 mg. Any-grade drug-related AEs occurred in 82.5% of pts, most commonly headache (25%) and infusion related reaction (IRR, 20%). Grade 3 drug-related AEs occurred in 22.5% of pts; amylase increase was the only one reported in > 1 pt (n = 2). There were no drug-related Grade 4 or 5 AEs. PK was dose-proportional over a range of 1.5 to 500 mg; elimination half-life was approximately 2 days. Anti-drug antibody incidence was low with minimal PK impact. MEDI1873 engaged GITR on $CD4^+$ T cells and increased $CD4^+Ki67^+$ T cells at doses ≥25 mg. Intratumorally, MEDI1873 induced a ≥ 25% decrease in $GITR^+/FOXP3^+$ T cells in 5 of 5 pts with evaluable cells. Immune PD changes were observed in 8 pts who underwent paired biopsies. Best overall response was stable disease (SD) in 42.5% of pts; 17.5% had SD ≥ 24 weeks. Three pts (pancreatic neuroendocrine tumor, lung cancer and mesothelioma) stayed on MEDI1873 for ≥52 weeks without progression.

Conclusions: MEDI1873 has an acceptable safety profile in heavily pretreated pts with solid tumors. PD changes in blood and tumor coupled with prolonged SD in several pts support further clinical exploration of doses ≥250 mg.

Clinical trial identification: NCT02583165, October 22, 2015.

Editorial acknowledgement: Medical editing support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Paul Glacken of Ashfield Healthcare Communications (Macclesfield, UK) and was funded by MedImmune (Gaithersburg, MD, USA).

Legal entity responsible for the study: MedImmune.

Funding: MedImmune.

Disclosure: C.S. Denlinger: Grant: MedImmune, during the conduct of the study; Grants and personal fees: Eli Lilly and Company; Grants: Bristol-Myers Squibb; Personal fees: Merck; Grants: Merrimack Pharmaceuticals; Grants: MedImmune LLC; Personal fees from EMD Serono, Carevive; Grants from Advaxis, Genentech, InCyte Corporation, OncoMed, Astex Pharmaceuticals, Macrogenics, Array Pharmaceuticals, AstraZeneca, outside the submitted work. J.R. Infante: Research funding: Aileron Therapeutics, ARMO BioSciences, AstraZeneca, BioMed Valley Discoveries, Bristol-Myers Squibb, Calithera Biosciences, Calithera Biosciences, Celldex, eFFECTOR Therapeutics, Genentech/Roche, GlaxoSmithKline, Immunocore, Janssen Oncology, MedImmune, Merck, Novartis, Pfizer, Phosplatin Therapeutics, Roche, Roche, Tesaro. A. Naing: Research funding: Amplimmune; ARMO BioSciences; Atterocor; Baxter (I); EMD Serono; Healios; Incyte; Karyopharm Therapeutics; MedImmune; National Cancer Institute; Novartis; Regeneron; Travel, accommodations, expenses: ARMO BioSciences. A. Chintakuntlawar: Principal investigator on clinical investigator initiated trials: Merck and Eisai. N.A. Rizvi: Consulting/Advisory board: Merck, AstraZeneca, Roche, Bristol-Myers Squibb, Novartis, Pfizer, Lilly, Abbvie, Merck KGaA, Regeneron; Shareholder: Gritstone Oncology, ARMOBiosciences. H. Ross: Research grant funding from AstraZeneca and MedImmune. M. Gordon: Full-time employment: Honor Health; Consultancy: Deciphera. R. Kumar, M. Ma, L. Yan, P. Vicini, N. Standifer, A. Perera, N. Durham. S. Krishnan: Full-time employment: MedImmune. J. Cann: Employee: Medimmune/AstraZeneca. A. Balmanoukian: Speakers' bureau: AstraZeneca, Genentech, BMS, Merck. All other authors have declared no conflicts of interest.

1155P Phase I adoptive cellular therapy trial with ex-vivo stimulated autologous CD8+ T-cells against multiple targets (ACTolog® IMA101) in patients with relapsed and/or refractory solid cancers

A-M. Tsimberidou[1], H. Ma[2], C. Stewart[2], O. Schoor[3], D. Maurer[3], R. Mendrzyk[3], A. Satelli[2], J. Fritsche[3], G. Stephens[2], A. Mohamed[2], P. Hwu[4], C. Yee[4], C. Reinhardt[3], T. Weinschenk[2], K. Gharpure[1], A. Stungis[1], D.J. Vining[4], H. Singh[2], S. Walter[2], B.S. Andersson[4]

[1]Investigatonal Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA, [2]Oncology, Immatics US., Inc., Houston, TX, USA, [3]Immunology, Immatics Biotechnologies GmbH, Martinsried, Germany, [4]Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

Background: Adoptive cellular therapy in patients (pts) with solid tumors is limited due to lack of cancer targets with high specificity or relapse often associated with loss of single antigen (Ag) expression. To address multiple novel tumor Ags, we utilized Ag-specific T cells (IMA101) against cancer targets. Target positive tumors were identified by qPCR. Expression levels predictive for Ag presentation were determined by mass spectrometry. Autologous T cells against ACTolog targets are in vitro primed in the presence of IL-21 followed by HLA tetramer-guided cell sorting and expansion prior to infusion.

Methods: HLA-A*02:01 positive pts with relapsed/refractory solid tumors are eligible for treatment if their tumors express ≥1 of 8 possible Ag targets from a predefined antigen warehouse. These pts undergo leukapheresis, followed by IMA101 cell manufacturing. Treatment consists of lymphodepletion (Fludarabine/Cyclophosphamide) followed by IMA101 infusion of up to 4 Ag-specific T cell products and IL-2.

Results: From 8/2017 to 5/2018, 86 pts were prescreened, 38 were HLA-A*02:01 positive, 18 had tumor biopsy, 11 had leukapheresis and 3 were treated so far: hormone receptor pos, HER2 neg. breast cancer (56 yr, fem.); synovial sarcoma (28 yr, fem.); and liposarcoma (36 yr, male); No. of prior therapies, 12, 6, 8, respectively. Respective time to recovery was: ANC >1.0: day 41, 8, and 61; Platelets > 50: day 47, no decrease <50, and 61. Pts developed Grade 1-2 cytokine release syndrome, without evidence of infection. The third patient developed bradycardia on day 9, which was reversible with discontinuation of IL-2. Peripheral blood analysis at 2 wks demonstrated that CD8+ T cells specific for cancer targets were 0.4%, 12%, and 46% of total circulating CD8+ T cells, respectively. Pts had disease stabilization at 6 wks.

Conclusions: In the 3 pts treated, treatment was tolerable. To our knowledge, this is the first time that pts received multiple defined Ag-specific products. Initial T-cell persistence data demostrated high prevalence and the expected T-cell phenotype, which are important prerequisites for clinical activity. The trial is ongoing.

Clinical trial identification: NCT02876510.

Legal entity responsible for the study: Immatics US, Inc.

Funding: Cancer Prevention Research Institute of Texas (DP150029).

Disclosure: H. Ma, C. Stewart, O. Schoor, D. Maurer, A. Satelli, G. Stephens, A. Mohamed, R. Mendrzyk: Employee: Immatics. P. Hwu, C. Yee: Stock option and scientific advisory board: Immatics. C. Reinhardt: Stock owner and employee: Immatics. H. Singh, S. Walter: Employee and stock option: Immatics. All other authors have declared no conflicts of interest.

1156P Initial safety assessment of MAGE-A4 SPEAR T-cells

D.S. Hong[1], M.O. Butler[2], M. Johnson[3], A.J. Olszanski[4], E. Norry[5], E. Van Winkle[5], K.D. Chagin[6], R.G. Amado[7]

[1]Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA, [2]Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA, [4]Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [5]Clinical, Adaptimmune, Philadelphia, PA, USA, [6]Clinical, Adaptimmune LLC, Philadelphia, PA, USA, [7]Clinical, Adaptimmune LLC, Philadelphia, PA, USA

Background: This ongoing study (NCT03132922) evaluates the safety and tolerability of genetically engineered autologous specific peptide enhanced affinity receptor (SPEAR) T-cells (MAGE-A4^{c1032}T cells) directed towards a MAGE-A4 peptide expressed on tumors in the context of HLA-A*02.

Methods: This first-in-human T-cell dose-escalation study utilizes a modified 3 + 3 design to evaluate safety, including dose-limiting toxicities (DLT). Patients who are HLA-A*02 positive (excluding *02:05 and *02:07) and have inoperable or metastatic (advanced) NSCLC, urothelial cancer, melanoma, synovial sarcoma, MRCLS, squamous cell head and neck, ovarian, gastric or esophageal tumors with MAGE-A4 expression and meet all other entry criteria are eligible for treatment. Following apheresis, T-cells are isolated, transduced with a lentiviral vector containing the MAGE-A4^{c1032}TCR, and expanded. Prior to transduced cell infusion, patients are given lymphodepleting chemotherapy (Flu 30 mg/m^2/d and Cy 600 mg/m^2/d, on days -7, -6 and -5 in dose groups 1 and 2, and additional Flu 30 mg/m^2/d on day -4 in dose group 3). Groups 1, 2 and 3 will consist of 3-6 patients, and transduced cell doses will be as follows: 0.1×10^9 (±20%), 1×10^9 (range: $0.5 – 1.2 \times 10^9$), and 5×10^9 (range: $1.2 – 6 \times 10^9$), respectively. The DLT observation period is the first 30 days following the infusion of SPEAR T-cells for each patient in all groups. Following dose escalation, up to 30 patients will be enrolled at 5×10^9 (range: 1.2×10^9 -10×10^9).

Results: 3 patients were treated with 0.1×10^9 MAGE-A4 SPEAR T-cells, and transduced cells are detectable in peripheral blood. AEs for the first 2 patients reported at grade (G) ≥3 include anemia, hypoglycemia, hyponatremia, lymphopenia, neutropenia, and thrombocytopenia. Serious AEs included G4 hyponatremia, G3 atrial fibrillation, G3 syncope (unrelated to T-cell therapy), G1 CRS and G2 encephalopathy syndrome (both related), and G2 generalized muscle weakness (possibly related). None of the events were considered DLTs by the Safety Review Committee.

Conclusions: MAGE-A4 SPEAR T-cells at the 0.1×10^9 transduced cell dose appear to show no evidence of on-target or off-target toxicity. Preliminary data support continued investigation of the TCR, and this trial is ongoing. Updated safety data will be presented.

Clinical trial identification: NCT03132922.

Editorial acknowledgement: Editorial assistance was provided by Envision Pharma.

Legal entity responsible for the study: Adaptimmune.

Funding: Adaptimmune.

Disclosure: E. Van Winkle, K.D. Chagin, R.G. Amado: Employee: Adaptimmune. All other authors have declared no conflicts of interest.

1157P Phase I trial of a novel hTERT vaccination strategy addressing T effector cells and immune-suppressor mechanisms

J. Spicer[1], V. Kwatra[1], C. Verma[2], K. Ioannou[3], R. Goldstein[1], T. Brier[1], J. Eremin[1], N. Zareian[1], L. Walker[4], D. Lobo[2], F. Farzaneh[3], O. Eremin[2]

[1]School of Cancer and Pharmaceutical Sciences, King's College London Guy's Hospital, London, UK, [2]Nottingham Digestive Diseases Centre, University of Nottingham, Nottingham, UK, [3]School of Cancer and Pharmaceutical Sciences, King's College London, London, UK, [4]Department of Cancer Rehabilitation, University of Hull, Hull, UK

Background: Inability to generate activated T effector cells and the presence of strong suppressor mechanisms have limited cancer vaccine efficacy. Human telomerase reverse transcriptase (hTERT) is expressed in > 90% of tumours but is HLA dependent, which has restricted its use to patients with a particular HLA haplotype. We sought to address these problems with a novel vaccination strategy.

Methods: Each vaccination was preceded by 10 days of metronomic low dose oral cyclophosphamide, designed to reduce Tregs. A vaccine consisting of 7 hTERT peptides, predicted to bind MHC Class I and II proteins, not HLA restricted, was given 3-weekly ID. Adjuvants (Montanide ID and topical imiquimod), were used to optimise hTERT presentation. The primary objective was safety, with secondary objectives of immunological and clinical efficacy. Blood lymphocyte phenotypic profiles were analysed ex vivo and post culture to identify activated T effector cells, checkpoint-regulatory T cells and Tregs. T cell receptor (TCR) sequencing was performed prior to and post vaccination.

Results: 17 patients (pts) have completed treatment. Vaccination was well tolerated, 1 withdrew following an injection site reaction. 4 pts (24%) had stable disease for >6 months (colorectal, lung, pancreas, prostate). Baseline activated T cells in pts (CD8+CTLA-4+, n = 9) were similar to healthy donors (HDs), but increased up to 3-fold post-vaccination (p = 0.017). T cells from 5 pts were cultured in vitro post-vaccination; peptide-specific activation of CD4+ and CD8+ T cells was seen in 4/5 and 3/5, respectively. Baseline checkpoint regulatory (PD-1+) CD4+/CD8+ T cells were 8-10 fold higher in pts (CD4+, p = 0.011; CD8+, p = 0.004) than HDs; post-vaccination levels fell but remained >HDs. Post-treatment Tregs fell significantly (FOXP3+PD-1+, p = 0.016). TCR sequencing demonstrated the emergence of clonally expanded T cells, including hTERT-specific clones.

Conclusions: This pan-tumour generic vaccine was safe, with sustained disease stabilisation in a subset of patients with a range of tumour types. Immune-suppressor T cell numbers fell, and hTERT-specific T effector cells were generated.

Clinical trial identification: EudraCT: 2014-003025-18.

Legal entity responsible for the study: King's Health Partners.

Funding: Candles Charity.

Disclosure: All authors have declared no conflicts of interest.

1158P Phase I/II, open-label, multiple ascending dose trial of AGEN2034, an anti–PD-1 monoclonal antibody, in advanced solid malignancies: Results of dose escalation in advanced cancer and expansion cohorts in subjects with relapsed/refractory cervical cancer

C. Drescher[1], K.N. Moore[2], J.F. Liu[3], D.M. O'Malley[4], E.W. Wang[5], J.S-Z. Wang[6], V. Subbiah[7], B.A. Wilky[8], G. Yuan[9], C.D. Dupont[10], A.M. Gonzalez[11], D. Savitsky[10], S. Coulter[12], O. Shebanova[13], E. Dow[14], W. Ortuzar[15], J.S. Buell[16], R.B. Stein[17], H. Youssoufian[12]

[1]Gynecologic Oncology, Pacific Gynecology Specialists Seattle, Seattle, WA, USA, [2]Gynecologic Oncology, Stephenson Cancer Center at the University of Oklahoma Health Sciences Center/Sarah Cannon Research Institute, Oklahoma City, OK, USA, [3]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [4]Obstetrics and Gynecology, The Ohio State University College of Medicine, Columbus, OH, USA, [5]Medical Oncology & Therapeutics Research, Penn State College of Medicine, Hershey, PA, USA, [6]Medical Oncology, Sarah Cannon, Sarasota, FL, USA, [7]Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA, [8]Department of Medicine, Division of Hematology/Oncology, Sylvester Comprehensive Cancer Center, Miami, FL, USA, [9]Statistics, Agenus Bio, Inc., Lexington, MA, USA, [10]Tcell Biology, Agenus Bio, Inc., Lexington, MA, USA, [11]Translational Medicine, Agenus Bio, Inc., Lexington, MA, USA, [12]Clinical Operations, Agenus Bio, Inc., Lexington, MA, USA, [13]Program and Portfolio Management, Agenus Bio, Inc., Lexington, MA, USA, [14]Development Management, Agenus Bio, Inc., Lexington, MA, USA, [15]Corporate Communications, Agenus Bio, Inc., Lexington, MA, USA, [16]Communications and External Affairs, Agenus Bio, Inc., Lexington, MA, USA, [17]Research Management, Agenus Bio, Inc., Lexington, MA, USA

Background: AGEN2034 is a fully-human immunoglobulin (IgG)-4 monoclonal antibody antagonist targeting programmed death protein 1 (PD-1). The objective was to assess safety, maximum tolerated dose, preliminary efficacy, and pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AGEN2034 in patients (pts) with advanced malignancies.

Methods: 30 pts were enrolled at dose cohorts of 1, 3, and 10 mg/kg. AGEN2034 is given intravenously Q2w for ≤2 years with cohorts at Q3w dosing at 6 and 10 mg/kg. A phase 2 expansion of AGEN2034 3 mg/kg Q2w in pts with relapsed/refractory cervical cancer is under way.

Results: 10 pts were enrolled at each dose level. Median age was 58 y, with ECOG scores 0–1. No dose-limiting toxicities were observed. Immune-related adverse events (AEs) consistent with this drug class were observed, including pneumonitis, colitis, diarrhea, rash, and pruritus. 21 of 30 pts had treatment-related AEs (TRAEs). 13 (43%) subjects discontinued (d/c) due to disease progression and 1 patient each d/c due to TRAEs of hepatitis and pneumonitis. At the time of data cutoff, in 25 evaluable heavily pretreated pts, 3 partial responses (2 confirmed) were noted in pts with cervical, ovarian, and breast cancers in the 1 and 3 mg/kg cohorts. 13 patients had stable disease, including 5 of 5 patients with ovarian cancer. AGEN2034 demonstrates a dose-proportional C_{max} of 19.6 μg/mL at 1 mg/kg and 73.6 μg/mL at 3 mg/kg in 12 pt samples analyzed in the first 2 cohorts. Average PD-1 receptor occupancy (RO) on circulating CD8$^+$ and CD4$^+$ effector memory T lymphocytes (n = 18) demonstrated >59% saturation at all dose levels at day 15 post infusion.

Conclusions: AGEN2034 is pharmacologically active, well-tolerated PD-1 antagonist antibody, demonstrating early signals of clinical activity in cervical and ovarian cancers. PK and RO results are comparable to commercial PD-1 antagonists. Updated safety and efficacy results for the dose escalation and the relapsed cervical cancer cohorts will be presented. (NCT03104699). A phase 2 combination study of AGEN2034 and AGEN1884 (CTLA-4) is under way.

Clinical trial identification: NCT03104699.

Editorial acknowledgement: Editorial support was provided by The Medicine Group, LLC (New Hope, PA, USA) and funded by Agenus Inc. (Lexington, MA, USA).

Legal entity responsible for the study: The licensed antibody AGEN2034 was originally developed under a Collaborative Research and Development Agreement between Ludwig Cancer Research, 4-Antibody AG (now Agenus Switzerland Inc.) and Recepta Biopharma S.A. This antibody is partnered with Recepta Biopharma S.A. for certain South American rights.

Funding: Agenus Inc. (Lexington, MA, USA).

Disclosure: K.N. Moore: Consulting or advisory role: Genentech/Roche, Immunogen, Advaxis, AstraZeneca, Clovis Oncology, Tesaro, VBL Therapeutics, Janssen Oncology; Travel, accomodations, expenses: Genentech/Roche; Research funding: PTC Therapeutics Lilly. J.F. Liu: Consulting or advisory role: Tesaro, AstraZeneca; Research

funding: Genentech/Roche, AstraZeneca, Merrimack, Boston Biomedical, Atara Biotherapeutics, Acetylon Pharmaceuticals, Bristol-Myers Squibb, Agenus, CytomX Therapeutics. D.M. O'Malley: Consulting or advisory role: Janssen Oncology, AstraZeneca, Clovis Oncology, Amgen, Tesaro, Novocure, Myriad Genetics; Research funding: Amgen, VentiRx, AstraZeneca, Genentech/Roche, Regeneron, Immunogen,Janssen Research & Development, Clovis Oncology, EMD Serono, Ergomed, Ajinomoto, Immunogen, Cerulean Pharma, PharmaMar, Array BioPharma, Bristol-Myers Squib, Agenus, Tesaro, Tracon Pharma, Stem CentRx; Honoraria: Clovis Oncology. J.S.-Z. Wang: Speakers' bureau: AstraZeneca/MedImmune. V. Subbiah: Consulting or advisory role: MedImmune; Travel, accomodations, expenses: PharmaMar, Bayer; Research funding: Novartis, GlaxoSmithKline, NanoCarrier, Northwest, Biotherapeutics, Genentech/Roche, Berg Pharma, Bayer, Incyte, Fujufilm, PharmaMar, D3 Oncology Solutions, Pfizer, Amgen, Abbvie, Multivir, Blueprint Medicines, Loxo, Vegenics, Takeda, Alfasigma, Agensys, Idera, Boston Biomedical. B.A. Wilky: Consulting or advisory role: Novartis, Janssen Oncology, Lilly; Travel, accomodations, expenses: Novartis, Lilly, Advenchen Laboratories; Research Funding: Novartis, Merck Sharp & Dohme, Daiichi Sankyo, ArQule, Agenus. G. Yuan, A.M. Gonzalez, D. Savitsky, S. Coulter, E. Dow, H. Youssoufian: Agenus Inc. or subsidiary there of (current or former employee). C.D. Dupont: Agenus Inc. or subsidiary there of (current or former employee); Vertex -An Immediate Family Member Rochester Eye Associates- An Immediate Family Member Travel, Accomodations, Expenses: Agenus Research Funding: Agenus; Vertex; Pfizer; Sanofi Stock and other ownership: Agenus O. Shebanova: Agenus Inc. or subsidiary there of (current or former employee); Travel, Accomodations, Expenses: Agenus; Stock and other ownership: Agenus. W. Ortuzar: Full time contracted consultant: Agenus Bio, Inc. J.S. Buell: Agenus Inc. or subsidiary there of (current or former employee); Travel, Accommodations, Expenses: Agenus. R.B. Stein: Agenus Inc. or subsidiary there of (current or former employee); Stock and other ownership: Agenus. All other authors have declared no conflicts of interest.

1159P Phase I/II study of spartalizumab (PDR001), an anti-PD1 mAb, in patients with advanced melanoma or non-small cell lung cancer

C-C. Lin[1], M. Taylor[2], V. Boni[3], P.F. Brunsvig[4], S.L. Geater[5], S. Salvagni[6], P. Garrido Lopez[7], M. Özgüroğlu[8], V. Sriuranpong[9], S. Ponce Aix[10], P.A. Ascierto[11], A. Fasolo[12], A. Sezer[13], D.M. Kowalski[14], J.E. Faris[15], S. Cameron[15], J. Mataraza[16], H. Wu[17], V. Antona[18], M. Ochoa de Olza[19]

[1]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan, [2]Division of Hematology & Medical Oncology, Oregon Health & Science University, Portland, OR, USA, [3]Medical Oncology, START Madrid CIOCC Hospital Universitario Sanchinarro, Madrid, Spain, [4]Department of Oncology, Oslo University Hospital, Oslo, Norway, [5]Internal Medicine, Prince of Songkla University, Songkhla, Thailand, [6]Policlinico S. Orsola-Malpighi, Bologna University Hospital, Bologna, Italy, [7]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [8]Medical Oncology, Istanbul University, Istanbul, Turkey, [9]Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and the King Chulalongkorn Memorial Hospital, Bangkok, Thailand, [10]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [11]Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, National Tumour Institute Fondazione G. Pascale, Naples, Italy, [12]Oncology, San Raffaele Hospital, Milan, Italy, [13]Department of Medical Oncology, Başkent University Medical Faculty, Adana, Turkey, [14]Oncology, Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland, [15]Translational Clinical Oncology, Novartis Institutes for BioMedical Research, Cambridge, MA, USA, [16]Translational Immuno-Oncology, Novartis Institutes for BioMedical Research, Cambridge, MA, USA, [17]Biostatistics, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [18]Translational Clinical Oncology, Novartis Institutes for BioMedical Research, Basel, Switzerland, [19]Research Unit for Molecular Therapy of Cancer (UITM), Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: Spartalizumab is a humanized IgG4 anti-PD1 mAb, which has previously shown favorable PK and safety, and preliminary clinical activity.

Methods: This Phase I/II, open-label, dose escalation/expansion study (NCT02404441) characterized the safety and efficacy of spartalizumab in patients (pts) with advanced solid tumors. In dose escalation, the recommended Phase II dose was declared as 400 mg Q4W (alternative: 300 mg Q3W). Here, we present expansion data for anti-PD(L)1-naïve cohorts with advanced melanoma and NSCLC. PD-L1 expression was assessed centrally (Dako PD-L1 IHC 22C3 pharmaDx).

Results: As of Nov 13, 2017, 61 pts with melanoma received 400 mg spartalizumab Q4W; 36% of pts were treatment-naïve, 20% had ≥2 prior therapies, and all were anti-PD(L)1-naïve. Suspected-related AEs (all grades, ≥5%) were fatigue (15%), decreased appetite (11%), hypothyroidism (8%), rash (8%), asthenia (7%), vitiligo (7%). ORR (confirmed responses) was 26% (16/61), including 1 CR. 41 pts (67%) had baseline PD-L1 data: 63% were PD-L1– (TPS <1%). ORR was 40% (6/15) for PD-L1 + (TPS ≥1%) and 19% (5/26) for PD-L1– pts. 118 pts with NSCLC received 400 mg Q4W (n = 59) or 300 mg Q3W (n = 59); all pts had received prior treatment, 27% had ≥2 therapies. Suspected-related AEs (≥5%) were diarrhea, nausea, decreased appetite, hypothyroidism (5% each). ORR (confirmed responses) was 9% (11/118). 77 pts (65%) had baseline PD-L1 data: 61% were PD-L1–. More Q3W than Q4W treated pts were PD-L1– (70% vs 52%). ORR was 6% (3/47) in PD-L1–, 11% (1/9) in PD-L1 1–49%, and 19% (4/21) in PD-L1 ≥50%. ORR was lower in Q3W (5%; 3/59) than Q4W treated pts (14%; 8/59) but was higher in PD-L1+ pts in both groups (Q3W: 18.2% vs 3.8%, Q4W: 15.8% vs 9.5%). PK analyses confirmed flat dosing (Q3W or Q4W) achieved drug exposure comparable with weight-based dosing.

Conclusions: Spartalizumab was well tolerated with a manageable safety profile. Efficacy was observed in pts with NSCLC (Q3W and Q4W) and melanoma (Q4W), and was as expected given the high proportion of pts with PD-L1– disease. ORRs were higher in PD-L1+ pts, corroborating previous findings that PD-L1 expression enriches for response to anti-PD1 agents in certain tumor types.

Clinical trial identification: NCT02404441, CPDR001X2101.

Editorial acknowledgement: Editorial assistance was provided by Laura Hilditch of ArticulateScience Ltd.

Legal entity responsible for the study: Novartis Pharmaceutical Corporation.

Funding: Novartis Pharmaceutical Corporation.

Disclosure: C-C. Lin: Consulting/advisory fees: Novartis, Boehringer Ingelheim; Expenses: Lilly. M. Taylor: Honoraria, consulting/advisory fees: BMS, Eisai, Novartis, Loxo, Blueprint; Speakers' bureau fees: BMS, Eisai; Expenses: BMS, Eisai, Loxo, Blueprint. S.L. Geater: Honoraria: AstraZeneca, Boehringer Ingelheim; Consulting/advisory fees: Boehringer Ingelheim; Research funding: AstraZeneca, Boehringer Ingelheim, Roche, Novartis. P. Garrido: Consulting/advisory fees: BMS, Novartis, AstraZeneca, Roche, MSD, Pfizer; Speakers' bureau fees: BMS, MSD, Roche, Pfizer, Gilead; Expenses from Roche, BMS, Gilead, MSD. M. Özgüroğlu: Honoraria: Janssen; Consulting/advisory fees: Janssen, Astellas. V. Sriuranpong: Honoraria, consulting/advisory fees, research funding: Novartis; P.A. Ascierto: Consulting/advisory fees: BMS, Roche-Genentech, MSD, Array, Novartis, Amgen, Merck Serono, Pierre-Fabre, Incyte, NewLink Genetics, Genmab, MedImmune, Sindax, AstraZeneca; Research funding: BMS, Roche-Genentech, Array. J.E. Faris: Employee: Novartis S. Cameron: Employee and has Stock: Novartis. J. Mataraza: Employee and has stock: Novartis; intellectual Property: Novartis, Merck. H. Wu: Employed and received expenses: Novartis. V. Antona: Employee and has stock: Novartis; Honoraria, expenses: Novartis. All other authors have declared no conflicts of interest.

1160P Phase I/II evaluation of intratumoral INT230-6 for the treatment of solid tumors

A. El-Khoeuiry[1], L.L. Siu[2], N. Azad[3], I.B. Walters[4], L. Bender[5], L. Kamen[5], A.J. Olszanski[6]

[1]Phase 1 Program, USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [2]Phase 1 Program, Princess Margaret Hospital, Toronto, ON, Canada, [3]Phase 1 Clinical Trials Group, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA, [4]Clinical Research, Intensity Therapeutics, Westport, CT, USA, [5]Clinical Research, Intensity Therapeutics, Westport, CT, USA, [6]Phase 1 Developmental Therapeutics Program, Fox Chase Cancer Center, Philadelphia, PA, USA

Background: INT230-6 is a formulation of cisplatin and vinblastine with an amphiphillic penetration enhancer to improve dispersion and diffusion into cancer cells. This is the first product designed for selective delivery into tumors with the potential to deliver high payload levels directly into cancer cells while sparing healthy cells. In colon 26 animal models, injection into a sentinel lesion led to tumor necrosis, recruitment of dendritic cells into the tumor and activation of CD4 and CD8 T-cells. Injected tumors experienced high rates of complete response (up to 80%). Importantly, untreated lesions distal to the injection site also responded. Efficacy was synergistic when combined with checkpoint inhibitors.

Methods: Initial cohort enrolled subjects with advanced solid tumors with superficial lesions amenable to local injection. INT230-6 was administered intratumorally at a ratio of 1ml for each 4 cubic cm of tumor volume, once each month for a total of 5 cycles. Both the maximal dose into one tumor and the total dose (over multiple lesions) could be escalated on repeat cycles if no DLTs. Patients were monitored for safety weekly. Pharmacokinetic(Pk) samples and peripheral blood were collected for flow cytometry and circulating cytokines. Subsequent cohorts of twice monthly injections into superficial tumors and monthly injection into deep tumors commenced after comprehensive review of safety data in superficial tumors.

Results: Thirteen subjects were treated with either melanoma, SCC, ovarian, chordoma, cholangiocarcinoma or H&N into single or multiple lesions. Pk analysis revealed negligible amounts of reduced platinum and vinblastine in blood, suggesting retention in the tumor compartments. No DLTs or drug related SAEs were reported. The most frequent adverse event was grade 1 or 2 injection site pain, or other local symptom (infection or blister). Subjectively, some injected lesions were noted to change as soon as 1 week with flattening and areas of necrosis.

Conclusions: INT230-6 was safe when administered locally to tumors at doses given. Updated results will be presented including biomarker and response data. Additional cohorts including higher drug concentrations and combination with an anti-PD1 antibody.

Clinical trial identification: NCT:03058289.

Legal entity responsible for the study: Ian B. Walters, MD.

Funding: Intensity Therapeutics.

Disclosure: A. El-Khoeuiry, L.L. Siu, N. Azad, A.J. Olszanski: Funding to institutions: Intensity Therapeutics. I.B. Walters: Employee and stockholder: Intensity Therapeutics. L. Bender: Founder and CEO of Intensity Therapeutics, named on the patents, stock holder and employee of the company which manufactures the product being studied. L. Kamen: Consultant and stock owner: Intensity therapeutics.

1161P OMTX705, a powerful stroma-targeting ADC to treat invasive tumors with low response to immunotherapeutic anti-PD-1 treatments

M. Fabre[1], C. Ferrer[1], S. Dominguez-Hormaetxe[1], R. Kontermann[2], K. Pfizenmaier[2], O. Seifert[2], P.P. López-Casas[3], M. Abbas[4], W. Richter[4], L. Simon[1], M. Hidalgo[5]

[1]R&D Department, Oncomatryx Biopharma S.L, Derio, Spain, [2]Institute of Cell Biology and Immunology, Stuttgart University, Stuttgart, Germany, [3]Gastrointestinal Cancer Clinical Research Unit, CNIO, Madrid, Spain, [4]R&D Department, Tube Pharmaceuticals, GmBH, Vienna, Austria, [5]Department of Medicine, Harvard Medical School, Boston, MA, USA

Background: Tumor microenvironment represents 20-60% of solid tumor mass and is increasingly recognized to play a key role in promotion, invasiveness and metastasis. Mounting evidence suggests that FAP-expressing CAFs, the predominant stroma cell type, is involved in the tumor immune response. A novel antibody-drug conjugate, OMTX705, was generated through CYS-based conjugation of a new anti-FAP humanized antibody, with high specificity and affinity, to a novel cytolysin, using an optimized vcPABA linker.

Methods: In vivo studies were performed in patient-derived xenograft models for pancreatic and NSCL cancer in immunodeficient and humanized mice. Tumor volume and animal weight were monitorized 3 times a week over 4 weeks of treatment with OMTX705, administered intravenously at different doses, either as single agent or in combination with chemotherapy such as Gemcitabine or Paclitaxel, or immunotherapy such as Pembrolizumab. FACS and IHC analysis of CD45, CD25, CD3, CD4, CD8 and Fox3P markers were performed on blood and tumor samples to study the effect of OMTX705 on immune system in these models.

Results: OMTX705 showed 100% tumor growth inhibition and regression in the PDX murine models for pancreatic and NSCL cancer, both as single agent and in combination with Gemcitabine and Nab-Paclitaxel, Paclitaxel, or Pembrolizumab, without weight loss. When treated with OMTX705 in combination with chemotherapy, the response was maintained for a longer period without further treatment: re-growth of tumors was delayed and tumors kept responding upon re-treatment, showing lack of resistance to OMTX705 treatment. In combination with Pembrolizumab immunotherapy in a humanized PDX model for lung cancer, OMTX705 efficacy was even higher at lower dose, inducing full regression and significant delay in tumor recurrence, through CD8(+) T cell dependent immunomodulation.

Conclusions: FAP-targeted OMTX705 represents a potent novel strategy for cancer treatment at invasive stages. Due to the broad expression of FAP in the tumor microenvironment of a wide array of carcinomas, OMTX705 is a highly promising candidate to treat different solid tumors with low response to anti-PD1 immunotherapies.

Legal entity responsible for the study: Oncomatryx Biopharma, S.L.

Funding: Oncomatryx Biopharma, S.L.

Disclosure: M. Fabre, C. Ferrer, S. Dominguez-Hormaetxe, L. Simon: Employment: Oncomatryx Biopharma, S.L. R. Kontermann, K. Pfizenmaier, M. Hidalgo: Member scientific advisory board: Oncomatryx Biopharma, S.L. M. Abbas: Employee: Tube Pharmaceuticals, GmBH. W. Richter: Employee and shareholder: Tube Pharmaceuticals, GmBH. All other authors have declared no conflicts of interest.

1162P Cemiplimab, a human monoclonal anti-PD-1, plus radiotherapy (RT) in advanced non-small cell lung cancer (NSCLC): Results from a phase I expansion cohort (EC 2)

V. Moreno[1], M. Gil-Martin[2], M. Johnson[3], R. Aljumaily[4], P. Lopez Criado[5], D.W. Northfelt[6], M. Crittenden[7], S. Jabbour[8], L. Rosen[9], P. Garrido Lopez[10], A. Hervás Morón[11], P. Rietschel[12], K.K. Mohan[12], J. Li[13], E. Stankevich[14], T. Rowlands[12], M. Feng[14], I. Lowy[12], M.G. Fury[12]

[1]Phase 1 Trials Unit, START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain, [2]Institut Català d'Oncologia, Barcelona, Spain, [3]Department of Medical Oncology, Sarah Cannon Research Institute, Nashville, TN, USA, [4]Department of Hematology/Oncology, Oklahoma University Medical Center, Oklahoma City, OK, USA, [5]Department of Medical Oncology, MD Anderson Cancer Center, Madrid, Spain, [6]Department of Internal Medicine, Division of Hematology/Oncology, Mayo Clinic, Phoenix, AZ, USA, [7]Robert W. Franz Cancer Center, Providence Portland Medical Center and The Oregon Clinic, Earle A. Chiles Research Institute, Portland, OR, USA, [8]Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA, [9]Division of Hematology-Oncology, UCLA, Los Angeles, CA, USA, [10]Medical Oncology Department, Hospital Universitario Ramon y Cajal, Madrid, Spain, [11]Department of Radiology, Hospital Universitario Ramón y Cajal, Madrid, Spain, [12]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [13]Biostatistics & Data Management, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA, [14]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA

Background: Cemiplimab (REGN2810), a human monoclonal antibody to PD-1, has exhibited substantial antitumour activities in patients (pts) with advanced malignancies in a Phase 1 study. Most patients with advanced NSCLC do not respond to PD-1 inhibitor monotherapy. Here we report results of the Phase 1 EC 2, a combination regimen of cemiplimab plus RT in advanced NSCLC (NCT02383212).

Methods: Pts with advanced NSCLC who had relapsed after or were refractory to at least first-line therapy and for whom palliative RT was clinically indicated, received cemiplimab 3 mg/kg every 2 weeks for up to 48 weeks plus RT (9 Gy × 3 times/week given 1 week after first dose of cemiplimab) to a single lesion. The co-primary objectives were to evaluate the safety, tolerability, and efficacy of cemiplimab plus RT. Tumour measurements (of non-irradiated target lesions) were performed by RECIST 1.1 every 8 weeks.

Results: As of 1 Sept, 2017, 33 pts (22 M/ 11 F; median age 67.0 years [range, 47–82]) were enrolled; 66.7% and 30.3% had an ECOG performance status of 1 and 0, respectively; the status of one pt was unknown. Overall response rate (ORR; complete response [CR] + partial response [PR]) was 18.2% (0 CR and 6 PRs) with a median duration of response of 14.9 months (95% CI: 5.5–14.9). Disease control rate (ORR + stable disease [SD]) was 72.7% (6 PRs + 18 SDs). The most common treatment-emergent adverse events (TEAEs) of any grade were decreased appetite (30.3%), fatigue (27.3%), and cough (24.2%). Grade $\geq$3 TEAEs occurring in $\geq$ 2 patients include anaemia (12.1%), hypophosphataemia, and urinary tract infection (each 6.1%). One patient had a TEAE of pneumonitis, considered related to study drug, with an outcome of death.

Conclusions: Cemiplimab plus RT demonstrated antitumour activity in pretreated pts with NSCLC. The safety profile is comparable with other anti-PD-1 agents and RT. The combination therapy regimen did not produce greater efficacy above that which can be achieved with PD-1 inhibitor monotherapy for advanced NSCLC.

Clinical trial identification: NCT02383212.

Editorial acknowledgement: Medical writing support under the direction of the authors was provided by Emmanuel Ogunnowo, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc. and Sanofi according to Good Publication Practice guidelines (http://annals.org/aim/article/2424869/good-publication-practice-communicating-company-sponsored-medical-research-gpp3).

Legal entity responsible for the study: Regeneron Pharmaceutical Inc.; Sanofi.

Funding: Regeneron Pharmaceutical Inc.; Sanofi.

Disclosure: M. Johnson: Consulting or advisory role: Astellas Pharma, Otsuka. M. Crittenden: Research funding: Jounce, Nanobiotix. S. Jabbour: Research funding grants: Merck, Nestle, outside the submitted work. L. Rosen: Research funding: Regeneron Pharmaceuticals, Inc. P. Garrido: Personal fees: Roche, BMS, MSD, Pfizer, Lilly, Abbvie, Regeneron, AstraZeneca, Novartis, Boerinhger-Ingelheim, outside the submitted work. P. Rietschel: Shareholder and an employee of, and has received honoraria: Regeneron Pharmaceuticals, Inc. K.K. Mohan, J. Li, T. Rowlands: Shareholder and employee of Regeneron Pharmaceuticals, Inc. E. Stankevich: Shareholder and employee: Regeneron Pharmaceuticals, Inc.; Shareholder: Celgene, Bristol-Myers Squibb, Merck. M. Feng: Shareholder and employee: Regeneron Pharmaceuticals, Inc.; Shareholder: Bayer. I. Lowy: Shareholder and employee of, and gained fees for travel and accommodation expenses as well as leadership: Regeneron Pharmaceuticals, Inc. M.G. Fury: Shareholder and an employee of, and holds patents, royalties, other intellectual property: Regeneron Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

1163P Study on treatment of stage IV solid tumors with mutant neoantigen specific T cells

Q. Song[1], J. Song[2], H. Sun[2], W. Du[3], L. Wu[1], L. Wang[1], Z. Wei[4], Y. Wang[2], Y. Guan[2], X. Xia[2], X. Yi[2], S. Jiao[1]

[1]Oncology Department, The General Hospital of People's Liberation Army, Beijing, China, [2]Research and Development Center, Geneplus-Beijing Institute, Beijing, China, [3]Medical Administration Division, The General Hospital of People's Liberation Army, Beijing, China, [4]Department of Health Care, Chinese PLA Joint Staff Headquarters Guard Bureau, Beijing, China

Background: As an important tumor immunotherapy, the specificity and efficiency of PD1 inhibitor is not yet satisfactory. The treatment of solid tumor with mutant neoantigen specific T (MNaS-T) cells developed in this study is an adoptive cell therapy which is specific for each patient. The aim is to explore the difference in safety and efficacy between MNaS-T cells and PD1 inhibitors, and to evaluate the charateristic of immune repertoire (IR) as predictive biomarker.

Methods: A total number of 11 patients with advanced solid tumors who failed after multiline treatments were recruited. They were treated with MNaS-T cells, PD1 inhibitors and BSC; other 11 patients were treated with PD1 inhibitors and BSC as control. Peripheral blood was collected at baseline and per cycle (21-28d) respectively. Multiple PCR and NGS on TCR beta chain was used to detect IR.

Results: PFS of two groups had a statistical significance ($P < 0.05$), suggesting MNaS-T cells prolong patients' PFS. The safety was analyzed from routine blood urine stool test, coagulation function, liver and kidney function. There was no significant difference at baseline ($P > 0.05$). Compared with C group, total protein and albumin in T group had a transient decrease in 3rd, 4th and 5th follow-up respectively ($P < 0.05$), however, It can be recovered autonomously before 6th cycle. Evenness index and Clonality indexe were examined to illuminate the diversity and clonality of IR seperately. Compared to baseline, T cell repertoir of disease-progression patients and no-disease-progression patients after 1st cycle showed significantly different changes: Evenness 3.29 vs 0.85, $P = 0.013$; Clonality 0.76 vs 1.20, $P = 0.015$. Elevated Clonality may indicate amplification of tumor specific T cells which could recognize mutant neoantigen specifically.

Table: 1163P Demographic and clinical characteristics of 22 patients

Characteristic		MNaS-T cells plus PD1 inhibitors plus BSC (N = 11)			PD1 inhibitors plus BSC (N = 11)
		Disease Progression (N=4)	No Disease Progression (N=7)	Total (N = 11)	
Age–no.(%)					
	<60	4 (100)	5 (71.4)	9 (81.8)	6 (54.5)
	> =60	0	2 (28.6)	2 (18.2)	5 (45.5)
Sex–no.(%)					
	Male	3 (75)	3 (42.9)	6 (54.5)	8 (72.7)
	Female	1 (25)	4 (57.1)	5 (45.5)	3 (27.3)
Previous treatments–no.					
	Chemotherapy	4	7	11	11
	Targeted therapy	4	7	11	11
ECOG–no.(%)					
	0	0	0	0	0
	1	1	6	7	6
	≥2	3	1	4	5
Stage–no.	IV	4	7	11	11
Peripheral IR Diversity–mean (SD)					
Evenness					
	Baseline	0.01 (0.01)	0.07 (0.08)	0.05 (0.07)	
	1st cycle	0.05 (0.05)	0.06 (0.07)	0.05 (0.06)	
	1st cycle / Baseline	3.29 (2.09)	0.85 (0.44)	1.74 (1.71)	
Clonality					
	Baseline	0.32 (0.09)	0.25 (0.18)	0.27 (0.15)	
	1st cycle	0.25 (0.12)	0.27 (0.16)	0.26 (0.14)	
	1st cycle / Baseline	0.76 (0.18)	1.2 (0.27)	1.04 (0.32)	

Conclusions: The combined immunotherapy of MNaS-T cells and PD1 inhibitors is more effective than PD1 inhibitor alone in prolonging the PFS, and has a good safety. IR Clonality change shows its potential as a predictive biomarker.

Legal entity responsible for the study: J. Shunchang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1164P Efficacy of racotumomab or nimotuzumab vs docetaxel as second-line therapy for advanced non-small cell lung cancer patients

M. Hernandez[1], E. Neninger[2], E. Santiesteban[3], K. Camacho[3], N. Hernandez[4], R. Amador[5], S. Acosta[6], Y. Gonzalez[7], Y. Jimenez[8], M. Corella[9], R.A. Ortiz[10], L. Bello[11], A. Calana[12], G. Pichs[13], M. Cala[14], Y. Flores[15], C. Viada[16], M. Robaina[17], T. Crombet[1]

[1]Clinical Research, Center of Molecular Immunology, Havana, Cuba, [2]Clinical Oncology, Hospital Clinico Quirurgico Hermanos Ameijeiras, Havana, Cuba, [3]Clinical Oncology, Jose R. Lopez Tabranes Hospital, Matanzas, Cuba, [4]Clinical Oncology, Miguel Enriquez Hospital, Havana, Cuba, [5]Clinical Oncology, III Congreso Hospital, Pinar del Rio, Cuba, [6]Clinical Oncology, Saturnino Lora Hospital, Santiago de Cuba, Cuba, [7]Clinical Oncology, Comandante Pinares Hospital, Artemisa, Cuba, [8]Clinical Oncology, Camilo Cienfuegos Hospital, Sancti Spiritus, Cuba, [9]Clinical Oncology, Vladimir I. Lenin Hospital, Holguin, Cuba, [10]Clinical Oncology, "Celestino Hernández" Hospital, Villa Clara, Cuba, [11]Clinical Oncology, Antonio Luaces Iraola Hospital, Ciego de Avila, Cuba, [12]Clinical Oncology, Gustavo Aldereguia Lima Hospital, Cienfuegos, Cuba, [13]Clinical Oncology, Celia Sanchez Manduley Hospital, Granma, Cuba, [14]Clinical Oncology, Juan Bruno Zayas Hospital, Santiago de Cuba, Cuba, [15]Clinical Oncology, National Institute of Oncology and Radiobiology, Havana, Cuba, [16]Clinical Research, Center of Molecular Immunology, Havana, Cuba, [17]Clinical Research, National Coordinating Center for Clinical Trials, Havana, Cuba

Background: Racotumomab-alum is an anti-idiotypic vaccine that induces immunological response against N-glycolilated gangliosides in NSCLC patients. Nimotuzumab is a humanized anti-EGFR monoclonal antibody that has shown activity in NSCLC patients. The aim of this study is to evaluate safety and efficacy of racotumomab-alum or nimotuzumab versus docetaxel as second line or switch maintenance therapy for advanced NSCLC.

Methods: This phase III, multicenter, open label, randomized trial is designed to enroll 743 stage IIIB-IV NSCLC patients, after first line therapy, with PS 0-2, with written informed consent. The primary endpoint is Overall Survival (OS). Patients are been randomized (2:2:1) to 3 arms: racotumomab-alum, nimotuzumab or docetaxel, and stratified according to response to first line (progressor or non-progressor patients). Racotumomab-alum treatment consists in 5 bi-weekly intradermal doses and re-immunizations every 4 weeks. Nimotuzumab arm receives 6 weekly infusions followed by bi-weekly doses. Docetaxel is used at 75 mg/m2 for 6 cycles, if there is no evidence of progressive disease after 3 cycles. As second-line therapy, both experimental drugs will be classified as non-inferior (NI) to docetaxel, if 1- year OS rate is 23.1 % and HR C/T=0.76, [d0 (0,28), d0= - ln HR(C/T)] using a 10% NI margin. Here we report the interim analysis in 255 progressor patients.

Results: 106 patients in racotumomab, 97 in nimotuzumab and 54 in docetaxel arm with at least 1 year follow up were analyzed (ITT). The median OS and 1-year survival rate were 4.67 months (CI: 4.0-5.3) and 14.5 % with nimotuzumab, 4.83 months (CI: 3.7-5.9) and 23.5 % with racotumomab-alum and 5.85 months (CI: 3.9-7.7) and 20.2 % with docetaxel, respectively. Most frequent treatment-related adverse events were induration (10.7%), local erythema in injection site (8.8%) and arthralgia (8.2%) with racotumomab-alum; myalgia (12.1%), fever (7.9%) and nausea (7.0%) with nimotuzumab, and nausea (16.5%), asthenia (13.2%) and vomiting (12.1%) after docetaxel.

Conclusions: These data do not confirm the non-inferiority of racotumomab-alum or nimotuzumab versus docetaxel as second-line therapy. Both experimental treatments were safely administered at primary level of health assistance.

Clinical trial identification: RPCEC0000017.

Legal entity responsible for the study: Center of Molecular Immunology.

Funding: Center for Molecular Immunology.

Disclosure: M. Hernandez, C. Viada, T. Crombet: Employed: Center of Molecular Immunology. All other authors have declared no conflicts of interest.

1165P Preliminary safety, pharmacokinetics (PK) and efficacy results from a phase I study of CS1001, an anti-programmed death ligand-1 (PD-L1) monoclonal antibody (mAb) in patients (pts) with advanced tumors

L. Shen[1], J. Cao[2], J. Gong[1], D. Ji[2], Z. Qin[3], H. Dai[3], K. Wu[3], J. Xu[3], J. Yang[3]

[1]Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China, [2]Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China, [3]Clinical Development, CStone Pharmaceuticals (Su Zhou) Co., Ltd., Shanghai, China

Background: Anti-PD-L1 mAbs have demonstrated anti-tumor activities in multiple indications. CS1001 is the first full-length, fully human anti-PD-L1 mAb developed by OMT transgenic animal platform, which mirrors natural IgG4 human antibody with expected PK profiles, and may potentially reduce the risk of immunogenicity and toxicity in pts.

Methods: A phase I, multi-center study was conducted to evaluate the safety, tolerability, PK and anti-tumor activity of CS1001 in pts with advanced tumors. A 3 + 3 dose-escalation design was undertaken. Pts received CS1001 intravenously once every three week (Q3W). Safety and tolerability were assessed by monitoring adverse events (AEs). Tumor assessments were performed per RECIST v1.1 (solid tumors) or Lugano 2014 (lymphomas).

Results: As of 8 Apr 2018, a total of 19 Asian pts [median age 50 (31–74) yrs] with advanced tumors were treated by CS1001 Q3W across 5 dose-escalating cohorts (3 mg/kg, N = 3; 10 mg/kg, N = 4; 20 mg/kg, N = 3; 40 mg/kg, N = 3; and 1200 mg, N = 6). All pts had received at least 1 prior line of anti-cancer treatment (median 2 [1–7]). Median duration of study treatment was 63 (6–172) days. 14 pts remain on study. No dose-limiting toxicity was observed, and maximum tolerated dose was not reached. The most frequent treatment-emergent AEs were grade (G) 1/2 anemia (n = 7), nausea (n = 6), decreased appetite (n = 5), blood bilirubin increased (n = 4), protein urine present (n = 4), white blood cell count decreased (n = 4) and proteinuria (n = 4). Immune-related AEs (G1-3) occurred in 5 pts. No treatment-related serious AE was reported. PK analysis was conducted using observed CS1001 serum concentrations from 16 pts across all 5 cohorts. The PK of CS1001 was linear and the terminal elimination half-life was about 12 days. Among 12 efficacy evaluable pts, four achieved unconfirmed partial response and all remain on treatment. Three additional pts achieved a best overall response of stable disease.

Conclusions: CS1001 appears to be generally well tolerated in pts with advanced tumors, with a linear PK profile. The preliminary safety profile and anti-tumor activity support continued exploration and development of CS1001.

Clinical trial identification: NCT03312842, October 18, 2017.

Legal entity responsible for the study: CStone Pharmaceuticals (Su Zhou) Co., Ltd.

Funding: CStone Pharmaceuticals (Su Zhou) Co., Ltd.

Disclosure: Z. Qin, H. Dai, K. Wu, J. Xu, J. Yang: Personal fees: CStone Pharmaceuticals, outside the submitted work. All other authors have declared no conflicts of interest.

1166P An oral dual inhibitor of IDO and TDO enhances anti-cancer immunity and synergizes with immune checkpoint blockade

C. Kim[1], N.K. Lee[1], J.S. Kim[2], W.R. Kim[3], D.H. Kim[4], D.J. Kim[5], J.S. Oh[4], S.K. Chang[6], J.W. Kim[3], H.J. Chon[1]

[1]Medical Oncology, Bundang Cha Medical Center, Seongnam, Republic of Korea, [2]Research Department, CMG Pharmaceutical, Seongnam, Republic of Korea, [3]Surgery, CHA Bundang Medical Center, Seongnam, Republic of Korea, [4]Internal Medicine, CHA Bundang Medical Center, Seongnam, Republic of Korea, [5]Radiology, CHA Bundang Medical Center, Seongnam, Republic of Korea, [6]Radiation Oncology, Bundang Cha Medical Center, Seongnam, Republic of Korea

Background: Indolamine 2,3-dioxygenase (IDO) blockade is a new therapeutic strategy to enhance cancer immunity. However, IDO blockade alone cannot completely block the immunosuppressive tryptophan-kynurenine (Trp-Kyn) pathway in the tumor microenvironment. Recent studies have demonstrated that Trp 2,3-dioxygenase (TDO) is an alternative enzyme employed by various tumors that can be used as a target for the Trp-Kyn pathway; therefore, here we developed an orally available dual inhibitor that targets IDO and TDO.

Methods: Small-molecule inhibitors for IDO and TDO were synthesized and screened by in vitro IDO/TDO enzyme and cell-based assays. CT26 colon or 4T1 breast tumor-bearing mice were treated with CB548 either alone or in combination with an anti-PD1 antibody. We monitored tumor growth and analyzed the tumor microenvironment using flow cytometry, qPCR, and confocal microscopy.

Results: A lead compound, CB548, showed potent inhibition of IDO and TDO in the enzyme and cell-based assays with various human and murine cancer cell lines. Oral administration of CB548 revealed a good pharmacokinetic profile, and the conversion of Trp to Kyn in tumors was effectively suppressed. Moreover, the CB548 monotherapy revealed a dose-dependent inhibition of CT26 colon or 4T1 breast cancer growth as well as markedly increased CD8+ T cell infiltration in the tumor microenvironment. Additionally, the combination immunotherapy of CB548 and anti-PD1 antibody suppressed tumor growth to a greater extent than did the monotherapy, and led to durable tumor regression. There was no significant systemic toxicity with the CB548 treatment.

Conclusions: Overall, our study demonstrates that CB548, a novel IDO/TDO dual inhibitor, can elicit a robust anti-cancer immunity and synergistically inhibit cancer progression in combination with an immune checkpoint inhibitor.

Legal entity responsible for the study: CHA Bundang Medical Center.

Funding: This work was supported by the Bio & Medical Technology Development Program of the National Research Foundation funded by the Ministry of Science & ICT of Republic of Korea.

Disclosure: J.S. Kim: Employee of the CMG Pharmaceutical. All other authors have declared no conflicts of interest.

1167P Phase I, open-label ascending dose trial of anti–CTLA-4 monoclonal antibody AGEN1884 in advanced solid malignancies, with expansion to patients refractory to recent anti–PD-1/PD-L1 therapy

B.A. Wilky[1], P. Kumthekar[2], R. Wesolowski[3], J.J. Hwang[4], S.I. Park[5], G. Yuan[6], C.D. Dupont[7], M. Lim[7], O. Shebanova[8], J-M. Cuillerot[9], E. Dow[10], W. Ortuzar[11], J.J. Raizer[12], E. Drouin[13], N. Wilson[14], A.M. Gonzalez[15], J.M. Goldberg[16], J.S. Buell[17], R.B. Stein[18], H. Youssoufian[19]

[1]Department of Medicine, Division of Hematology/Oncology, Sylvester Comprehensive Cancer Center, Miami, FL, USA, [2]Department of Neurology and Department of Medicine, Northwestern Memorial Hospital, Chicago, IL, USA, [3]Internal Medicine, The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH, USA, [4]Hematology/Medical Oncology, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA, [5]Hematology and Oncology, Levine Cancer Institute, Northern Division, Charlotte, NC, USA, [6]Statistics, Agenus Bio, Inc., Lexington, MA, USA, [7]Tcell Biology, Agenus Bio, Inc., Lexington, MA, USA, [8]Program and Portfolio Management, Agenus Bio, Inc., Lexington, MA, USA, [9]Medical Oncology, Agenus Bio, Inc., Cambridge, MA, USA, [10]Development Management, Agenus Bio, Inc., Lexington, MA, USA, [11]Corporate Communications, Agenus Bio, Inc., Lexington, MA, USA, [12]Department of Medicine, Agenus Bio, Inc., Lexington, MA, USA, [13]Medical Oncology, Jounce Therapeutics, Inc., Cambridge, MA, USA, [14]Medical Oncology, Gilead Sciences, Lexington, MA, USA, [15]Translational Medicine, Agenus Bio, Inc., Lexington, MA, USA, [16]Hematology and Oncology, Agenus Bio, Inc., Lexington, MA, USA, [17]Communications and External Affairs, Agenus Bio, Inc., Lexington, MA, USA, [18]Research Management, Agenus Bio, Inc., Lexington, MA, USA, [19]Medical Oncology, Agenus Bio, Inc., Lexington, KY, USA

Background: AGEN1884 is a novel anti–cytotoxic T-lymphocyte-associated antigen (CTLA)-4 fully human immunoglobulin (IgG)-1 monoclonal antibody. Objective: Assess safety, maximum tolerated dose, and pharmacokinetics (PK)/pharmacodynamics of AGEN1884 in patients (pts) with advanced/refractory malignancies and in pts refractory to recent anti–programmed death 1 (PD-1)/PD-L1 therapy.

Methods: Adult pts with relapsed/refractory lymphoma or solid tumors received AGEN1884 at 0.1, 0.3, 1, 3, or 6 mg/kg (3 + 3 design). 10 more pts each were enrolled in 1 and 3 mg/kg expansion cohorts. 10 pts with disease progression after prior treatment with approved or investigational PD-1/PD-L1 inhibitor as most recent therapy (2–5 weeks [wks] before first study drug) will be enrolled at 1 mg/kg. AGEN1884 was administered intravenously Q3 wks for 4 doses, then Q3, 6, or 12 wks at investigator's discretion.

Results: 33 pts enrolled as of 03Jan2018: 0.1 mg/kg (n = 5; 2 not evaluable [NE] for dose-limiting toxicity [DLT]); 0.3 mg/kg (n = 3); 1 mg/kg (n = 10); 3 mg/kg (n = 12; 2 NE for DLT); 6 mg/kg (n = 3). Median age: 61 y (range 26–88); baseline ECOG scores: 0 (n = 4), 1 (n = 25), unknown (n = 4); median 10 (range 3–26) prior therapies. No DLTs reported as of 31Jan2018. Immune-related adverse events (AEs) reported in 10 (30.3%) pts: 0.1 mg/kg (1, 20.0%), 0.3 mg/kg (1, 33.3%), 1 mg/kg (1, 10%), 3 mg/kg (6, 50%); included hypophysitis, colitis, diarrhea, rash, pruritus. Most were mild-moderate, consistent with other CTLA-4 inhibitors. 6 (18.2%) pts came off study due to disease progression or AEs, none treatment-related. Of 11 pts evaluable for response, 1 had complete response (angiosarcoma, 0.1 mg/kg). Stable disease (SD) in 3 pts: 1 with adenoid cystic carcinoma (0.3 mg/kg, 53 wks of SD) and 2 with breast cancer (3 mg/kg, SD at wks 6 and 12, respectively).

Conclusions: AGEN1884 was well tolerated at 0.1, 0.3, 1, and 3-mg/kg dose levels. Enrollment is ongoing at 6 mg/kg. Updated safety, PK, and results for the anti–PD-1/PD-L1 refractory expansion cohort will be presented. A starting dose of 1 mg/kg is being evaluated in ongoing trials in combination with PD-1 blockade.

Clinical trial identification: NCT02694822.

Editorial acknowledgement: Editorial support was provided by The Medicine Group, LLC (New Hope, PA, USA) and funded by Agenus Inc. (Lexington, MA).

Legal entity responsible for the study: The licensed antibody AGEN1884 was originally developed under a Collaborative Research and Development Agreement between Ludwig Cancer Research, 4-Antibody AG (now Agenus Switzerland Inc.) and Recepta Biopharma S.A. This antibody is partnered with Recepta Biopharma S.A. for certain South American rights.

Funding: This analysis was funded by Agenus Inc. (Lexington, MA, USA).

Disclosure: B.A. Wilky: Employment: Novartis, Janssen Oncology, Lilly; Travel, accommodations, expenses: Novartis, Lilly, Advenchen Laboratories; Research funding: Novartis, Merck Sharp & Dohmn, Daiichi Sankyo, ArQule, Agenus. R. Wesolowski: Consulting or advisory role: Novartis, Agenus, Pfizer; Research funding: Acerta Pharma. J.J. Hwang: Consulting or advisory role: Genentech/Roche, Amgen, Bayer, Taiho Pharmaceutical, Bristol-Myers Squibb, Boehringer Ingelheim, Ipsen; Speakers bureau: Genentech/Roche, Amgen, Celgene, Ipsen, Bristol-Myers Squibb. G. Yuan, M. Lim, J-M. Cuillerot, J.J. Raizer, E. Drouin, N. Wilson, A.M. Gonzalez, J.M. Goldberg, J.S. Buell, R.B. Stein, H. Youssoufian: Employee: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA. C.D. Dupont: Employee: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA; An immediate family member: Employee: Vertex; An immediate family member: Employee: Rochester Eye Associates; Travel, accommodations, expenses: Agenus; Research funding: Agenus; An immediate family member: Vertex, Pfizer, Sanofi. Stock and other ownership: Agenus; An immediate family member: Vertex. O. Shebanova: Employee: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA; Travel, accommodations, expenses: Agenus; Stock and other ownership: Agenus.

E. Dow: Employee: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA; Employment: Baxalta/Shire; Foundation Medicine stock and other ownership: Baxalta/Shire, Foundation Medicine. W. Ortuzar: Full time contracted consultant: Agenus Bio, Inc. All other authors have declared no conflicts of interest.

1168P Phase I/II study of CTLA-4 inhibitor AGEN1884 + PD-1 Inhibitor AGEN2034 in patients with advanced/refractory solid tumors, with expansion into 2L cervical cancer and solid tumors

J. Coward[1], C. Lemech[2], T. Meniawy[3], C.D. Dupont[4], A.M. Gonzalez[5], M. Lim[6], D. Savitsky[4], M. Carini[7], S. Hu[8], O. Shebanova[9], E. Dow[10], W. Ortuzar[11], J.S. Buell[12], R.B. Stein[13], H. Youssoufian[7]

[1]Clinical Trials, Icon Cancer Care, South Brisbane, Australia, [2]Clinical Trials, Scientia Clinical Research (Sydney), Randwick, Australia, [3]Clinical Trials, Linear Clinical Research, Perth, Australia, [4]Tcell Biology, Agenus Bio, Inc., Lexington, MA, USA, [5]Translational Medicine, Agenus Bio, Inc., Lexington, MA, USA, [6]Medical Oncology, Agenus Bio, Inc., Lexington, MA, USA, [7]Clinical Operations, Agenus Bio, Inc., Lexington, MA, USA, [8]Biostatistics and Data Management, Agenus Bio, Inc., Lexington, MA, USA, [9]Program and Portfolio Management, Agenus Bio, Inc., Lexington, MA, USA, [10]Development Management, Agenus Bio, Inc., Lexington, MA, USA, [11]Corporate Communications, Agenus Bio, Inc., Lexington, MA, USA, [12]Communications and External Affairs, Agenus Bio, Inc., Lexington, KY, USA, [13]Research Management, Agenus Bio, Inc., Lexington, MA, USA

Background: Cytotoxic T-lymphocyte-associated antigen (CTLA)-4 and programmed death 1 (PD-1) pathways have important, distinct roles in T-cell modulation; blockade of both has been synergistic in vitro and in the clinic. This study will assess safety and tolerability of AGEN1884 (anti–CTLA-4 human immunoglobulin [IgG]-1 monoclonal antibody [mAb]) in combination with AGEN2034 (anti–PD-1 human IgG4 mAb) in patients (pts) with advanced/refractory solid tumors, with expansion into select solid tumors.

Methods: A dose-escalation phase and expansion focusing on adult female pts with recurrent/metastatic cervical cancer that has relapsed after platinum-containing doublet treatment. Phase 1 (Ph1) pts (n = 20) will be enrolled to 2 dose regimens of AGEN1884 + AGEN2034 (starting: 1 mg/kg AGEN1884 Q6w + 1 mg/kg AGEN2034 Q2w; escalating: 1 mg/kg AGEN1884 Q6w + 3 mg/kg AGEN2034 Q2w). Escalation phase primary endpoints: safety, determination of recommended Ph2 dose (RP2D); Ph2 (n = 40) also includes best overall response assessment by Independent Endpoint Review Committee per RECIST 1.1. Secondary endpoints: AGEN1884 and AGEN2034 pharmacokinetic (PK)/pharmacodynamic (PD) profiles, objective response rate, duration of response, progression-free and overall survival.

Results: 0 pts were enrolled 01Dec2017–10Apr2018 in 3 Australia centers: 7 pts at starting dose, 3 pts at escalating dose. No dose-limiting toxicity has been observed; most common toxicities observed were expected for therapeutic class. 8 pts experienced toxicity, mostly grade 1 or 2. Most common toxicities: diarrhea/nausea/vomiting, n = 6; rash/pruritus, n = 2; transaminases elevated, n = 1; fever/flu-like, n = 3; fatigue, n = 2. There was 1 serious adverse event and grade 3 toxicity unrelated to study drug. No discontinuation due to study drug, no deaths observed. Median dose administered was 1 for AGEN1884, 3 for AGEN2034. Dose level 2 was determined for RP2D. Updated safety, efficacy, and PK/PD of AGEN1884 + AGEN2034 will be presented.

Conclusions: AGEN1884 (1 mg/kg Q6w) + AGEN2034 (3 mg/kg Q2w) is well tolerated and being evaluated in Ph2 combination in 2L cervical cancer and other solid tumors.

Clinical trial identification: ACTRN12618000003279.

Editorial acknowledgement: The Medicine Group, LLC (New Hope, PA, USA) and funded by Agenus Inc. (Lexington, MA).

Legal entity responsible for the study: The licensed antibodies AGEN1884 and AGEN2034 were originally developed under a Collaborative Research and Development Agreement between Ludwig Cancer Research, 4-Antibody AG (now Agenus Switzerland Inc.) and Recepta Biopharma S.A. These antibodies are partnered with Recepta Biopharma S.A. for certain South American rights.

Funding: Agenus Inc. (Lexington, MA, USA).

Disclosure: J. Coward: Amgen: ESMO conference 2018 sponsorship MSD: Tumour agnostic advisory board Dec 2017. C.D. Dupont: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA Vertex-An Immediate Family Member Rochester Eye Associates- An Immediate Family Member; Travel, accommodations, expenses: Agenus Research Funding: Agenus; Vertex-family member Pfizer Sanofi Stock and other ownership: Agenus Vertex-family member. A.M. Gonzalez, M. Lim, D. Savitsky, M. Carini, S. Hu, H. Youssoufian: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA. O. Shebanova: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA Travel, Accommodations, Expenses Agenus Stock and other ownership: Agenus. E. Dow: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA employment: Baxalta/Shire; Foundation Medicine Stock and other ownership: Baxalta/Shire; Foundation ;Medicine W. Ortuzar: Full time contracted consultant for Agenus Bio, Inc. J.S. Buell: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA Travel, Accommodations, Expenses: Agenus. R.B. Stein: Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA Stock and other ownership: Agenus. All other authors have declared no conflicts of interest.

1169P RORγ agonist LYC-55716 in combination with pembrolizumab to treat metastatic non-small cell lung cancer: An open-label, multicenter phase Ib trial

D.R. Camidge[1], S.M. Gadgeel[2], H.J. Wilkins[3], G. Weems[3], R. Santana-Davila[4], M. Johnson[5]

[1]Division of Medical Oncology, University of Colorado Cancer Center, Aurora, CO, USA, [2]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA, [3]Clinical Development, Lycera Corp., Plymouth Meeting, PA, USA, [4]Medical Oncology, Seattle Cancer Care Alliance, Seattle, WA, USA, [5]Lung Cancer Program, Sarah Cannon Research Institute, Nashville, TN, USA

Background: The first-in-class, oral, small-molecule agonist of retinoic acid receptor–related orphan receptor γ (RORγ), LYC-55716, is an investigational agent under development as an immunotherapy for solid tumors. A Phase 1/2a trial demonstrated the safety of LYC-55716 as monotherapy and provided evidence of clinical activity, including a confirmed partial response in a patient with non–small cell lung cancer (NSCLC). Based on pre-clinical testing, the combination of RORγ agonist and a PD-1 inhibitor may enhance immune activation and the favorable effects of PD-1 inhibition on the tumor microenvironment. This ongoing open-label, multicenter Phase 1b trial is assessing the safety as well as clinical and biologic activity of LYC-55716 in combination with pembrolizumab (L+P) in patients with NSCLC.

Methods: A run-in cohort of patients (n = 3) is receiving L+P to monitor for safety signals. After determining a dose for further study, 1 main cohort (n = 15) will receive L+P until disease progression or unacceptable toxicity. Pre- and post-treatment biopsies will be obtained for patients in the main study cohort. Primary endpoints are safety (monitoring of adverse events, physical examination, lab results) and incidence of dose-limiting toxicities during the run-in period and ongoing treatment. Secondary endpoints include cellular and molecular immune response and biomarkers, objective response rate, duration of response determined via response evaluation criteria in solid tumors (RECIST) v1.1 and immune-related RECIST, and pharmacokinetics. Immune biomarkers are being assessed by immunohistochemistry (IHC) and a comprehensive gene profiling panel using a NanoString platform.

Results: Enrollment of patients in the run-in cohort is pending. IHC assay validation for RORγ and other immune markers is complete. Results of safety, preliminary efficacy, and biomarker evaluation will be available for patients initially enrolled at the time of presentation.

Conclusions: The LYC-55716 safety profile and clinical activity as a monotherapy agent support investigation of L+P to treat patients with metastatic NSCLC.

Clinical trial identification: NCT03396497.

Editorial acknowledgement: Autumn Kelly, MA, CMPP, of Simcoe Consultants, Inc, on behalf of Lycera Corp.

Legal entity responsible for the study: Lycera Corp.

Funding: Lycera Corp.

Disclosure: D.R. Camidge: Research funding: Takeda. S.M. Gadgeel: Advisory roles: Pfizer, Genentech/Roche, Ariad, AstraZeneca, Bristol-Myers Squibb, Abbvie; Speakers' bureau: AstraZeneca; Research funding: Merck; Research funding to institution: Pfizer, Merck, Genentech/Roche, Incyte, Millennium, AstraZeneca/MedImmune, Bristol-Myers Squibb, Halozyme, Acerta Pharma, ACEA Biosciences, Janssen Oncology, Novartis, Five Prime Therapeutics, OncoMed. H.J. Wilkins, G. Weems: Employee and shareholder: Lycera Corp. M. Johnson: Research funding to institution: OncoMed, BerGenBio, Lilly, EMD Serono, Kadmon, Janssen, Mirati Therapeutics, Genmab, Pfizer, AstraZeneca, StemCentRx, Novartis, Checkpoint Therapeutics, Array BioPharma, Regeneron, Merck, Hengrui Pharmaceutical, Lycera Corp., BeiGene, Tarveda Therapeutics, Loxo, Abbvie, Boehringer Ingelheim, Guardant Health, Foundation Medicine, Daiichi Sankyo, Sanofi, Mersana. All other authors have declared no conflicts of interest.

1170P ABP-100: A tetravalent bispecific T-cell engaging antibody for HER2+ solid tumors

A. Boudot[1], X. Huang[1], S. Murphy[1], V. Appleman[1], H. Xu[2], N-K. Cheung[2], G. Macbeath[1]

[1]Therapeutics, Abpro, Woburn, MA, USA, [2]Nai-Kong Cheung Lab, Memorial Sloan Kettering, New York, NY, USA

Background: Clinical success with CAR-T therapy highlights the value of engaging cytotoxic T cells (CTLs) to treat cancer. Bispecific antibodies that link CTLs to tumor cells in an MHC-independent manner offer an off-the-shelf solution to T cell therapy that is accessible and scalable. Most bispecific antibodies are built as heterodimers, with monovalent binding to a highly expressed antigen on the tumor cell and to CD3 on the T cell. Here, we describe ABP-100, a HER2-specific T-cell engaging antibody built using a tetravalent bispecific (TetraBi) format that provides several significant advantages over the traditional format of bi-specific antibodies

Methods: ABP-100 was constructed by fusing a CD3-binding scFv to the light chain of an aglycosylated anti-HER2 IgG1, resulting in two binding sites each for HER2 and CD3. This TetraBi format was compared with a clinical-stage heterodimeric antibody that is monovalent for HER2 and CD3. The biophysical features of the two formats were compared, along with functional characteristics associated with both efficacy and safety.

Results: We observed that bivalent binding to HER2 provides a stronger association with HER2+ tumor cells than monovalent binding, but that locating the CD3-binding domains in the hinge regions of ABP-100 results in functionally monovalent binding to CD3. ABP-100 showed a similar safety profile (cytokine release) to the heterodimer molecule both in vitro and in vivo. In models of HER2+ cancer, however, ABP-100 showed highly potent antitumor activity, resulting in complete responses in mice at doses as low as 0.1 mg/kg with no evidence of tumor regrowth after treatments were stopped. Overall, the efficacy of ABP-100 was strongly dependent on HER2 levels and synergistic effects were observed when ABP-100 was combined with a PD-L1 inhibitor.

Conclusions: The TetraBi format of ABP-100 provides a potentially larger therapeutic index than more traditional bispecific formats that feature monovalent recognition of HER2. Moreover, because ABP-100 is designed to engage CTLs, it provides a novel mechanism for treating HER2+ disease relative to current therapies. These data support the clinical development of ABP-100 in HER2+ solid tumors.

Legal entity responsible for the study: Abpro

Funding: Abpro

Disclosure: A. Boudot, X. Huang, S. Murphy, V. Appleman, G. Macbeath: A. Boudot, X. Huang, S. Murphy, V. Appleman, and G. MacBeath: Employee: Abpro. H. Xu: Employee: Abpro; Research conducted funded in part: Abpro. N.-K. Cheung: Employee: Abpro; Member: SAB of Abpro; Research conducted funded in part: Abpro.

1171P Phase I expansion cohort results of cemiplimab, a human PD-1 monoclonal antibody, in combination with radiotherapy (RT), cyclophosphamide and GM-CSF, in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC)

H.M. Babiker[1], I. Brana[2], D. Mahadevan[3], T.K. Owonikoko[4], E. Calvo[5], D. Rischin[6], V. Moreno[7], K.P. Papadopoulos[8], M. Crittenden[9], S. Formenti[10], J. Giralt[11], P. Garrido Lopez[12], A. Hervás Morón[13], K.K. Mohan[14], M.G. Fury[14], I. Lowy[14], E. Stankevich[15], M. Feng[15], J. Li[16], M. Mathias[14]

[1]Department of Medicine, University of Arizona Cancer Center, Tucson, AZ, USA, [2]Medical Oncology Department, Vall D'Hebron Institute of Oncology, Barcelona, Spain, [3]The University of Arizona Cancer Center, Formerly of The University of Tennessee Health Science Center and West Cancer Center, Memphis, TN, USA, [4]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA, [5]START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain, [6]Department of Medical Oncology, Peter MacCallum Cancer Centre, and the University of Melbourne, Melbourne, Australia, [7]START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain, [8]Clinical Research, START, San Antonio, TX, USA, [9]Earle A. Chiles Research Institute, Robert W. Franz Cancer Center, Providence Portland Medical Center and The Oregon Clinic, Portland, OR, USA, [10]Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, USA, [11]Radiation Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain, [12]Medical Oncology Department, Hospital Universitario Ramon y Cajal, Madrid, Spain, [13]Department of Radiology, Hospital Universitario Ramón y Cajal, Madrid, Spain, [14]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [15]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA, [16]Biostatistics & Data Management, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA

Background: Most pts with R/M HNSCC do not respond to PD-1 inhibitor monotherapy. Cemiplimab is a human monoclonal anti-PD-1. An expansion cohort in the phase 1 study (NCT02383212) combined cemiplimab with other potential immune-supportive treatments for pts with R/M HNSCC.

Methods: Pts with R/M HNSCC who were refractory to at least first-line therapy and for whom palliative RT is clinically indicated received cemiplimab 3 mg/kg Q2W for up to 48 weeks plus RT (9 Gy × 3 times/week beginning 6–8 days after first dose of cemiplimab), cyclophosphamide (200 mg/m^2 every 14 days for 4 doses), and GM-CSF (200 µg daily for 7-days after each of the first 4 doses of cemiplimab). The co-primary objectives were to characterise the safety, tolerability, and efficacy of cemiplimab in combination with RT, cyclophosphamide and GM-CSF in 15 pts with R/M HNSCC. Tumour assessments were performed by RECIST 1.1 Q8W.

Results: As of 1 Sept, 2017, 15 pts (9 M/ 6 F) had been enrolled. Median (range) age was 62.0 (45–78) years; ECOG performance status was 1 in 12 pts (80%), and 0 in 3 (20%); and 14 (93.3%) had received prior RT. The primary site of cancer was upper aerodigestive tract of head and neck. With a median (range) duration of follow-up of 3.3 (0.5–10.2) months, treatment is ongoing in 3 pts (20.0%) and 12 (80%) had discontinued, mainly due to disease progression/recurrence (53.3%). The most common treatment-emergent adverse events (TEAEs) of any grade were fatigue (40.0%), constipation (26.7%), asthenia, dyspnoea, maculo-papular rash and pneumonia (each 20%). The only grade ≥3 TEAE that occurred in > 1 pts was pneumonia (13.3%). By investigator-assessment, there was 1 partial response (6.7%); disease control rate was 40.0% (95% CI: 16.3–67.7; 5 stable disease), 7 pts had progressive disease and 2 were not evaluable. Median progression-free survival by investigatorassessment was 1.8 months (95% CI: 1.7–4.7).

Conclusions: The combination therapy regimen did not demonstrate efficacy above that which can be achieved with PD-1 inhibitor monotherapy for R/M HNSCC.

Clinical trial identification: NCT02383212.

Editorial acknowledgement: Medical writing support under the direction of the authors was provided by Emmanuel Ogunnowo, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc. and Sanofi according to Good Publication Practice guidelines (http://annals.org/aim/article/2424869/good-publication-practice-communicating-company-sponsored-medical-research-gpp3).

Legal entity responsible for the study: Regeneron Pharmaceutical, Inc.; Sanofi.

Funding: Regeneron Pharmaceutical, Inc.; Sanofi.

Disclosure: H.M. Babiker: Honoraria: Bayer, Sirtex; Consulting or advisory role fees: Celgene, Endocyte. D. Mahadevan: Speakers' bureau and travel, accommodation expenses: Abbvie. T.K. Owonikoko: Fees for a consulting or advisory role: Novartis, Celgene, Lilly, Sandoz, Abbvie, Eisai, G1 Therapeutics, Takeda, Seattle Genetics, Bristol-Myers Squibb, MedImmune. E. Calvo: Research funding: Boehringer Ingelheim, Roche/Genentech, BMS, Novartis, PsiOxus, Nanobiotix, Janssen, Abbvie, PharmaMar, PUMA, Sanofi, Lilly, Pfizer, Merck, Nektar, Amcure, Amgen, AstraZeneca, Principia, Bayer, CytomX, H3, Incyte, Kura, loxo, Macrogenics, Menarini, Merck, Serono, Merus, Millenium, Rigontec, Tahio, TesaroReceipt; Honoraria/consultation fees: Novartis, Nanobiotix, Janssen-Cilag, PsiOxus Therapeutics, Seattle Genetics, Pierre Fabre, Boehringer Ingelheim, Cerulean Pharma, EUSA, Abbvie, Celgene; speaker's bureau: Novartis. D. Rischin: Research funding: Genentech/Roche, Merck, Amgen, Regeneron, Bristol-Myers Squibb. M. Crittenden: Research funding: Jounce and Nanobiotix. P. Garrido: Personal fees: Roche, BMS, MSD, Pfizer, Lilly, Abbvie, Regeneron, AstraZeneca, Novartis, Boerinhger-Ingelheim, outside the submitted work. K.K. Mohan: Employee and shareholder: Regeneron Pharmaceuticals, Inc. M.G. Fury: Shareholder and an employee of, and holds patents, royalties, other intellectual property: Regeneron Pharmaceuticals, Inc. I. Lowy: Shareholder and employee of, and gained fees for travel and accommodation expenses as well as leadership: Regeneron Pharmaceuticals, Inc. E. Stankevich: Shareholder and employee: Regeneron Pharmaceuticals, Inc., Shareholder: Celgene, Bristol-Myers Squibb, Merck. M. Feng: Shareholder and employee: Regeneron Pharmaceuticals, Inc.; Shareholder: Bayer. J. Li, M. Mathias: Shareholder and employee: Regeneron Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

1172P A first-in-class, first-in-human phase I/IIa trial of CAN04, targeting interleukin-1 receptor accessory protein (IL1RAP), in patients with solid tumors

A. Awada[1], F.A.L.M. Eskens[2], D.G. Robbrecht[2], U.N. Lassen[3], M. Sorensen[3], J.H.M. Schellens[4], J.S. de Groot[4], C. Jungels[1], P.G. Aftimos[1], S.O. Fretland[5], L. Thorsson[6], T.K. Guren[5]

[1]Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, [2]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [3]Onkologisk Klinik/Dept. of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [4]Division of Clinical Pharmacology, Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [5]Radiumhospitalet, Oslo University Hospital, Oslo, Norway, [6]Clinical Development, Cantargia AB, Lund, Sweden

Background: CAN04 is a first-in-class fully humanized monoclonal antibody targeting IL1RAP, a co-receptor for the IL-1 receptor which is expressed on human cancer cells. CAN04 binds to IL1RAP with high affinity in a manner that blocks signal transduction from IL-1 and IL-33 into the cells. Binding of CAN04 to IL1RAP also allows NK-cells to recognize tumor cells and subsequent killing by antibody dependent cellular cytotoxicity (ADCC).

Methods: The primary objective was to assess safety and tolerability of weekly CAN04 in order to define the Maximum Tolerated Dose/Recommended Phase 2 Dose. Patients with relapsed or refractory non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), breast or colorectal cancer were included in the initial part of the trial using a 3 + 3 dose escalation design. Key eligibility criteria were ECOG ≤1, normal organ function and no bleeding disorder or coagulopathy. Tumor responses were evaluated according to irRC every 8 weeks. Plasma samples were obtained for pharmacokinetic evaluation and for assessment of circulatory biomarkers of immunological activity (e g IL-1α, IL-1β, IL-1RA, IL-6, IL-8, IL-33 and TNF-α).

Results: Nine subjects were enrolled across 3 initial cohorts (1-3 mg/kg). Demography: mean age 66 yrs (48-77); gender 5 M and 4 F; median number of prior lines of therapy 5 (range 2-11). No dose limiting toxicities (DLTs) were observed and MTD has not been reached yet. AEs occurred mainly following the first dose and the most common AEs were: fatigue (67%), nausea (44%), pyrexia (44%), infusion related reaction (IRR) (44%) and pruritus (44%). AE grade 3 or 4: one grade 3 IRR following an initial dose of 1.0 mg/kg in cohort 3. Stable disease was achieved in 2/6 and progressive disease in 4/6 patients after 8 weeks of treatment.

Conclusions: CAN04 demonstrated a manageable safety profile in the initial 3 cohorts with no DLTs observed and the dose escalation will be continued as planned. The dose expansion phase of the trial will then evaluate CAN04 as monotherapy as well as in combination with standard of care therapy for NSCLC and PDAC in separate arms.

Clinical trial identification: NCT03267316.

Legal entity responsible for the study: Cantargia AB.

Funding: Cantargia AB.

Disclosure: A. Awada: Honorarium for advisory board: Cantargia AB. P.G. Aftimos: Honoraria: Synthon, Boehringer Ingelheim, Macrogenics, Amgen, Novartis; Travel grants: Amgen, Merck, Roche. L. Thorsson: Employee and shareholder: Cantargia AB. All other authors have declared no conflicts of interest.

1173P Immunostimulatory AdCD40L gene therapy in patients with advanced solid tumours

S. Irenaeus[1], J. Wenthe[2], E. Eriksson[2], J. Krause[3], A. Sundin[3], H. Ahlström[3], T. Tötterman[2], A. Loskog[2], G. Ullenhag[1]

[1]Department of Immunology, Genetics and Pathology and Department of Oncology, Uppsala University Hospital, Uppsala, Sweden, [2]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden, [3]Department of Surgical Sciences, Section of Radiology and Department of Radiology, Uppsala University Hospital, Uppsala, Sweden

Background: CD40-CD40L is a key activator of adaptive immunity. AdCD40L is a replication-deficient adenovirus carrying the CD40 ligand gene. We have conducted a phase I/II study (NCT01455259) for patients with advanced cancer receiving intratumoral injections of AdCD40L. Patients with metastatic malignant melanoma were treated in the first three cohorts in which we demonstrated that low dose cyclophosphamide before the first and fourth intratumoral injection given in the second and the third cohort was of clinical value with four patients surviving >1 year, while radiotherapy combination was not. In these patients, AdCD40L increased the Teffector to Tregulatory cell ratio showing its action via T cell activation. We now report the results of the fourth and final cohort treating patients with other solid malignancies.

Methods: Six patients with metastatic solid cancer underwent treatment with four weekly percutaneous intratumoral injections of $2.5x10^{11}$ VP AdCD40L and low dose cyclophosphamide conditioning (300 mg/m^2) before the first and fourth injection. All patients had good performance status at inclusion. The primary tumor was kidney cancer (n = 2) or cholangiocarcinoma (n = 1), rectal- (n = 1), ovarian- (n = 1), and breast cancer (n = 1). Correlation analysis between immunological data and survival was performed.

Results: The treatment was generally well tolerated. Patients received the injection in metastases located in the liver (n = 4), lymph node (n = 1), or muscle (n = 1). The performance status for one patient improved during the treatment and this patient was therefore accepted for re-treatment. The median survival was 54 weeks ranging from 5 to 101 weeks compared to the melanoma patients that had a median survival of 27 weeks (5 to 220 weeks). Immunological data from five of the patients showed a significant negative correlation between IL10 concentrations at week 3 and survival ($p = 0.0283$). In addition, TNFα and IL12 was higher post-treatment in the two patients with the longest survival.

Conclusions: Intratumoral injections of AdCD40L in combination with cyclophosphamide is feasible in patients with solid cancer. Desirable immune effects were noted and the potential of the treatment was also demonstrated in one patient who improved clinically.

Clinical trial identification: NCT01455259 Realease date: September 2011.

Legal entity responsible for the study: Landstinget Region Uppsala.

Funding: Supported by grants to Dr Ullenhag by the research foundation Stiftelsen Onkologiska Kliniken i Uppsala Forskningsfond and Lions's Cancer Fund at Uppsala University Hospital and by grants to Dr Tötterman and Dr Loskog from the Swedish Cancer Society, Medical Faculty at Uppsala University and the Swedish State Support for Clinical Research and Lion's Cancer Fund at Uppsala University Hospital.

Disclosure: H. Ahlström: Founder and employee: Antaros Medical AB. T. Tötterman: Royalty agreement: Alligator Bioscience AB; Board member and shareholder: Immuneed AB. Advisor of Alligator Bioscience AB. A. Loskog: CEO, board member, royalty agreement and research grant: Lokon Pharma AB; Advisor: Nexttobe AB; Chairman of the board: Vivolux AB; Chairman of the board: Repos Pharma AB; Board member: Hansa Medical AB; Board member: Bioimics AB; Royalty agreement: Alligator Bioscience AB. G. Ullenhag: Medical advisor: Lokon Pharma AB. All other authors have declared no conflicts of interest.

1174P Patterns of progression to immune checkpoint targeted monoclonal antibodies in phase I trials

A. Bernard-Tessier[1], C. Baldini[1], E. Castanon Alvarez[1], S. Ammari[2], P. Martin Romano[1], S. Champiat[3], A. Hollebecque[1], S. Postel-Vinay[1], A. Varga[1], R. Bahleda[1], A. Gazzah[1], J-M. Michot[1], V. Ribrag[1], J-P. Armand[1], A. Marabelle[1], J-C. Soria[1], C. Massard[1]

[1]Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, [2]Imaging, Gustave Roussy, Villejuif, France, [3]Drug Development Department (DITEP), Gustave Roussy, Villejuif, France

Background: New patterns of progression under immune checkpoint targeted (ICT) monoclonal antibodies (mAb) have been described such as pseudoprogression (PsPD). Except for melanoma, variations between studies reveal difficulties to establish their real incidence. This study aims to assess different patterns of progression in ICT mAb phase I trials.

Methods: All patients participating in ICT mAb phase I trials at the Drug Development Department at Gustave Roussy for solid tumors excluding melanoma, were enrolled. Radiological evaluations according to iRECIST 1.1 were correlated with prospectively registered patient characteristics and outcomes.

Results: Among 360 patients included between August 2015 and November 2017, 70.6% received ICT mAb combination: 58.3% with another ICT mAb, 27.9% with targeted therapy and 13.8% with radiotherapy. Patients received a median of 2 previous lines of therapy (range 0-10). The objective response rate was 17.2%. PsPD were observed in 10 (2.8%) of patients (1 NSCLC, 1 microsatellite-high colon cancer, 1 hepatocarcinoma, 2 renal, 2 bladder, 1 cervix, 1 thyroid and 1 thymic cancer). PsPD patients had a median PFS (until confirmed PD according to iRECIST) of 17.3 months (95%CI[4.8-N.R]) that was comparable to other responders patients PFS (median unreached 95%CI[13.8-N.R]; HR, 2.0; 95%CI[0.7-6.1]; p = 0.2). Dissociated responses (defined as a concomitant progressing and responding lesions) were reported for 4.2% of patients with a median PFS of 4.8 months (95%CI[3.0-15.6]) comparable to stable disease patients (median PFS 5.0 months 95%CI[4.3-6.4]; HR, 0.9; p = 0.6). Among the 203 patients who progressed at first evaluation, 139 (68%) were withdrawn from the phase I study at first assessment, whereas 64 (32%) continued ICT mAb and underwent another CT scan evaluation one-month later.

Conclusions: We showed a low rate of PsPD and dissociated response in a large cohort of patients excluding melanoma. Using iRECIST, 32% of progressing patients underwent another CT scan at one month confirming PD, which may delay the initiation of a new regimen. This work suggests that prognosis or on-treatment biomarkers are needed to identify early patients who should (or not) continue ICI treatment once a first progression is evidenced.

Legal entity responsible for the study: Institut Gustave Roussy.

Funding: Has not received any funding.

Disclosure: A. Hollebecque: Honoraria: Merck Serono; Advisory role: Amgen, Lilly; Travel and accommodation expenses: Amgen, Servier. S. Postel-Vinay: Honoraria: AstraZeneca. A. Marabelle: Honoraria/consultancy fees: Medimmune, Lilly, Amgen, BMS, Merck Serono, Sanofi Genzyme, Janssen, Astellas, Genentech, Orion, Ipsen. J-C. Soria: Full time employed in Medimmune since September 2017; Consultancy fees in the last 2 years: AstraZeneca, Astex, Clovis, GSK, Gammamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen, Takeda. C. Massard: Honoraria/consultancy fees: Sanofi Genzyme, Janssen, Astellas, Genentech, Orion, Medimmune, Ipsen. All other authors have declared no conflicts of interest.

1175P Prognostic value of response according to tumour growth rate in a phase I trial on vaccine therapy

A. Bellucci[1], C. Nevoret[1], C. De Bazelaire[2], S. Oudard[3], L.O. Teixeira[4], R. Defrance[5], T. Huet[5], L.D. Pierre[5], V. Doppler[5], J. Medioni[6], S. Culine[7], L. Fournier[1]

[1]Radiology, Hopital European George Pompidou, Paris, France, [2]Radiology, Hôpital St. Louis, Paris, France, [3]Immunothérapie et Traitement Antiangiogénique en Pathologie Cancérologique, Hopital European George Pompidou, Paris, France, [4]Oncology, Hôpital St. Louis, Paris, France, [5]Clinical Development, Invectys, Paris, France, [6]Oncology, Gh Diaconesses Croix Saint-Simon, Paris, France, [7]Medical Oncology, Hôpital St. Louis, Paris, France

Background: Vaccine therapy INVAC-1 (a DNA vaccine encoding human telomerase reverse transcriptase (hTERT)), is a new class of anti-cancer agents and was evaluated in a Phase 1 trial (INVAC1-CT-101 study) in patients with advanced cancer. We propose to study tumour patterns of response on imaging evaluations of patients under vaccine in a retrospective CT study.

Methods: The tumour growth rate (TGR) of the tumor burden (sum of lesions) was calculated before and during therapy. Patients with decrease of the TGR after initiation of therapy were considered responders whereas patients with stability or increase of the TGR were considered non responders. Overall survival (OS) and response according to anatomical location were also analysed.

Results: 10/19 patients were responders according to the tumour growth rate. The median [IQR] of OS was 9.6 month [6.8, 13.3] versus 5.3 month [5.1, 15.0] for non-responders (p = 1.3.10-5). Regarding organ sensitivity to vaccine therapy, we observed that none of the liver metastases responded to treatment, whereas the majority of lymph node lesions responded.

Conclusions: The decrease of the tumor growth rate in patients treated by vaccine therapy INVAC-1 could predict a benefit in terms of overall survival. The efficiency could vary depending on the location of the metastases.

Legal entity responsible for the study: Invectys.

Funding: Invectys.

Disclosure: R. Defrance, T. Huet, L.D. Pierre, V. Doppler: Salaried: Invectis. L. Fournier: Funded: Invectys; Speaker fees: Novartis, Merck, Pfizer. All other authors have declared no conflicts of interest.

1176P Oncolytic virotherapy for multiple myeloma targeting CD40, 41BB and/or IL6R

J. Wenthe, S. Naseri, A-C. Hellström, E. Eriksson, A. Loskog

Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Background: Despite current treatment options in multiple myeloma (MM), most patients acquire resistance to therapy and relapse. As MM remains incurable, novel therapies are needed. A potentially promising approach is immunostimulatory therapy via an armed oncolytic adenovirus. The herein investigated LOAd viruses are serotype Ad5/35 chimera and therefore infect cells via CD46, which is often upregulated in MM. Viral replication is restricted to tumor cells due to a deletion in E1A. LOAd viruses express transgenes under the control of a CMV promoter. LOAd703 encodes for trimerized membrane-bound (TMZ) CD40L and 4-1BBL, whereas LOAd713 carries a gene encoding a single chain fragment against the IL-6 receptor in combination with TMZ-CD40L. IL-6 is identified as an essential growth and survival factor in MM. Hence, LOAd713 therapy may be of special interest as it not only induces immune cell activation via TMZ-CD40L but also blocks IL-6R signaling.

Methods: A panel of MM cell lines (ANBL-6, L363, LP-1, OPM-2, RPMI-8226, U266-84) were infected with LOAd viruses. Viral replication was evaluated with qPCR detecting viral DNA and viability was analyzed by MTS assay. Surface expression of TMZ-CD40L, 4-1BBL and markers for an immunogenic phenotype were analyzed by flow cytometry. Cell culture supernatants were investigated by multiplex analysis.

Results: All MM cell lines were sensitive to LOAd infection, leading to viral replication and decreased cell viability. TMZ-CD40L and 4-1BBL were expressed in all cells infected with the respective viruses carrying the transgenes. LOAd infection induced an immunogenic phenotype with the upregulation of molecules that facilitate recognition and killing by the immune system. These included CD40, 4-1BB, Fas, HLA-DR, CD80 and CD86. In the supernatants of infected cells, the pro-inflammatory cytokine MIP-1α was increased in 4/6 cell lines. The suggested MM growth factor MCP-1 as well as sIL2R were decreased in 3/6 cell lines.

Conclusions: LOAd viruses infected and replicated in MM cells. The encoding transgenes induced transgene expression and subsequently an immunogenic phenotype in infected cells. Immunostimulatory oncolytic LOAd viruses may be an attractive approach for MM therapy.

Legal entity responsible for the study: Uppsala University, Department of Immunology, Genetics and Pathology, Loskog group.

Funding: The Swedish Cancer Society, The Swedish Research Council, Lokon Pharma AB.

Disclosure: A. Loskog: CEO, board member, royalty agreement, research grant: Lokon Pharma AB; Advisor: Nexttobe AB; Board member: Hansa Medical, Bioimics; Chairman: Repos Pharma, Vivolux; Royalty agreement: Alligator Bioscience. All other authors have declared no conflicts of interest.

1177P Humanized knock-in mouse models for evaluating in vivo efficacy of immune-oncology drugs targeting stimulatory immune checkpoint molecules

T. Gan[1], J. Xiang[2], C. Guo[1], Y. Guo[1]

[1]Pharmacology Study Platform, Beijing Biocytogen Co., Ltd., Beijing, China, [2]Pharmacology Study Platform, Biocytogen LLC, Worcester, MA, USA

Background: Cancer immunotherapy is one of the most promising research areas in the field of cancer therapy. Many pharmaceutical and biotech companies in the world are devoting great effort to develop cancer immunity-related treatment antibodies. However, along the IO drug development process, in vivo efficacy models have always been a rate-limiting step.

Methods: In most cases, a human monoclonal antibody does not have mouse cross-reactivity. Mouse surrogate antibodies were often used in immune-competent syngeneic mouse models to evaluate in vivo efficacy of IO drugs. However, the efficacy of a surrogate antibody cannot fully represent the human drug in the clinical scenario. Therefore, we generated humanized knock-in mice to evaluate the in vivo efficacy of human IO antibodies.

Results: For example, human 4-1BB knock-in (B-h4-1BB) mice were generated with a chimeric 4-1BB receptor, which is recognizable by stimulatory human 4-1BB antibodies. Additionally, more knock-in mice targeting stimulatory immune checkpoint molecules were developed and validated, such as B-hCD3e, B-hCD40, B-hOX40, B-hGITR, B-hCD27, B-hCD28 et al.

Conclusions: All these mouse models response well to the corresponding human IO antibodies, proving that they are powerful tools for in vivo efficacy evaluation of human stimulatory immune checkpoint antibodies.

Legal entity responsible for the study: Beijing Biocytogen Co., Ltd.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1178P Tackling fratricide to manufacture clinical grade NKG2D-CAR T cells for cancer therapy

B. Demoulin, B. Eytan, D. Gilham

R&D, Celyad SA, Mont Saint Guibert, Belgium

Background: T cells bearing a chimeric antigen receptor (CAR) T-cell consisting of the fusion of the NKG2D NK receptor with the intracellular domain of CD3zeta (CYAD-01) can recognize eight stress ligands expressed in a large variety of cancers. However, activated T cells undergo stress and transiently express NKG2D ligands (NKG2DL). Consequently, CYAD-01 T cells kill sister cells preventing the large-scale manufacturing of CYAD-01 for clinical application.

Methods: Inclusion of the PI-3K inhibitor LY294002 into the manufacturing process was the first strategy used as an initial effort focused upon blunting the activity of the CAR T cells. We subsequently developed a process that included a NKG2D blocking antibody during the expansion phase of cell culture.

Results: LY294002 was shown to reversibly reduce NKG2D expression at the cell surface. Consequently, this inhibitor partially controlled fratricide during manufacturing and enhanced viability post-thawing which enabled the initiation of the THINK (NCT03018405) clinical trial. As the trial moved through the dose-escalation phase towards the upper dose level (production of more than 10^{10} cells), there was an increase in the level of manufacturing failures. This was largely linked to the effect of LY294002 upon T cell proliferation and the challenge faced manufacturing CAR T cells from patients with advanced cancer. Therefore, we subsequently developed a process that included a NKG2D blocking antibody during the expansion phase of cell culture. This strategy enabled the expansion of CYAD-01 T cells to the levels required for the THINK clinical trial. After fine tuning the process, the CYAD-01 CAR T cells generated showed high comparability to the CYAD-01 CAR T cells produced in the first part of the trial. This process has been in place for the THINK trial since January 2018.

Conclusions: Together, these results indicate that when fratricide is an issue preventing clinical development, CAR T cells can be efficiently manufactured through PI-3K inhibition and antibody mediated receptor blockade.

Legal entity responsible for the study: Celyad SA.

Funding: Has not received any funding.

Disclosure: B. Demoulin B. Eytan, D. Gilham: Employee of Celyad SA.

1179P The high expression of NKG2D ligands on tumor and the lack of surface expression on healthy tissues provides a strong rationale to support NKG2D-based therapeutic approaches for cancer

S. Agaugue[1], A. Hargreaves[2], P. De Sousa[3], P. De Waele[4], D. Gilham[1]

[1]R&D, Celyad SA, Mont Saint Guibert, Belgium, [2]R&D, Pathcelerate, Cheshire, UK, [3]R&D, PDC Line Pharma, Liège, Belgium, [4]R&D, Advanced Therapies Consulting Ltd, Ghent, Belgium

Background: The NKG2D receptor is a type II transmembrane glycoprotein playing an important role in anti-tumor responses. In humans, NKG2D binds to eight ligands, MHC class I–related chain MICA and B and unique long 16 (UL16)-binding proteins ULBP 1-6. The surface expression of NKG2D ligands (NKG2DL) is highly regulated to avoid inappropriate immune responses in physiological conditions but is induced by various stress situations such as malignant transformation or inflammation. NKG2DL expression on tumors has been reported in the literature. However, a systematic study on all NKG2DL in a large array of normal tissues and tumor samples is lacking. Celyad is pursuing the clinical development of NKG2D based chimeric antigen receptor (CAR) T cell therapy and robust data are thus required to adequately support this work.

Methods: We performed an extensive immunohistochemistry study on primary tumors and normal adjacent tissues from patients suffering from pancreatic, breast, ovarian, bladder, colorectal and lung carcinomas and on a series of normal tissues from non-cancer patients.

Results: MICA/B were the most frequently and highly expressed. Interestingly the subset of triple negative breast cancers (TNBC) showed strong membranous staining for all NKG2DL on tumor cells making this patient subpopulation a very attractive therapeutic target for NKG2D-based therapies. There was no clear correlation between the expression of NKG2DL and the clinical stage of the tumors indicating that every stage of the diseases could be targeted. In bladder, TNBC, CRC and pancreatic tumors, tumor cells were frequently stained for multiple NKG2DL implying that these tumors would not be susceptible to immune escape. Tumor-associated fibrovascular structures displayed generally membranous staining within the endothelial compartment suggesting that NKG2D-based CAR T therapy can target simultaneously both the tumor and the tumor microenvironment.

Conclusions: In conclusion, this extensive immunohistochemistry study supports the concept of targeting NKG2DL for cancer therapy.

Legal entity responsible for the study: Celyad SA.

Funding: Has not received any funding.

Disclosure: S. Agaugue, D. Gilham: Employee: Celayd SA. A. Hargreaves: Employee: Pathcelerate SA. P. De Sousa: Employee: PDC lines SA. All other authors have declared no conflicts of interest.

1180P Combination of pegilodecakin and docetaxel shows synergy in tumor rejection in immune resistant TNBC model

N. Ratti[1], N. Shifrin[1], S. McCauley[1], R. Verma[1], P. Van Vlasselaer[1], M. Oft[1], J. Leveque[2]
[1]Pre-Clinical and Clinical Development, ARMO BioSciences, Redwood City, CA, USA, [2]Scientific Affiars, ARMO BioSciences, Redwood City, CA, USA

Background: Immune checkpoint inhibitors (ICI) induce durable tumor responses and increased overall survival (OS) of cancer patients. Patients with low PD-L1, low tumor mutational burden (TMB) or without intra-tumoral CD8+ T cells, have a poor response rate to ICIs. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10, which overcomes tumor immune escape by stimulating the activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin up-regulates IFNγ in CD8+ T cells and MHC expression, which facilitates antigen presentation even in tumors with low CD8+ T cells and low TMB. Here we explore the combination of Pegilodecakin with SOC docetaxel in an ICI resistant mouse triple negative breast cancer model.

Methods: 4T1 cells were established SC for two weeks prior to treatment. Pegilodecakin was administered at suboptimal doses, docetaxel was dosed at the MTD. Quantitation of T cell infiltration and tumor cell death was quantified by IHC. Intra-tumoral and systemic cytokine and T cell activity were evaluated.

Results: Docetaxel did not induce regressions but inhibited tumor growth by 65%. Pegilodecakin alone induced tumor growth inhibition and delayed tumor regression in 75% of mice with an 80% reduction of tumor size after 4 weeks of treatment. Pegilodecakin + docetaxel lead to a synergistic tumor control and complete responses in 75% of mice. While pegilodecakin induced T cell infiltration and tumor cell apoptosis with 95% of the measurable tumor being reduced to scar tissue, the tumor size initially continued to increase, indicative of pseudo-progression. In contrast, Pegilodecakin / docetaxel therapy led to a complete eradication of the tumor without pseudoprogression.

Conclusions: The determination of clinical efficacy of immune therapy can be difficult due to delayed immune responses and pseudoprogression related to immune effector cell infiltration. Here we show that largely necrotic tumors on pegilodecakin may have a delayed clearance despite overwhelming anti-tumor efficacy. The combination of immunotherapy with chemotherapy may facilitate clearance of the necrotic tumor mass leading to complete responses of measurable tumor burden.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: N. Ratti, N. Shifrin, S. McCauley, R. Verma, P. Van Vlasselaer, M. Oft, J. Leveque: Employee: ARMO BioSciences.

1181P Mutations in interferon gamma and antigen presentation pathways are frequent in hiper/ultra-mutated (HiMut) tumors and could be result of immune-editing processes in HiMut tumors

J.M. Piulats Rodriguez[1], S. Garcia-Mulero[1], L. Valle[2], V. Moreno[3], X. Matias-Guiu[4], R. Sanz-Pamplona[3]
[1]Medical Oncology, Institut Catala d'Oncologia (ICO), Barcelona, Spain, [2]Translational Research Laboratory, Institut Catala d'Oncologia (ICO), Barcelona, Spain, [3]Prevención del Cancer, Institut Catala d'Oncologia (ICO), Barcelona, Spain, [4]Pathology, Hospital de Bellvitge, Barcelona, Spain

Background: Tumors with a phenotype associated with a high mutational load such as POLE-mutated or those showing microsatellite instability (MSI) are more likely to have clinical responses to immune-checkpoints blockade therapy. Indeed, several clinical trials are currently on-going targeting PD-1 in a variety of cancer types. However, some of these patients do not respond to immunotherapy. Recently, mutations in JAK1 and JAK2 has been reported to be responsible for this resistance.

Methods: Here we explore the effect of functional mutations in genes in the interferon gamma (IFG) signaling and antigen presentation (AP) pathway in endometrial, colorectal, and gastric POLE-mutated and MSI tumors extracted from TCGA.

Results: As a result, we have found that POLE-MSI tumors accumulated more mutations in IFG and AP pathways than randomly expected. Using gene expression data, we corroborate that IFN pathway is under-expressed in IGF/AP mutant tumors. MSI IGF/AP mutant tumors over-express T cell receptor pathway probably as a compensatory mechanism. Moreover, when cell infiltration was assessed, these tumors have a tendency to present higher levels of cytotoxic lymphocytes than non-mutated tumors. However, they showed over-expression of pathways related to anti-PD1 resistance such as epithelial to mesenchymal transition or angiogenesis. These results suggest that despite being infiltrated, IGF/AP mutant tumors are able to evade immune surveillance. Regarding survival, although overall these tumors have a very good prognosis, we observed that IGF/AP mutated endometrial tumors showed higher clinical grade than the non-mutated ones.

Conclusions: Based on these results, we show that regardless of cancer type, HiMut tumors with functional mutations in IFG and AP pathways shows a more aggressive phenotype, and present activation of cellular processes that have been related to immune-resistance, probably to evade destruction by a very active T-cell stroma due to the high amount of neoantigens. This phenotype is even more evident in ultra-mutated POLE tumors. Therefore, HiMut tumors could be exploited as a surrogate to understand mechanisms of immune-resistance.

Legal entity responsible for the study: Institut de Recerca Biomédica de Bellvitge (IDIBELL).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1182P Anti-CTLA4 toxicity associates with genetic variation correlating with serum antibody diversity

D. Simpson[1], R. Ferguson[1], M. Gowen[2], K.M. Giles[2], J. Tchack[2], H. Zhou[3], U. Moran[1], Z. Dawood[2], A. Pavlick[4], S. Hu[5], M.A. Wilson[4], H. Zhong[6], M. Krogsgaard[7], J.S. Weber[8], I. Osman[2], T. Kirchhoff[9]
[1]Perlmutter Cancer Center, New York University Medical Center, New York, NY, USA, [2]Dermatology, New York University Medical Center, New York, NY, USA, [3]Bioinformatics Core, New York University Medical Center, New York, NY, USA, [4]Department of Medicine, New York University - Perlmutter Cancer Center - Langone Medical Center, New York, NY, USA, [5]CDI Laboratories, CDI, Baltimore, MD, USA, [6]Biostatistics, New York University Medical Center, New York, NY, USA, [7]Department of Pathology, New York University Medical Center, New York, NY, USA, [8]Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA, [9]Perlmutter Cancer Center, New York University, New York, NY, USA

Background: While anti-CTLA4 immunotherapy (IT) improves survival in metastatic melanoma patients, it manifests with severe toxicity. Recently, we identified serum antibody signatures associated with toxicity outcomes following anti-CTLA4 IT. In this study, capitalizing on our recent data showing that the expression of autoimmunity risk genes is controlled by germline genetic variation in melanoma survival, we tested whether antibody profiles linked with IT-related toxicity are impacted by underlying genetic variation.

Methods: We have integrated serum data from 37 anti-CTLA4 IT-treated patients, profiled by HuProt human proteome array with germline whole-exome sequencing (WXS), comparing 28 patients with none/mild toxicity (CTCAE score 0-2) and 9 patients with severe toxicity (CTCAE score 3-5). The associations between toxicity and germline genetic variation were assessed by gene-burden analysis (SKAT). SKAT was integrated with differential proteome analysis of toxicity to identify individual proteins coded by genes and/or pathway enrichment putatively controlled by genetic variation associated with anti-CTLA4 related toxicity.

Results: The proteomic analysis identified 915 proteins that were differentially expressed ($p < 0.05$) in non/mild versus sever toxicity outcomes in anti-CTLA4 IT. SKAT analysis of genetic variation identified 1947 significant genes ($p < 0.05$) associated with toxicity, of which 78 were also significant ($p < 0.05$) in the proteomic analysis. The functional pathway analysis of 78 proteins showed enrichment for the regulation of interferon production, and a significant enrichment was observed for molecular pathways involved in autoimmunity.

Conclusions: We present a novel framework integrating germline genetic information and serum protein expression levels to identify associations with toxicity in anti-CTLA4 IT. We found enrichment for interferon production and pathways involved in autoimmunity controlled by genetic variation. The data strongly support the importance of genetic variation in immune system regulation and its effect on IT-related toxicity. The effect of genetic variants on protein expression is currently further tested in the context of toxicity response to IT treatment.

Legal entity responsible for the study: Tomas Kirchoff.

Funding: NIH

Disclosure: S. Hu: Scientist at CDI laboratories. J.S. Weber: Consulting or advisory role: Celldex, Ichor Medical Systems, cCam Biotherapeutics, Lion Biotechnologies, Pieris Pharmaceuticals, Altor BioScience, Bristol-Myers Squibb, Merck, Genentech, Roche, Amgen, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo, Abbvie, Eisai, CytomX Therapeutics, Nektar, Novartis, Medivation, Sellas Life Sciences, WindMIL; Stock and ownership options: Altor BioScience, Celldex, CytomX Therapeutics, Biond. All other authors have declared no conflicts of interest.

1183P PD-L1 expression is strongly associated with TIGIT, FOXP3 and LAG3 across advanced cancers, but not OX40, TIM3 and IDO

S.K. Pal[1], A.M. Vanderwalde[2], C. Szeto[3], S. Reddy[3], O. Hamid[4]
[1]Medical Oncology and Therapeutics Research, City of Hope, Duarte, CA, USA, [2]Hematology/Oncology, University of Tennessee, Memphis, TN, USA, [3]Bioinformatics, NantOmics, Culver City, CA, USA, [4]Research/Immuno-Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA

Background: Multiple trials are ongoing to evaluate combinations of immune checkpoint inhibitors (ICIs) across a variety of tumor types. Most of these studies utilize programmed death-1(PD-1) or programmed death-ligand 1 (PD-L1) inhibitors as a backbone. We interrogate the relationship of PD-L1 with other immune checkpoints to inform rational combination strategies.

Methods: We performed whole transcriptomic sequencing (RNA-Seq; ~200x10^6 reads/tumor) across 1,467 unselected clinical cases (NantHealth; Culver City, CA). Cases reflected 38 distinct histologies; the most common histologies were breast (17.8%), colon (9.5%) and lung (7.9%). High and low PD-L1 was delineated as the top

and bottom 15th percentile of expression values. Co-expression of checkpoint markers (TIGIT, FOXP3, LAG3, OX40, TIM3 and IDO) was analyzed within PD-L1-defined categories, along with putative markers of ICI resistance (e.g, VEGF-A/B/C). Tumor mutational burden (TMB; defined as exonic nonsynonymous mutations) was characterized across checkpoints.

Results: High PD-L1 expression was strongly associated with high expression of TIGIT, FOXP3 and LAG3 ($P < 0.001$ for each). In contrast, there was no significant difference in expression of OX40, TIM3 and IDO in groups subdivided by high and low PD-L1 expression. High expression of PD-L1 was associated with elevated levels of VEGF-C, but there was no relationship with VEGF-A or VEGF-B expression. Very limited concordance was seen between elevated TMB (> 200 nonsynonymous mutations) and checkpoint expression.

Conclusions: Recent results of combination trials assessing IDO and PD-1 inhibitors may be attributable to a lack of concomitant expression of these markers, thereby limiting synergy. Combinations of PD-1/-L1-directed therapies with TIGIT and LAG3 inhibitors may therefore be of greater interest. Enrichment strategies using TMB for these combinations may be challenging, given the lack of association with checkpoint expression.

Legal entity responsible for the study: Sumanta Pal.

Funding: Has not received any funding.

Disclosure: S.K. Pal: Consultant: Pfizer, Inc., Novartis, Aveo Pharmaceuticals, Inc., Myriad Genetics, Genentech, Inc., Exelixis, Bristol-Myers Squibb Company, Astellas Pharma, Inc.; Research/grant support: Medivation, Inc,; Honorarium: Novartis, Medivation, Inc., and Astellas Pharma, Inc. C. Szeto, S. Reddy: Employee and stockholder: NantOmics LLC. O. Hamid: Consultant: Amgen, Novartis, Roche, BMS, Merck; Speaker: BMS, Genentech, Novartis, Amgen; Contracted research (for institution): AstraZeneca, BMS, Celldex, Genentech, Immunocore, Incyte, Merck, Merck-Serono, MedImmune, Novartis, Pfizer, Rinat, Roche. All other authors have declared no conflicts of interest.

1184P Pharmacodynamic (PD) changes in tumors and peripheral blood T cell receptor (TCR) repertoire in a phase I study combining OX40 (PF-04518600) and 4-1BB (utomilumab) agonistic monoclonal antibodies (mAbs)

O. Hamid[1], S. Hu-Lieskovan[2], W. Ros[3], A. Diab[4], A.B. El-Khoueiry[5], J.A. Thompson[6], F.A. Eskens[7], J-P. Spano[8], E. Angevin[9], N.A. Rizvi[10], J.S. Wasser[11], P.A. Ott[12], A. Chiappori[13], T. Joh[14], H.I. Krupka[14], S. Potluri[14], X. Wang[14], B.J. Ganguli[14], J. Chou[14], T. Doi[15]

[1]Translational Research and Immunotherapy, The Angeles Clinic and Research Institute, Los Angeles, CA, USA, [2]Medicine, UCLA School of Medicine, Los Angeles, CA, USA, [3]Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands, [4]Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [5]Medical Oncology, USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [6]Medical Oncology, University of Washington Seattle Cancer Care Alliance, Seattle, WA, USA, [7]Medical Oncology, Erasmus University Medical Center, Rotterdam, Netherlands, [8]Medical Oncology, Groupe Hospitalier Pitié Salpetriere, Paris, France, [9]Medical Oncology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [10]Hematology and Oncology, Columbia University Medical Center College of Physicians & Surgeons, New York Presbyterian Hospital, New York, NY, USA, [11]Hematology and Medical Oncology, University of Connecticut School of Medicine, Farmington, CT, USA, [12]Center for Immuno-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [13]Thoracic Oncology Program, H. Lee Moffitt Cancer Center University of South Florida, Tampa, FL, USA, [14]Pfizer, Inc., New York, NY, USA, [15]Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: PF-04518600 (PF-8600) and utomilumab (uto) are human IgG2 agonistic mAbs against the tumor necrosis factor superfamily receptors OX40 and 4-1BB, respectively. Both receptors play key roles in T cell survival, proliferation, and activation. PF-8600 has been shown to increase proliferation and activation of peripheral CD4 memory T cells and uto has a similar effect on CD8 memory T cells. Previously, in patients treated with PF-8600, PD changes have been observed in tumor biopsy samples, including enrichment of gene sets associated with immune activation as well as CD4/8 T cell clonal expansion in peripheral blood. PD changes in tumors and peripheral TCR repertoire for PF-8600 + uto are reported here.

Methods: Paired biopsy samples at baseline and week 6 were collected from 5 dose cohorts (0.1/20, 0.3/20, 0.3/100, 1.0/100, 3.0/100; dose of PF-8600 in mg/kg / flat dose of uto in mg) during dose escalation. Biopsy tissues were analyzed by IHC and RNAseq to evaluate the PD effects of PF-8600 + uto. CD4, CD8, OX40, and FoxP3 expression was measured by IHC. Changes in transcriptional profile were measured by RNAseq analysis and gene ranking-based gene set enrichment analysis. CD4/8 cells were isolated from blood samples at the same time points. DNA was extracted and submitted for high-throughput sequencing of TCRβ.

Results: In an analysis of paired biopsy samples from dose cohorts including ≥ 0.3 mg/kg PF-8600, OX40 was among the genes that showed increased expression. The top gene sets exhibiting significant enrichment by RNAseq were associated with immune activation. TCR sequencing revealed clonal expansion of CD4/8 T cells at all dose levels.

Conclusions: Increases in immune-related markers including OX40 and enrichment of gene sets associated with immune activation were observed in tumor tissue, providing evidence of an active, immunomodulatory mechanism for PF-8600 + uto. Peripheral CD4/8 T cell populations exhibited clonal expansion at all dose levels, further suggesting an immune-activating PD effect. Further evaluation of PF-8600 + uto safety, efficacy, and PD continues in NSCLC and melanoma cohorts.

Clinical trial identification: NCT02315066.

Editorial acknowledgement: Editorial support was provided by Engage Scientific Solutions, Southport, CT.

Legal entity responsible for the study: Pfizer.

Funding: Pfizer.

Disclosure: O. Hamid, S. Hu-Lieskovan, J.A. Thompson: Research funding: Pfizer. A.B. El-Khoueiry: Research funding: AstraZeneca and Astex; Consulting honoraria: BMS, Bayer, Eisai, CytomX, EMD Serono. J-P. Spano: Consulting honoraria: Pfizer. N.A. Rizvi: Consulting honoraria: Merck, AstraZeneca, Roche, BMS, Novartis, Pfizer, Lilly, Abbvie, Merck KGaA, Regeneron; Shareholder: Gritstone Oncology, ARMO Biosciences. J.S. Wasser: Research funding: Merck, Incyte, Pfizer, Guardent; Speakers bureau honoraria: Novartis; Consulting honoraria: Amgen; Equity ownership in Pfizer, Merck, Bristol-Meyers Squibb. P.A. Ott: Consulting or advisory role: Amgen, Bristol-Myers Squibb, Alexion, CytomX Therapeutics, Celldex, Genentech, Novartis, Pfizer, Neon Therapeutics; Speaking fees: Merck & Co., Inc.; Research funding to institution: Bristol-Myers Squibb, Merck & Co., Inc., Astra Zeneca/MedImmune, Celldex, Neon Therapeutics, Pfizer, CytomX, and ARMO BioSciences. A. Chiappori: Research funding: AstraZeneca, BMS, Novartis; Consulting/speakers' bureau honoraria: AstraZeneca, Boehringer, Celgene, Genentech, Merck, Novartis, Takeda. T. Joh, H.I. Krupka, S. Potluri, X. Wang, B.J. Ganguli, J. Chou: Employee: Pfizer at the time of this study. All other authors have declared no conflicts of interest.

1185P Using MultiOmyx™ to analyze correlations between immunosuppressive cells and tumor-infiltrating lymphocytes in the pancreatic tumor microenvironment

A. Juncker-Jensen, J. Fang, J. Kuo, M.L. Nagy, R.K. Padmanabhan, E. Leones, F. Sahafi, S. Zhu, Q. Au, N. Hoe, J. William

MultiOmyx, NeoGenomics, Aliso Viejo, CA, USA

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive forms of cancer with a five-year survival rate that has remained below 10% for the past two decades. While immunotherapy-based treatment in recent years has demonstrated great success in stimulating anti-tumor T cell immunity in a wide variety of cancers, immunotherapy has had very limited success in pancreatic cancer patients. PDAC is characterized by a highly immunosuppressive tumor microenvironment (TME), dominated by Myeloid Derived Suppressor Cells (MDSCs), Type 2 Tumor-Associated Macrophages (M2 TAMs), and T regulatory cells (Tregs). While the presence of these cell types in the PDAC TME is well characterized, much still remains to be understood about how they function within the TME and how they co-operate with each other and tumor-resident lymphocytes to regulate antitumor immunity.

Methods: MultiOmyx™, a novel hyperplexed multi "omic" technology, enables visualization and characterization of multiple biomarkers on a single 4 µm tissue section. MultiOmyx protein immunofluorescence (IF) assays utilize a pair of directly conjugated Cyanine dye-labeled (Cy3, Cy5) antibodies per round of staining. Each round of staining is imaged and followed by novel dye inactivation chemistry, enabling repeated rounds of staining and deactivation for up to 60 protein biomarkers. In this study, MultiOmyx hyperplexed IF assay was utilized to measure CD11b, CD14, CD15, CD16, CD33, CD45RO, CD68, CD163, FoxP3, HLA-DR, Arginase1, PD-1, PD-L1, granzymeB, Ki67, and PanCK protein expression from a single 4 µm FFPE section.

Results: Using the MultiOmyx™ multiplexing assay in combination with proprietary algorithms for specific biomarker classification, we will report on the correlation between the presence of monocytic MDSCs (CD11b+CD33+CD14+CD15-HLA-DR-), granulocytic MDSCs (CD11b+CD33+CD15+CD14-HLA-DR-), M2-TAMs (CD68+CD163+), Tregs (CD3+CD4+FoxP3+) and the activation state of TILs, as well as their spatial relationship in tumor tissue from patients with PDAC.

Conclusions: Using the MultiOmyx™ multiplexing assay will allow us to analyze correlations between immunosuppressive cells and TILs in the pancreatic TME.

Legal entity responsible for the study: NeoGenomics.

Funding: NeoGenomics, a Pharma and Clinical services company.

Disclosure: A. Juncker-Jensen, J. Fang, J. Kuo, M.L. Nagy, R.K. Padmanabhan, E. Leones, F. Sahafi, S. Zhu, Q. Au, N. Hoe, J. William: Employee: NeoGenomics.

1186P Interim results from exploratory study to determine S-588410-induced tumor infiltrating lymphocytes and changes in the tumor microenvironment in esophageal cancer patients

T. Kojima[1], T. Marafioti[2], T. Fujiwara[3], Y. Shirakawa[3], T. Nakatsura[4], K. Kato[5], I. Puccio[2], M. Nagira[6], N. Ide[7], K. Stoeber[8], A. Arimura[7], H. Daiko[9]

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [2]Department of Cellular Pathology, University College London Hospital, London, UK, [3]Gastroenterological Surgery, Okayama University Hospital, Okayama, Japan, [4]Cancer Immunotherapy, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Kashiwa, Japan, [5]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, [6]Drug Discovery & Disease Research Laboratory, Shionogi & Co., Ltd., Osaka, Japan, [7]Project Management Department, Shionogi & Co., Ltd., Osaka, Japan, [8]Business Development, Shionogi & Co., Ltd., Osaka, Japan, [9]Esophageal Surgery Division, National Cancer Center Hospital, Tokyo, Japan

Background: S-588410 is a cancer peptide vaccine composed of 5 HLA-A*24:02-restricted peptides derived from 5 cancer-testis antigens, DEPDC1, MPHOSPH1, URLC10, CDCA1 and KOC1, all of which have been found to be upregulated in esophageal cancer. The aim of this study is to evaluate the effects of S-588410 on the number of tumor-infiltrating CD8-positive lymphocytes (TIL) and PD-L1 expression in the tumor tissue before and after the short-term treatment with S-588410 in the pre-surgical treatment.

Methods: HLA-A*24:02-positive patients (pts) with esophageal cancer who can start the treatment more than 30 days prior to the surgery were eligible. S-588410 was injected subcutaneously once weekly, 5 times or more in total. Tumor tissues of pre- and post-treatment were collected for immunohistochemistry (IHC) analysis for target antigens, CD8, PD-L1 and HLA class I. Peptide-specific CTLs in PBMC were evaluated using ELISpot assay.

Results: As Apr 13, 2018, total 15 pts were enrolled and tumor tissues of the first half of the pts, 8 pts were analyzed. 8 pts received 3 to 6 injections of S-588410. All 5 antigens and HLA class I on tumor tissues were detected in all pts except for one whose tumor expressed 4 target antigens. CTL activity circulating in blood markedly increased in all 8 pts at least for 1 of 5 peptides. IHC analysis demonstrated that TIL density and PD-L1 expression on post-treatment tissues clearly increased compared to the baseline; $CD8^+$ TIL density at baseline was $\leq$ 1% in 5 pts and 1%-10% in 3 pts and that for post-treatment 1%-10% in 2 pts, 10%-50% in 6 pts, and PD-L1 expression at base line was $\leq$ 1% in 7 pts and 1%-5% in one patient and that for post-treatment was $\leq$ 1% in one patient, 1%-5% in 4 pts and 5%-50% in 3 pts.

Conclusions: The short-term treatment with S-588410 generated peptide-specific CTL and markedly increased $CD8^+$ TIL density and PD-L1 expression on tumor tissue of esophageal cancer pts. These interim results suggest that the combination of S-588410 with anti-PD-1/PD-L1 antibody is expected to be more effective than monotherapy, particularly in pts with low TIL/PD-L1 status.

Clinical trial identification: UMIN000023324.

Legal entity responsible for the study: Shionogi & Co., Ltd.

Funding: Shionogi & Co., Ltd.

Disclosure: T. Kojima: Travel grants: Shionogi & Co., Ltd.; Grants: Ono Pharmaceutical, MSD, Oncolys BioPharma, Astellas Amgen BioPharama. M. Nagira, N. Ide, K. Stoeber, A. Arimura: Employee: Shionogi & Co., Ltd. All other authors have declared no conflicts of interest.

1187P Clinical implication of PDL1 expression and TILs in male breast cancer: More hype or new hope? Results from the UMBREAC trial (NCT03240510)

S. Abdeljaoued[1], I. Bettaieb[1], A. Goucha[1], O. Adouni[1], H. El Mokh[1], H. Bouzaiene[2], J. Ben Hassouna[2], H. Boussen[3], K. Rahal[2], A. Gamoudi[1]

[1]Immuno-Histo-Cytology, Institut Salah Azaïz, Tunis, Tunisia, [2]Surgical Oncology, Institut Salah Azaïz, Tunis, Tunisia, [3]Department of Medical Oncology, Hopital Abderrahman Mami, Ariana, Tunisia

Background: Whether PDL1 or TILs have any indication for prognosis in male breast cancer (MBC) patients remains unknown. In this study, we investigated the relationship between the expression and degree of PDL1 and TILs and evaluated the prognostic value of these factors in MBC.

Methods: We retrospectively identified 150 MBC patients diagnosed between 2003 and 2013 at Salah Azaïz Cancer Institute. PDL1, Stromal (str) CD8+ and CD4+ TILs were evaluated immunohistochemically. TILs levels were evaluated following 2014 International TILs Working Group guidelines.

Results: Fifty three percent of MBC patients had low str-TILs and 47% had moderate str-TILs. No lymphocyte predominant breast cancer was identified. Only 12% of MBC patients had high str-CD8+TILs and 11% had high str-CD4+TILs. TNBC subtype and HER2 enriched tumors had higher median levels of str-CD8+TILs, str-CD4+ TILs and str-TILs at diagnosis. On univariate analysis, higher levels of str-CD8+TILs, str-CD4+ TILs and str-TILs were associated with better OS ($p = 0.035$, $p = 0.043$ and $p = 0.040$ respectively). Multivariate analysis identified str-CD8+ TILs and str-TILs as independent prognostic factors for OS ([HR = 0.851 (0.706-0.997), $p = 0.000$] and [HR = 0.69 (0.43-0.96), $p = 0.045$] respectively). High expression of PD-L1 was observed in 64.5% of MBC samples. Patients with high PD-L1 expression had significantly shorter overall survival (OS) than patients with low expression ($p = 0.002$, hazard ratio HR = 5 [2.624 –10.642]). Multivariate analysis identified PD-L1 as independent prognostic factor for OS ($p < 0.001$, HR = 0.775 [0.680–0.870]).

Conclusions: PD-L1 expression, Str-CD8+ T cells and str-TILs represents promising novel biomarkers with prognostic significance in MBC. Thus, successful inclusion of these markers in prognostic clinical models is becoming a realistic hope in MBC.

Clinical trial identification: NCT03240510.

Legal entity responsible for the study: Institut Salah Azaïz.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1188P Identification of prognostic and predictive factors for durvalumab efficacy by modeling of tumor response and overall survival (OS) in patients with non-small cell lung cancer (NSCLC)

Y. Zheng[1], R. Narwal[2], C. Jin[1], P. Baverel[3], A. Gupta[4], P. Mukhopadhyay[5], B.W. Higgs[6], L. Roskos[2]

[1]Clinical Pharmacology & DMPK, MedImmune, South San Francisco, CA, USA, [2]Clinical Pharmacology & DMPK, MedImmune, Gaithersburg, MD, USA, [3]Clinical Pharmacology & DMPK, MedImmune, Cambridge, UK, [4]Immuno-Oncology Global Medicines Development, AstraZeneca, Gaithersburg, MD, USA, [5]Biometrics & Information Sciences, AstraZeneca, Gaithersburg, MD, USA, [6]Translational Medicine, MedImmune, Gaithersburg, MD, USA

Background: Durvalumab, a human anti–PD-L1 mAb, is currently approved for treatment of patients with Stage III unresectable NSCLC. The objectives of this analysis were to identify prognostic and predictive factors for tumor growth and shrinkage, as well as for OS in NSCLC patients treated with durvalumab.

Methods: Longitudinal tumor size (TS) and OS data obtained from NSCLC patients in Study 1108 (all comers) and ATLANTIC (Stage III and above) who received durvalumab were analyzed using a nonlinear mixed effect model that describes the growth and regression of sensitive and insensitive tumor cells, as well as delay in immune response leading to tumor killing. A linked OS-dropout model was developed by relating model-predicted tumor changes to OS and dropout probability over time. Potential prognostic and predictive factors were evaluated in a multivariate covariate analysis using the models.

Results: The longitudinal TS and OS data from NSCLC patients in both studies are generally well described by the models. Liver metastasis, neutrophil-to-lymphocyte ratio (NLR), EGFR mutation, and durvalumab clearance (CL) are identified as prognostic factors for tumor growth, and tumor cell PD-L1 expression (TC) and baseline tumor size as predictive factors for tumor killing ($p < 0.01$). The significant factors for OS after accounting for the tumor size changes included TC and immune cell PD-L1 expression (IC), NLR, lactate dehydrogenase, as well as CL ($p < 0.01$). Among all factors tested, NLR is the most influential factor on the predicted 1-year survival rates (~60% vs. 30% with NLR below and above the median [4.56]). Positive PD-L1 expression (TC or IC $\geq$ 25%) is predicted to result in ~10-20% increase in one-year survival rates. Increasing the cutoff value is not predicted to result in substantially greater improvement in the survival rate.

Conclusions: The modeling results provided quantitative assessments of the impact of various prognostic and predictive factors, as well as biomarker cutoff values on the efficacy of durvalumab in NSCLC patients, and can be used to inform patient selection criteria in future monotherapy or combination studies.

Clinical trial identification: NCT01693562.

Legal entity responsible for the study: MedImmune, LLC.

Funding: MedImmune.

Disclosure: Y. Zheng, R. Narwal, C. Jin, P. Baverel, A. Gupta, B.W. Higgs, L. Roskos: Employee: MedImmune; Stock and/or stock interests or options: AstraZeneca. P. Mukhopadhyay: Employee, Stock and/or stock interests or options: AstraZeneca.

1189P Intrinsic and extrinsic regulation of PD-L2 expression by transcription factor STAT3 or c-FOS in oncogene-driven non-small cell lung cancer

D. Shibahara[1], K. Tanaka[2], E. Iwama[2], N. Kubo[2], K. Ota[3], K. Azuma[4], T. Harada[2], J. Fujita[1], Y. Nakanishi[5], I. Okamoto[2]

[1]Infectious Disease, Respiratory and Digestive Medicine, Ryukyu University Hospital, Okinawa, Japan, [2]Respiratory Medicine, Kyushu University Hospital, Fukuoka, Japan, [3]Respiratory, Kyushu University Hospital, Fukuoka, Japan, [4]Respirology, Neurology, and Rheumatology, Kurume University School of Medicine, Fukuoka, Japan, [5]Research Institute for Diseases of the Chest, Kyushu University Hospital, Fukuoka, Japan

Background: Treatment with antibodies that target programmed cell death 1 (PD-1) or its ligand programmed death ligand 1 (PD-L1) has demonstrated durable efficacy for various malignant tumors. Programmed death ligand 2 (PD-L2), which is another ligand of PD-1, has recently been shown to be implicated in tumor immune escape. The regulation of PD-L2 expression in tumor cells has remained unclear, however. We here examined intrinsic and extrinsic regulation of PDL2 expression in NSCLC.

Methods: PD-L2 expression was evaluated by reverse transcription and real-time polymerase chain reaction analysis and by flow cytometry.

Results: BEAS-2B cells stably expressing an activated mutant form of the epidermal growth factor receptor (EGFR) or the EML4-ALK fusion oncoprotein manifested increased expression of PD-L2 at both mRNA and protein levels. Furthermore, treatment of NSCLC cell lines that harbor such driver oncogenes with corresponding EGFR or ALK tyrosine kinase inhibitors or depletion of EGFR or ALK by siRNA transfection suppressed expression of PD-L2, demonstrating that activating EGFR mutations or EML4-ALK fusion intrinsically induce PD-L2 expression. We also found that interferon-γ extrinsically induced expression of PD-L2 via STAT1 signalingin NSCLC cells. Oncogene-driven expression of PD-L2 in NSCLC cells was inhibited by knockdown of the transcription factors STAT3 or c-FOS. Interferon-γ also activated STAT3 and c-FOS. Knockdown of STAT3 or c-FOS decreased Interferon-γ-induced expression of PD-L2, suggesting that these proteins may also contribute to the extrinsic induction of PD-L2 expression.

Conclusions: Expression of PD-L2 is induced intrinsically by activating EGFR mutations or EML4-ALK fusion as well as extrinsically by interferon-γ, with STAT3 and c-FOS possibly contributing to both intrinsic and extrinsic pathways. Our results thus provide insight into the complexity of tumor immune escape in NSCLC.

Legal entity responsible for the study: an individual person.

Funding: Has not received any funding.

Disclosure: K. Azuma: Personal fees: AstraZeneca; Grants and personal fees: Boehringer Ingelheim, Ono Pharmaceutical, MSD Oncology, Bristol-Myers Squibb, and Chugai Pharma outside the submitted work. I. Okamoto: Grants and personal fees: AstraZeneca, Taiho Pharmaceutical, Boehringer Ingelheim, Ono Pharmaceutical, MSD Oncology, Lilly, Bristol-Myers Squibb, Chugai Pharma; Grants: Astellas Pharma Novartis; Personal fees: Pfizer outside the submitted work. All other authors have declared no conflicts of interest.

1190P Microsatellite instability detection by targeted sequencing of cell-free DNA

A. Artyomenko[1], M. Sikora[1], M. Lefterova[2], V.M. Raymond[2], D. Gavino[2], C. Barbacioru[1], C. Artieri[2], E. Helman[1], D. Chudova[1], R.B. Lanman[2], J. Odegaard[3], J.A. Willis[4], M. Fakih[5], S. Kopetz[6], A. Talasaz[3]

[1]Bioinformatics, Guardant Health, Redwood City, CA, USA, [2]Medical Affairs, Guardant Health, Redwood City, CA, USA, [3]Guardant Health, Redwood City, CA, USA, [4]Oncology, The University of Texas MD Anderson Cancer Center, Huston, TX, USA, [5]Medical Oncology Department, City of Hope, Duarte, CA, USA, [6]Department of Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

Background: Microsatellite instability (MSI) is a guideline-recommended biomarker used in assessment of prognosis and treatment choices, including checkpoint inhibitors recently approved for cancers with MSI-high (MSI-H) status. Plasma-based next generation DNA sequencing (NGS) tests are increasingly used for comprehensive genomic profiling of cancer; however, sensitive methods to detect MSI status from cell-free DNA (cfDNA) are not available for clinical patient care. Additionally, the impact of variable tumor shedding on MSI detection has not been evaluated.

Methods: We developed an accurate method to assess MSI status using targeted sequencing of cfDNA using the Guardant360® clinical platform across a many cancer types, which allows broad coverage of simple repeats. For each microsatellite locus, the number of differently-sized repeats in experimental samples is quantified using a probabilistic log likelihood-based score designed to accurately discriminate biological signal derived from cfDNA fragments of somatic origin from noise arising from technical artifacts. Loci are considered unstable if the likelihood score is greater than a threshold computed from a cohort of normal samples. MSI status of a sample is determined by the presence of a minimum 5 unstable microsatellite loci among the 91 scored.

Results: We simulated MSI high (MSI-H) samples across a range of tumor fractions by combining data from 82 healthy donor samples with in silico spike-ins of differentially sized repeats. Simulated data demonstrates a sensitivity of 94% at 0.2% (limit of detection) tumor content for an expected specificity of 99.9% estimated from healthy donor samples. When applied to a prospective test set of 134 advanced cancer samples, this method demonstrated 98.5% (125/127) specificity and 86% sensitivity (6/7) relative to standard tissue PCR-based MSI assessment across a ctDNA range of 0.1%-15%.

Conclusions: Targeted sequencing of cfDNA data can enable highly accurate detection of MSI in cancer samples, even for samples with low tumor shedding. This novel approach enables non-invasive assessment of MSI status concurrent with comprehensive genomic profiling and allows potential access to immunotherapies for patients whose tumor types are not routinely tested for MSI.

Legal entity responsible for the study: Guardant Health, Inc.

Funding: Guardant Health, Inc.

Disclosure: A. Artyomenko, M. Sikora, M. Lefterova, V.M. Raymond, D. Gavino, C. Barbacioru, C. Artieri, E. Helman, D. Chudova, R.B. Lanman, J. Odegaard, A. Talasaz: Employee: Guardant Health, Inc. All other authors have declared no conflicts of interest.

1191P Immune checkpoints and T-lymphocytes as immunotherapeutic target in the treatment of sebaceous gland carcinoma

L. Singh[1], M.K. Singh[2], N. Pushker[3], S. Bakhshi[4], M.A. Rizvi[1], S. Sen[2], S. Kashyap[2]

[1]Biosciences, Jamia Millia Islamia, New Delhi, India, [2]Ocular Pathology, All India Institute of Medical Sciences, New Delhi, India, [3]Ophthalmology, All India Institute of Medical Sciences, New Delhi, India, [4]Medical Oncology, All India Institute of Medical Sciences, New Delhi, India

Background: Immune checkpoint blockade strategies have gained attention in the treatment/prognosis of cancers via targeting the PD-1/PD-L1 pathway or in combination with the CTLA-4 blockade and are currently in clinical trials. The present study investigated the expression of PD-1, PD-L1, CTLA-4, CD4 and CD8 proteins and their prognostic value in the tumor microenvironment of sebaceous gland carcinoma patients (SGC).

Methods: Stromal and tumor cells expressing PD-1, PD-L1, CTLA-4, CD4 and CD8 protein were assessed in 52 cases of sebaceous gland carcinoma by Immunohistochemistry and their mRNA expression was measured by quantitative Reverse-Transcriptase PCR (qRT-PCR). Kaplan–Meier curves and Cox proportional hazard models, analyzed the correlation of proteins with clinicopathological parameters and disease-free survival.

Results: Pagetoid spread was the frequent histopathological high-risk factor in our study. Expression of PD-L1 was found to be more common in tumor cells than stromal cells. In univariate analysis, patients expressing PD-1 and PD-L1 in tumor cells were associated with reduced disease-free survival, whereas stromal-PD-L1 showed an increased survival of the patients ($p < 0.05$). However, in multivariate analysis, expression of PD-1 in tumor cells was found to be an independent prognostic factor for poor survival.

Conclusions: This is the first report describing the association of clinicopathological features and outcomes of immune checkpoint expression along with T-Lymphocytes in sebaceous gland carcinoma. These results support the consideration that PD-1/PD-L1 pathway might play an important role in tumor microenvironment for mediating immune response in the pathogenesis of sebaceous gland carcinoma patients.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1192P Evaluation of OX40 receptor density, influence of IgG Isotype and dosing paradigm in anti-OX40-mediated efficacy and biomarker responses with PD-1 blockade

H. Jackson[1], S. Bhattacharya[1], P. Bojczuk[1], D. Kilian[1], L. Seestaller Wehr[1], A. Hahn[1], H. Shi[1], M. Bi[1], M. Adam[1], J. Jing[1], P. Morley[2], C. Hopson[1], E. Paul[1], A. Hoos[1], J. Smothers[1], R. Srinivasan[1], N. Yanamandra[1]

[1]Immuno-Oncology Combinations DPU, GlaxoSmithKline USA, Collegeville, PA, USA, [2]Biopharm Molecular Discovery, GlaxoSmithKline USA, Stevenage, UK

Background: GSK3174998 is an agonistic IgG1-anti-OX40 (aOX40) monoclonal antibody (mAB) that binds to OX40 receptors expressed on activated T cells. GSK3174998 engages the immune system via several T cell-mediated pathways. The following studies examine 1) OX40 receptor expression and enumeration in T cell populations in patient tumors 2) influence of IgG isotype on GSK3174998-mediated FcγRIIIa engagement 3) dosing regimen effects on efficacy and pharmacodynamic response with the anti-OX40 /anti-PD-1 (aPD-1) combination in preclinical models.

Methods: In vitro, an FcγRIIIa reporter assay was used to compare GSK3174998 with other IgG isotype variants and its combination with pembrolizumab. In vivo studies were performed to evaluate tumor growth and survival following concurrent and sequential dosing regimens of aOX40 ± aPD-1 mAbs. Biomarkers of response were monitored by flow cytometry, NanoString, TCRb sequencing and multiplex cytokine analysis.

Results: OX40 receptor density was observed as highest on intra-tumoral Tregs (compared to CD4 effectors and CD8+ T cells) in several primary tumor samples. FcγRIIIa engagement correlated strongly with receptor density and was dependent on an IgG1 wild type Fc isotype. GSK3174998 in combination with pembrolizumab increased inflammatory and Th1 cytokine production in human PBMCs. In vivo studies suggest that concurrent dosing of aOX40 with aPD-1 offers superior anti-tumor efficacy and survival compared to sequential regimens. Furthermore, combination with aPD-1 led to enhanced expression of inflammatory and Th1 cytokines, increased T cell activation, proliferation and cytotoxicity compared to either monotherapy. Concurrent treatment also significantly increased T cell clonal expansion in the periphery, increased clonality both in blood and tumor and induced migration of the expanded clones into the tumors over monotherapy.

Conclusions: Overall, the combination of aOX40 and aPD-1 elicited stronger qualitative and quantitative changes in immune markers both in vitro and in vivo. The potential synergy of concurrent dosing formed the basis for combining GSK3174998 with pembrolizumab in phase I/II clinical studies.

Legal entity responsible for the study: GlaxoSmithKline Inc.

Funding: Has not received any funding.

Disclosure: H. Jackson, D. Kilian, S. Bhattacharya, P. Bojczuk, L. Seestaller Wehr, A. Hahn, H. Shi, M. Bi, M. Adam, J. Jing, P. Morley, C. Hopson, E. Paul, A. Hoos, J. Smothers, R. Srinivasan, N. Yanamandra: Stockholder, Employee: Glaxosmithkline Pharmaceuticals.

1193P Impact of tissue processing and interferents on the reproducibility and robustness of a multi-plex gene expression assay measuring tumor inflammation

B. Wallden[1], S. Church[1], I. Pekker[1], S. Zimmerman[1], S. Popa[1], A. Sullivan[1], C. Ngouenet[1], E. Harris[1], N. Dowidar[1], A. Bergdahl[1], C. Schaper[1], P. Danaher[2], S. Ferree[1]

[1]Dx Development, NanoString Technologies, Seattle, WA, USA, [2]Bioinformatics, NanoString Technologies, Seattle, WA, USA

Background: The Tumor Inflammation Signature (TIS) is an investigational use RNA expression assay on the NanoString nCounter Dx Analysis System, which provides a measure of tumor inflammation across multiple solid tumor types. TIS measures immune genes in tumors from multiple origins, and it is possible that inclusion of tissue-specific interferents, such as non-tumor lymphoid aggregates (NTLA) could influence TIS performance. Here we describe the validation of the reproducibility of the TIS assay starting from FFPE tissues and robustness of the TIS across 8 potential tissue interferents.

Methods: TIS includes both review of an H&E tumor slide by a Pathologist and sample processing of unstained slides by an assay user. Analytical validation of the reproducibility of the TIS assay from 3 different Pathologists and 3 different assay users was performed using at least 10 patient specimens for 11 different tumor types (>110 independent tumors tested) from excisional and core biopsies. The robustness of the TIS assay to potential tissue interferents (genomic DNA, adjacent non-tumor tissue, NTLA, mucin, hemorrhagic, necrotic, and fibrotic tissue) was also assessed.

Results: The assay was validated to be reproducible with $\geq$ 95% concordance in assay results between independent pathologists. The total standard deviation of the TIS score was less than 2% of the score range from tissue including different pathology review and users. The interference studies demonstrated that the presence of mucin, necrotic, hemorrhagic and fibrotic tissue did not influence TIS results. However, if not properly removed, contamination with large concentrations of genomic DNA, non-tumor tissue, and NTLA can reduce biomarker concordance by increasing the TIS score.

Conclusions: The analytical performance of the NanoString TIS assay has been validated to be reproducible between users and pathologists when potential interferents are removed as instructed in the assay procedures. TIS is well suited for decentralized clinical testing and use as a potential biomarker to enrich for patients based on their inflamed phenotype across multiple tumors.

Legal entity responsible for the study: NanoString Technologies, Inc.

Funding: NanoString Technologies, Inc.

Disclosure: B. Wallden, S. Church, S. Zimmerman, S. Popa, A. Sullivan, C. Ngouenet, E. Harris, N. Dowidar, A. Bergdahl, S. Ferree: Employee, Stockholder: NanoString Technologies, Inc. I. Pekker, P. Danaher: Employee, Stockholder at the time of the study: NanoString Technologies, Inc. C. Schaper: Paid consultant: NanoString Technologies, Inc.

1194P Translational endpoints in patients with metastatic microsatellite-stable colorectal cancer (MSS-CRC) treated with durvalumab plus monalizumab (anti-NKG2A)

J.R. Diamond[1], N. Standifer[2], M.L. Ascierto[3], C. Morehouse[3], H. Ghadially[4], J. Rodriguez Canales[3], M.C. Rebelatto[3], J. Naidoo[5], L. Mazzarella[6], S. Patel[7], M.J. Flor Oncala[8], T. Alonso Gordoa[9], D. Wang[10], X. Song[3], D.C. Jones[4], X. Li[11], S. Marshall[11], S. Abdullah[11], M. Jure-Kunkel[11], M.D. Hellmann[12]

[1]Oncology, University of Colorado Denver, Denver, CO, USA, [2]Oncology, MedImmune, Mountain View, CA, USA, [3]Oncology, MedImmune, Gaithersburg, MD, USA, [4]Oncology, MedImmune, Cambridge, UK, [5]Oncology, Johns Hopkins University, Baltimore, MD, USA, [6]Oncology, Istituto Europeo di Oncologia, Milan, Italy, [7]Oncology, University of California San Diego, San Diego, CA, USA, [8]Oncology, Hospital Universitario Virgen del Rocío, Seville, Spain, [9]Oncology, University Hospital Ramón y Cajal, Madrid, Spain, [10]Oncology, Henry Ford Hospital, Detroit, MI, USA, [11]MedImmune, Gaithersburg, MD, USA, [12]Memorial Sloan Kettering Cancer Center, New York, NJ, USA

Background: PD-1/L1 blocking agents have transformed the treatment of multiple cancers, but some tumor types including MSS-CRC appear to be refractory. Monalizumab (anti-NKG2A) and Durvalumab (anti-PD-L1) may promote antitumor immunity via non-redundant mechanisms targeting innate and adaptive immunity. The safety and preliminary efficacy of this combination (NCT02671435) was previously reported (ASCO 2018). Here, we present the results of baseline and longitudinal pharmacodynamic biomarker assessments in peripheral blood and tumor in patients with MSS-CRC treated with Monalizumab plus Durvalumab.

Methods: Peripheral biomarkers evaluated included NKG2A receptor occupancy (RO), and frequency and functional status of immune cells (N = 23). In tumors, changes in NK and CD8 cells in pre/post-tumor biopsies were evaluated by immunohistochemistry (IHC, N = 7). Gene expression profiling of tumors was determined by RNAseq in N = 15 pretreated and N = 4 paired biopsies.

Results: In peripheral blood, full and sustained NKG2A RO was observed. Expansion of activated or proliferating NK cells was detected in 14/23 and 10/20 patients respectively, while increases in T cell proliferation ($KI67^+$) were observed at levels expected for Durvalumab monotherapy (1.5-2-fold). In an in vitro assay system, similar changes on T/NK cell phenotyping were observed upon exposure to Monalizumab and Durvalumab. No consistent pharmacodynamics changes in tumoral NK and CD8 cells by gene expression or IHC were observed. However, modulation of pathways associated with metabolism, DNA repair and cell cycle were detected in tumors on treatment.

Conclusions: In peripheral blood, pharmacodynamic effects consistent with the proposed mechanism of action of Monalizumab and Durvalumab were observed in patients with MSS-CRC.

Clinical trial identification: NCT02671435; February 22, 2016.

Legal entity responsible for the study: MedImmune.

Funding: MedImmune.

Disclosure: N. Standifer, M.L. Ascierto, C. Morehouse, H. Ghadially, J. Rodriguez Canales, M.C. Rebelatto, X. Song, D.C. Jones, X. Li, S. Marshall, S. Abdullah, M. Jure-Kunkel: Employee: MedImmune. All other authors have declared no conflicts of interest.

1195P Alterations in peripheral T cell subsets, T cell activation markers and immune checkpoint molecules in advanced pancreatic cancer patients receiving FOLFIRINOX or gemcitabine + nab-paclitaxel

L.E. Sams[1], S. Kruger[1], V. Heinemann[1], D. Bararia[2], S. Haebe[1], S. Alig[1], B. Westphalen[1], M. Haas[1], T. Kirchner[3], S. Ormanns[3], S. Endres[4], O. Weigert[2], M. von Bergwelt-Baildon[1], S. Kobold[4], F. Rataj[4], S. Boeck[1]

[1]Medizinische Klink und Poliklinik III Großhadern, LMU Klinikum der Universität München, Munich, Germany, [2]Experimentelle Leukämie - und Lymphom-Forschung (ELLF), Medizinische Klinik und Poliklinik III Ludwigs Maximilians Universität, Munich, Germany, [3]Pathologisches Institut, Ludwig Maximilians Universität - Campus Innenstadt, Munich, Germany, [4]Abteilung für Klinische Pharmakologie, Medizinische Klinik IV, Ludwig Maximilians Universität - Campus Innenstadt, Munich, Germany

Background: Efforts to develop successful immunotherapeutic treatments in pancreatic cancer have failed so far. One possible strategy might be the combination of established chemotherapeutic regimens (FOLFIRINOX or gemcitabine plus nab-paclitaxel [gem/nab-pac]) with checkpoint inhibitors. The goal of the present pilot study is to provide a better understanding of alterations in the expression of T cell activation markers and immune checkpoint molecules in patients with advanced pancreatic cancer receiving FOLFIRINOX or gem/nab-pac.

Methods: We conducted a prospective single-center study with selected advanced pancreatic cancer patients who received FOLFIRINOX or gem/nab-pac between 2015 and 2017. Blood samples (15 ml heparinized blood, 10 ml serum) were taken at day 1 and 30 of first-line chemotherapy. Ficoll density gradient separation was used to isolate peripheral blood mononuclear cells (PBMCs). After short-term storage at -80 °C, flow cytometry was performed using a LSR Fortessa flow cytometer (BD Biosciences). CD3+ CD4+ and CD3+ CD8+ T cell count as well as the expression of FoxP3, PD-1, CTLA4, CCR7, CD62L, CD69, Tim3 and LAG 3 on CD3+ T cells was analyzed.

Results: 25 eligible patients were included in the study. Two consecutive blood samples were available for 21 of these patients (FOLFIRINOX: n = 18, gem/nab-pac: n = 3). We found a broad variability within T cell subsets and change of expression in T cell activation/immune checkpoint molecules during therapy. While the majority of patients (n = 13/21, 62%) is still in follow-up, first results indicate a correlation of an increase of FOXP3+ T cells in peripheral blood during chemotherapy and worse outcome. No correlation between increase of PD-1 on peripheral T cells and prognosis was observed.

Conclusions: A comprehensive RNA based (nanostring nCounter®) analysis of intratumoral immune cell infiltration of all included patients is currently ongoing. It will provide further insights on the interplay between tumoral and peripheral (T cell) immunity during chemotherapy in advanced pancreatic cancer.

Legal entity responsible for the study: Stefan Böck.

Funding: Friedrich-Baur-Stiftung.

Disclosure: All authors have declared no conflicts of interest.

1196P Resistance to anti-PD-1 therapy is associated with the retention of CXCR3+ CD4+ CD8- T cells in blood

X. Han[1], T. Tan[2], J. Sun[1], X. Chen[1], X. Cai[1], P. Lin[1], Y. Tan[2], B. Wang[1], Y. Wang[1], J. Wang[1], Z. Yu[1], X. Wu[2], Q. Xu[2], Y. Gu[1]

[1]Department of Oncology, The First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital), Nanjing, China, [2]State Key Laboratory of Pharmaceutical Biotechnology and Collaborative Innovation Center of Chemistry for Life Sciences, Nanjing University, Nanjing, China

Background: Immune checkpoint blockades have received significant clinical efficacy in the past decade in many malignancies. However, both primary and acquired resistance becomes one of the major obstacles that cannot be ignored, which seriously limits its clinical efficacy. To predict immunotherapy efficacy remains challenging. Dynamic

changes in the systemic immune signature in response to multiple infusions of anti-PD-1antibody are poorly understood.

Methods: We collected whole blood samples from cancer patients before and after every cycle anti-PD-1 infusion and isolated PBMCs using Ficoll gradient centrifugation. PBMCs were stained for mass cytometry analyses, and the data were acquired on a CyTOF 2 Helios (Fluidigm). We evaluated tumour responses using Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1) by computed tomography (CT). In addition, we conducted animal experiments to verify our experimental results.

Results: We revealed a marked increase in the percentage of $CXCR3^+$ $CD4^+$ $CD8^-$ T cells in blood from cancer patients after the first pembrolizumab infusion. Intriguingly, the percentage went down after the second infusion in responding patients. Interestingly, a continuous high percentage of $CXCR3^+$ $CD4^+$ $CD8^-$ T cells was observed from patients with progressing disease, while a low percentage with stable disease or partial response confirmed by conventional flow cytometry. Furthermore, depletion of $CXCR3^+$ cells abolished the improvement of melanoma by anti-PD-1 treatment in mice.

Conclusions: The dynamic changes in $CXCR3^+$ $CD4^+$ $CD8^-$ T cells in blood could be a prognostic factor and a continuous high percentage of $CXCR3^+$ $CD4^+$ $CD8^-$ T cells may reflect resistance to anti-PD-1 therapy.

Legal entity responsible for the study: The First Affiliated Hospital of Nanjing Medical University.

Funding: National Natural Science Foundation of China Jiangsu Province Key Medical Talents.

Disclosure: All authors have declared no conflicts of interest.

1197P Cerebrospinal fluid lymphocytosis: A hallmark of neurological immune related adverse events (irAEs) during checkpoint inhibitor treatment

K.P. Suijkerbuijk[1], F.Y.F.L. De Vos[1], J.J. Koldenhof[1], T.J. Snijders[2]

[1]Medical Oncology, University Medical Center Utrecht Cancer Center, Utrecht, Netherlands, [2]Brain Center Rudolf Magnus, Department of Neurology & Neurosurgery, University Medical Center Utrecht, Utrecht, Netherlands

Background: Checkpoint inhibitors have reshaped the oncology landscape, but their success comes at the price of immune related adverse events (irAEs). Although rare, neurological irAEs are often disabling and in some cases fatal.

Methods: We analyzed the clinical data of all patients who were treated with checkpoint inhibitors and were subsequently diagnosed with neurological irAEs in our institute since January 2015. Alternative diagnoses such as progressive disease and infectious causes were ruled out by MRI and cerebrospinal fluid (CSF) cytology and PCR.

Results: Neurological irAEs were diagnosed in six patients. All patients received anti-PD1, in two cases combined with ipilimumab. Three patients were diagnosed with aseptic meningitis, two with encephalitis and one patient with radiculitis. In all cases, there was a remarkable cerebrospinal fluid (CSF) lymphocytosis (70-99%). All six patients were treated with high-dose steroids. Subsequent intravenous immunoglobulins were administered in three patients. All patients experienced improvement of neurological symptoms after immunosuppressive treatment, with complete resolution of symptoms in three patients.

Conclusions: These data illustrate that CSF lymphocytosis is a hallmark of neurological checkpoint inhibitor toxicity and can be used as a diagnostic aid. Since lymphocytic pleiocytosis is not pathognomonic for neurological irAEs, alternative explanations for lymphocytic pleiocytosis such as viral infections should be ruled out. We encourage clinicians to assess leukocyte differentiation in patients with neurological symptoms that are treated with immune checkpoint inhibitors.

Legal entity responsible for the study: University Medical Center Utrecht.

Funding: Has not received any funding.

Disclosure: K.P. Suijkerbuijk: Consulting, Advisory: Bristol-Myers Squibb, MSD; Honoraria (institution): Novartis, Roche. F.Y.F.L. De Vos: AbbVie, BioClin, Novartis. All other authors have declared no conflicts of interest.

1198P Serum markers as predictors of immune checkpoint inhibitors (ICI) related adverse events in a real-world scenario

D. Iacono[1], M.G. Vitale[2], F. Cortiula[2], M. Cinausero[2], A. Tullio[3], F. Valent[3], M. Macerelli[1], A. Follador[1], A. Vogrig[4], A.M. Minisini[1], F. Puglisi[2], G. Fasola[1]

[1]Department of Oncology, ASUIUD Santa Maria della Misericordia, Udine, Italy, [2]Department of Medicine (DAME), University of Udine, Udine, Italy, [3]Hygiene and Clinical Epidemiology Unit, ASUIUD Santa Maria della Misericordia, Udine, Italy, [4]Department of Neurosciences, ASUIUD Santa Maria della Misericordia, Udine, Italy

Background: Immune checkpoint inhibitors (ICI), both anti CTLA-4 and anti PD-1/PD-L1 agents, have drastically changed the cancer therapies landscape. However, by unleashing the host immune system, a new class of immune related adverse events (irAEs) have emerged. It is still unknown if any biomarker may predict irAEs onset.

Methods: A retrospective series of 130 consecutive patients (pts) treated with anti PD-1/PD-L1 or anti CTLA-4 agents from Jan 2012 to Dec 2017 was analyzed. IrAEs were graded according to CTCAE v.4.0. The aim of the study was to evaluate changes in serum markers in pts with irAEs onset. Wilcoxon's signed rank test was used to assess the statistical significance of changes in biomarkers. Gray's test was used to assess differences in the cumulative incidence function of irAEs among groups of pts.

Results: Pts with a diagnosis of NSCLC n = 64 (49%), melanoma n = 55 (42%), kidney n = 9 (7%) and others n = 2 (2%) were investigated. Median age was 69 years. Baseline ECOG PS was ≤ 1 in 96% of the pts. ICI represented first line treatment for 27% pts, second line for 57% and third or further line for the remaining 16%. In detail, 18% were treated with ipilimumab and 82% with anti PD-1/PD-L1 agents (nivolumab 60%, pembrolizumab 21%, atezolizumab 1%). Overall, 41 (36% of pts) irAEs occurred, 39% of those were grade 1, 39% grade 2, 15% grade 3 and 7% grade 4. Among pts who developed irAEs, 50% (21 pts) required immunosuppressive treatment, 25% (11 pts) needed hospitalization and 25% (11 pts) required ICI discontinuation. In patients with irAEs, eosinophilic count increased significantly from the therapy start ($p = 0.03$). Higher NLR (neutrophil to lymphocytes ratio) was associated with lower risk to develop colitis or diarrhea ($p = 0.04$). Additionally, absolute lymphocytic count decreased in patients with irAEs ($p = 0.07$) and monocyte count increased in patients with irAEs ($p = 0.07$) and endocrine irAE ($p = 0.06$). No statistically significant differences in irAEs incidence were seen according to age ($>$ or ≤ 65 years) or sex. Ipilimumab had higher rates of irAEs ($p = 0.03$).

Conclusions: These results suggest changes in the white cell subpopulation count in pts who experience irAEs. Further studies are needed to confirm our findings.

Legal entity responsible for the study: Iacono Donatella.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1199P Clinical and molecular characteristics associated with efficacy of PD-1/PD-L1 inhibitors for solid tumors: A meta-analysis

M. Peng[1], Y. Weng[2], Y. Yao[1], Q. Song[2]

[1]Oncology, Renmin Hospital of Wuhan University, Wuhan, China, [2]Cancer Center, Enmin Hospital of Wuhan University, Wuhan, China

Background: In the new era of precision medicine, identifying clinical or molecular factors that predict benefit of immune checkpoint inhibitors is crucial to prevent patients from autoimmune adverse effects and high cost of such agents.

Methods: We conducted this meta-analysis on the basis of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement. Two reviews independently completed a search of PubMed and Web of science to identify relevant clinical trials. The search was conducted using keywords "nivolumab", "pembrolizumab", "atezolizumab" and "immune checkpoint". The search was limited to randomized controlled trails (RCTs) published in English.

Results: Eleven eligible studies, including 5,663 patients, were included in this meta-analysis. In our analysis, PD-1/PD-L1 inhibitor was associated with a 31% reduction in the risk of death (HR = 0.69; 95%CI, 0.64-0.74; $P < 0.00001$). In subgroup analysis, patients got overall survival (OS) benefit from PD-1/PD-L1 inhibitors regardless of PD-L1 expression, and a dose effect relationship between expression of PD-L1 and OS benefit from PD-1/PD-L1 inhibitors was observed (Interaction, $P < 0.00001$). Patients with smoking history achieved greater OS benefits (HR = 0.69, 95% CI 0.61-0.77; $P < 0.00001$) than never smoker (HR = 0.88, 95% CI 0.70-1.11; $P = 0.28$). Compared with second or later line treatment, there was better OS benefits in first line treatment subgroup (Interaction, $P = 0.02$). The OS benefits were similar according to age (Interaction, $P = 0.74$), sex (Interaction, $P = 0.43$), performance status (Interaction, $P = 0.68$), central nervous system (CNS) metastasis (Interaction, $P = 0.59$), tumor histology (Interaction, $P = 0.64$) and treatment type (Interaction, $P = 0.36$).

Conclusions: In conclusion, PD-L1 expression, smoking status and line of treatment were potential biomarkers for PD-1/PD-L1 inhibitors. Besides, patients $>$ 75 years of age might not get OS benefits from this treatment. These results may improve treatment strategies and patient selection for PD-1/PD-L1 inhibitors.

Legal entity responsible for the study: Y. Weng.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1200P Serum biomarkers during the first cycle of anti-PD-1 antibody therapies in non-small cell lung cancer

T. Ota[1], T. Takeda[2], T. Fukui[3], Y. Nakahara[3], K. Kudo[4], T. Okabe[5], H. Hayashi[6], S. Otani[3], Y. Hiyoshi[3], K. Yonesaka[6], T. Sugiura[1], T. Suzumura[7], M. Terashima[1], Y. Nakano[1], Y. Hasegawa[1], H. Tsukuda[1], K. Matsui[1], N. Masuda[1], M. Fukuoka[1]

[1]Medical Oncology, Izumi City General Hospital, Izumi, Japan, [2]Respiratory Medicine, Uji-Tokushukai Medical Center, Uji, Japan, [3]Respiratory Medicine, Kitasato University School of Medicine, Sagamihara, Japan, [4]Medical Oncology and Respiratory Medicine, National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan, [5]Medical Oncology, Nara Hospital Kindai University Faculty of Medicine, Ikoma, Japan, [6]Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan, [7]Clinical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan

Background: PD-1 blockade by anti-PD-1 antibodies restore the function of exhausted T cells and release perforin, granzyme B and cytokines which induce cytotoxic activity against tumor cells. We examined serum perforin, granzyme B and immune modulators as biomarkers of response to PD-1 blockade in non-small cell lung cancer (NSCLC) patients.

Methods: Advanced NSCLC patients treated with nivolumab or pembrolizumab were studied. Serum were collected on days 1, 2, 8 and 15 for nivolumab and on days 1, 2, 8, 15 and 22 for pembrolizumab. Concentration of perforin was determined by enzyme-linked immunosorbent assay (ELISA) and ten immune modulators, including granzyme B, were measured by a multiplex immunoassay. Best objective response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Patients were followed more than 3 months.

Results: Plasma samples were obtained from 29 patients with nivolumab and 18 patients with pembrolizumab. With nivolumab, in 57% of responding patients, there were two aspects; (i) baseline levels of perforin concentration were higher in responders than in non-responders, or (ii) a ratio of perforin concentration on day 2 to the baseline was elevated (≧1.2). With pembrolizumab, there were no significant differences in baseline concentration between responders and non-responders. If patients who passed away within 3 months were excluded, in responding patients, a ratio of perforin concentration on day 22 to the baseline were significantly higher than in non-responders (partial response vs. progressive disease, $p = 0.0330$). The multiplex assay was performed on a part of samples (nivolumab, $n = 10$ and pembrolizumab, $n = 6$). By the multiplex assay, two out of 10 immune modulators were detected in more than 30% of samples; CD137 and FAS ligand. The correlation between these two analytes and the response to anti-PD-1 antibodies were hard to determine.

Conclusions: From serum, most immune modulators were difficult to measure. Sequential changes in perforin levels and the efficacy by two different anti-PD-1 antibodies were dissimilar. Concentration of serum perforin during the first cycle could be used to predict response to anti-PD1 antibody therapies in advanced NSCLC patients.

Legal entity responsible for the study: Takayo Ota.

Funding: The Osaka Medical Research Foundation for Intractable Diseases.

Disclosure: All authors have declared no conflicts of interest.

1201P Association of immune-related adverse (irAEs) with immune-checkpoint inhibitors (ICIs) efficacy in solid tumors

M. Riudavets Melia[1], L.P. del Carpio[1], I. Gabriela Sullivan[1], A. Barba Joaquín[1], P. Maroto Rey[1], G. Anguera Palacios[1], D. Páez López-Bravo[1], A. Callejo Pérez[1], C. González Blanco[2], D. Castillo Villegas[3], C. Facundo Molas[4], E. Garcia Planella[5], I. Genua Trullos[1], A. López Pousa[1], A. Sebio García[1], C. Martín Lorente[1], A.C. Virgili Manrique[1], O. Gallego Rubio[1], A. Barnadas Molins[1], M. Majem Tarruella[1]

[1]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2]Endocrinology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]Pneumology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [4]Nephrology, Puigvert Foundation, Barcelona, Spain, [5]Gastroenterology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Background: ICIs can induce irAEs that may compromise treatment continuation. We report the incidence of irAEs in patients (pts) with solid tumors receiving ICIs and its correlation with efficacy.

Methods: We retrospectively analyzed 178 pts with solid tumors receiving ICIs in our institution from 3/2014 to 1/2018. IrAEs were graded following CTCAE v4.0. Kaplan Meier and log-rank tests were used to evaluate progression-free and overall survival (PFS, OS).

Results: Median age was 64.1 [33-88] years, 72% male. Most common tumors were lung (63.5%), bladder (14.6%) and melanoma (11.8%). 96% had advanced disease. Most frequent ICIs were nivolumab (38.2%), pembrolizumab (28.7%) and atezolizumab (17.4%), used as monotherapy (74.7%) or in combination with ICIs (3.4%), chemotherapy (17.4%) or targeted therapies (4.5%). Median duration of treatment was 2.1 [0.5-26.5] months. 95 (53.4%) pts developed 158 irAEs, mean 1.2 [0-4] irAEs/pts. Most frequent irAEs were rash (24.7%), diarrhea (17.7%), pruritus (17.7%), thyroid dysfunction (13.3%), arthritis (6.9%), hepatitis (3.8%), pneumonitis (3.2%). 12 (6.7%) pts presented grade (G) 3-4 irAEs: 4 diarrhea, 2 liver dysfunction, 1 pneumonitis, 1 hypopituitarism, 1 mucositis, 1 arthritis, 1 nephritis and 1 haemolytic anemia. 2 treatment-related deaths due to pneumonitis were reported. 15 (8.4%) pts discontinued treatment due to irAEs. At the time of data analysis, 89.2% of irAEs had improved. With a median follow-up of 7.0 [0.5-46.3] months, median OS was superior in pts with advanced disease experiencing irAEs: 37.3 [95%CI, 19.2-51.4] vs 7.8 [95%CI, 4.9-10.8] months ($p < 0.0001$). Similarly, PFS was higher: 7.9 [95%CI, 4.4-11.4] vs 2.6 [95%CI, 2.0-3.2] months ($p < 0.0001$). 82 (46%) pts required systemic corticosteroids during therapy, 31.7% for irAEs management. OS was longer in pts who did not receive steroids: 35.3 [95%CI, 13.5-57.1] vs 10.2 [95%CI, 4.7-15.7] months (p 0.007). No association was found between efficacy and use of antibiotics in the 3 months before first ICIs injection or during treatment.

Conclusions: Development of irAEs in pts with advanced solid tumors treated with ICIs was associated with efficacy. A negative correlation between use of systemic corticosteroids and outcomes was found.

Legal entity responsible for the study: Medical Oncology Department, Hospital de la Santa Creu i Sant Pau.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1202P Use of immune checkpoint inhibitors (CPI) in patients with cancer and concomitant myasthenia gravis (MG)

H. Safa[1], N. Abdel-Wahab[2], V.A. Trinh[1], D.H. Johnson[3], T.E. Rodgers[1], M. Suarez-Almazor[2], A. Diab[1]

[1]Department of Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Internal Medicine, Section of Rheumatology & Clinical Immunology, MD Anderson Cancer Center, Houston, TX, USA, [3]Melanoma, MD Anderson Cancer Center, Houston, TX, USA

Background: The safety of CPI in patients (pts) with autoimmune diseases was never fully assessed since they were always excluded from clinical trials for fear of unleashing the underlying autoimmunity, and susceptibility to severe immune-related adverse events (irAEs). Pts with MG require special consideration as they are known to have severe morbidities and might be susceptible to life-threatening complications.

Methods: We identified from pharmacy records pts who had received CPI between January 2004 and June 2017 at our institution ($n = 4,406$). Claims data were obtained for all pts from 6 months prior to first infusion to last follow-up or death. ICD 9 & 10 diagnostic codes were used to identify pts with MG. We systematically reviewed the literature databases through March 2018 to identify similar pts.

Results: A total of 39 pts were retrieved; 5 from institutional databases and 34 from literature. Median age was 73 (57-86) years; 56% male, 49% had metastatic melanoma and other cancer types. Most received anti-PD1/PD-L1 agents (79%). A prior diagnosis of MG was reported in 23%; most were maintained on corticosteroids, anticholinesterase, azathioprine, or mycophenolate mofetil, and only one had active disease symptoms at initiation of CPI. In the remaining 77%, MG manifested clinically only after initiation of CPI therapy. Overall, 38% developed respiratory failure requiring mechanical ventilation, including 8 pts who needed urgent intubation. MG symptoms occurred with other irAEs (myositis, myocarditis, polyneuropathy, and Guillain Barre Syndrome) in 15%. Most pts required treatment with high dose corticosteroids (90%), intravenous immunoglobulin (45%), and plasmapheresis (42%). Other treatments included azathioprine, mycophenolate mofetil, rituximab, or infliximab. Discontinuation of CPI was recommended in 87%. Most pts (81%) improved with treatment. In melanoma pts, 54% (7/13) achieved partial or complete response to CPI. In all pts, death was reported in 40%, primarily because of respiratory failure in 11%.

Conclusions: CPI seems to be associated with serious consequences and high rate of death in pts with MG. Further studies are needed to establish the risk-benefit profile in this population.

Legal entity responsible for the study: UT MD Anderson Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1203P Safety assessment of anti-PD(L)1 rechallenge after immune-related adverse events

Simonaggio[1], J.-M. Michot[2], S. Champiat[2], A. Vozy[3], A. Lapera[1], A. Marabelle[2], J. Le Pavec[4], A.-L. Voisin[5], A. Lallart[6], G. Cengizalp[6], O. Lambotte[7]

[1]Ile de France, Gustave Roussy DITEP, Villejuif, France, [2]Drug Development Department (DITEP), Institut Gustave Roussy, Villejuif, France, [3]Oncology, Institut Gustave Roussy, Villejuif, France, [4]Ile de France, Hôpital Marie Lannelongue, Le Plessi Robinson, France, [5]Pharmacovigilance Unit, Gustave Roussy Institute, Villejuif, France, [6]Ile de France, Gustave Roussy Pharmacovigilance, Villejuif, France, [7]Department of Internal Medicine and Clinical Immunology, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

Background: Immune checkpoint inhibitors (ICI) have demonstrated efficacy in many cancers. Patients can experience immune-related adverse events (irAE) and their management become crucial. Evidence-based guidance regarding the safety of rechallenge remains scarce. This study aims to prospectively investigate the safety of patients rechallenged after irAE.

Methods: Patients rechallenged after irAE grade ≥2 induced by anti-PD(L)1 and referred at the multidisciplinary board committee of immune toxicity (iTOX) of Gustave Roussy between August 2015 and December 2017 were included in this study.

Results: One hundred eighteen patients had a confirmed irAE. Median age was 62. Tumour types were melanoma (25.4%, n = 30), lung carcinoma (22.9%, n = 27), colorectal cancer (8.5%, n = 10), lymphoma (7.6%, n = 9), renal cell carcinoma (7.6%, n = 9), urothelial (6.8%, n = 8) and others (21.2%, n = 25). IrAE distribution was grade 2 (n = 56, 47.5%), grade 3 (n = 44, 37.3%) and grade 4 (n = 18, 15.2%). IrAE toxicities were hepatitis (15.2%, n = 18), skin toxicities (14.4%, n = 17), pneumonitis (13.6%, n = 16), colitis (10.2%, n = 12), arthralgia (8.4%, n = 10), hematologic (7.6%, n = 9) muscular (6.8%, n = 8), neurologic (5.9%, n = 7), ocular (5.1%, n = 6) toxicities, lipase increases (4.2%, n = 5), endocrine (4.2%, n = 5), nephrologic (2.5%, n = 3), cardiac toxicities (0.8%, n = 1) and infused related reaction (0.8%, n = 1). Forty patiens (33.8%) were hold and then rechallenged. Rechallenged and non-rechallenged patients didn't differ in term of age, distributions and grades of toxicity and steroids use. Patients were rechallenged after an irAE grade 2 (n = 18, 45%), grade 3 (n = 17, 42.5%) grade 4 (n = 5, 12.5%). 40% (16/40) had no recurrence, 35% (14/40) had recurrence of the same irAE, 15% (6/40) experienced a new irAE, and 10% (4/43) had multiple irAE. No patient had died after rechallenge. IrAE recurrence rates rates were 3/5 for colitis, 3/6 for arthralgia, 3/5 for hepatitis, 1/5 for pneumonitis, 0/3 for pancreatitis, 2/3 for neutropenia, 3/7 for skin toxicities. Recurrence rates were not different in grade 2 compared to grades 3-4.

Conclusions: The rechallenge of ICI after mild or severe irAE was associated with 60% of irAE grade ≥2 recurrence or new irAE. Toxicity profile was acceptable but required a close monitoring.

Legal entity responsible for the study: Département des Innovations Thérapeutiques et Essais Précoces, Gustave Roussy, Université Paris-Saclay.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1204P Long term disease control and abscopal effects by stereotactic radiotherapy for growing metastases during anti-PD1

K.P. Suijkerbuijk[1], S.Y. El Sharouni[2], P.P. Damen[2], A.V. Lindert[3], G. Groenewegen[1], J.J.C. Verhoeff[2]

[1]Medical Oncology, University Medical Center Utrecht Cancer Center, Utrecht, Netherlands, [2]Radiation Oncology, University Medical Center Utrecht Cancer Center, Utrecht, Netherlands, [3]Pulmonary Oncology, University Hospital Utrecht, Utrecht, Netherlands

Background: Recent reports have described the safety and clinical utility of combining anti-PD1 checkpoint inhibition with radiotherapy. Abscopal effects - radiotherapy inducing clinically meaningful distant responses in unirradiated sites - have been hypothesized, though clinical proof is scarce.

Methods: We analyzed efficacy and toxicity of combined stereotactic ablative radiotherapy (SABR) and anti-PD1 in consecutive melanoma and non-squamous cell lung cancer (NSCLC) patients that underwent stereotactic radiotherapy for a limited number of growing metastases during anti-PD-1 in our institute since January 2017.

Results: Ten patients, 8 with metastatic melanoma and 2 patients with metastatic NSCLC, were included in this series. SABR was given at a median of 11,5 months (range 3-21 months) after the start of anti-PD1 treatment (nivolumab or pembrolizumab). A single metastasis was irradiated in 8 patients, 2 simultaneously in 1 patient and 3 in the last patient. Disease control of the irradiated lesion was established in all 10 patients. With a median follow-up of 5,5 months (range 1-16 months) all patients were still alive without the need to start a subsequent systemic therapy. Additionally, abscopal effects, defined as a significant decrease of unirradiated metastases that were previously stable under immunotherapy, were seen in 4/10 patients after SABR. One patient developed a pneumonitis (outside high dose radiation field) shortly after SABR that was considered to be related to nivolumab. No other severe toxicities of the combined treatments were observed.

Conclusions: These data show that combining SABR and checkpoint inhibition for patients with oligo-progressive disease during PD1-inhibition is a strategy that can induce long-term disease control and additionally can lead to abscopal effects in unirradiated tumor sites. In order to explore feasibility for all patients with oligo-progressive disease during PD1-inhibition, prospective clinical studies are needed.

Legal entity responsible for the study: University Medical Center Utrecht.

Funding: Has not received any funding.

Disclosure: K.P. Suijkerbuijk: Consulting, Advisory relationship: Bristol-Myers Squibb, MS; Honoraria (institution): Novartis, Roche. G. Groenewegen: Consulting, Advisory relationship: BMS, MSD; Speakers fee: Astellas; Honoraria received paid to institution. All other authors have declared no conflicts of interest.

1205P Clinical impact of hypothyroidism and PD-L1 SNPs in patients with non-small cell lung cancer treated with nivolumab

T. Yamamoto, T. Nomizo, H. Ozasa, T. Tsuji, Y. Yasuda, H. Yoshida, Y. Sakamori, T. Hirai, Y.H. Kim

Respiratory Medicine, Kyoto University-Graduate School of Medicine, Kyoto, Japan

Background: Nivolumab improves the prognosis of lung cancer, but its use can cause immune-related adverse events (irAEs). However, patients with irAEs are reported to have a longer progression free survival (PFS). We previously reported an association between Programmed death ligand 1 (PD-L1) single nucleotide polymorphisms (SNPs) and PFS following nivolumab treatment. We hypothesized that the irAEs were associated with PFS and the SNPs of Programmed death l (PD-1) and PD-L1.

Methods: Between January 2016 and June 2017, a total of 79 consecutive patients who were diagnosed with non-small lung cancer (NSCLC) and who had not undergone definitive operation were treated with nivolumab at Kyoto University Hospital. Of these 79 patients, 68 participated in this study. We retrospectively analyzed patients to evaluate the relationship between adverse events and PFS, and to assess the relationship between these adverse events and the PD-1/PD-L1 SNPs.

Results: The response rate was 13% and the median PFS was 61 days. A significantly longer PFS was observed in patients with the adverse event of hypothyroidism than without hypothyroidism (56 days vs. N.R.; P = 0.016). Occurence of hypothyroidism, which is defined as the low free T4 level, was associated with the SNPs of PD-L1; rs1411262 and rs822339. Hypothyroidism developed in patients with the T/T and C/T genotypes of rs1411262 (P = 0.0269) and with the A/A and A/G genotypes of rs822339 (P = 0.0216). A significantly longer PFS was also associated with the T/T genotype than with the C/T and C/C genotypes of rs1411262 (P = 0.031) and the A/A genotype than the A/G and G/G genotypes of rs822339 (P = 0.017).

Conclusions: Patients with advanced NSCLC who developed hypothyroidism after nivolumab treatment had a significantly longer PFS when compared with those without hypothyroidism, and patients with the T allele of rs1411262 and the A allele of rs822339 tended to develop hypothyroidism. The T/T genotype of rs1411262 and the A/A genotype of rs822339 were significantly associated with longer PFS. The SNPs of PD-L1 might be associated with maintained functioning of the PD-1 and PD-L1 pathway following nivolumab treatment.

Legal entity responsible for the study: Kyoto University.

Funding: Has not received any funding.

Disclosure: T. Hirai: Chugai Pharmaceutical Co., Ltd Y.H. Kim: Supported: Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K. (Japan), Ono Pharmaceutical Co., Ltd. (Japan), Bristol-Myers Squibb K.K. (Japan), Boehringer Ingelheim Japan, Inc. (Japan), Eli Lilly Japan K.K (Japan) as honorarium recipient. All other authors have declared no conflicts of interest.

1206P Incidence of immune related adverse events in patients 70 years old treated with anti-PD-(L)1 therapy

C. Baldini[1], P. Martin-Romano[1], A-L. Voisin[2], F.X. Danlos[1], S. Champiat[1], S. Laghouati[3], M. Kfouri[1], H. Vincent[4], C. Nagera[5], S. Postel-Vinay[1], A. Varga[6], V. Ribrag[1], B. Besse[7], A. Hollebecque[1], O. Lambotte[7], J-M. Michot[1], J-C. Soria[8], C. Massard[9], A. Marabelle[1]

[1]Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, [2]Drug Development, Institut Gustave Roussy, Villejuif, France, [2]Pharmacovigilance Unit, Gustave Roussy Institute, Villejuif, France, [3]Pharmacovigilance Unit, Institut Gustave Roussy, Villejuif, France, [4]Medical Oncology, Gustave Roussy, Villejuif, France, [5]DITEP, Gustave Roussy, Villejuif, France, [6]Dept of Cancer Medicine, Gustave Roussy Institut de Cancérologie, Villejuif, France, [7]Ile de France, Hospital Kremlin Bicetre, Kremlin Bicetre, France, [8]DITEP, Medimmune, Gaithersburg, USA, [9]DITEP, Gustave Roussy Institut de Cancérologie, Villejuif, France

Background: Advanced age is an important risk factor of cancer and is associated with poor prognosis. Changes in the immune system called immunosenescence may occur with older age. However, the impact of aging on efficacy and safety of immune checkpoint inhibitors (ICI), such as anti-PD(L)1, remains undetermined.

Methods: Patients with advanced solid tumours treated with an anti-PD(L)1 agent monotherapy between June 2014 and October 2017 and prospectively included within the Gustave Roussy ICI-dedicated pharmacovigilance registry REISAMIC (Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie) were retrospectively reviewed. Incidence of immune-related adverse events (irAEs) of grade ≥2 was compared between patients aged ≥ 70 and < 70 years old using Chi-squared test.

Results: Among the 615 patients included in the analysis, 191 were ≥ 70 years old (OP) and 424 < 70 years old (YP). The median age of OP and YP were respectively 77 (70 - 93) and 59 (17 - 69). A total of 165 irAEs were included in the analysis (103 Grade 2 and 58 Grade 3-4). The overall occurrence of irAEs grade ≥ 2 was higher in OP compared to YP (33% versus 25%, p = 0.03). Statistical significance was lost when stratifying irAEs according to their severity grade, suggesting that this effect was constant whatever the grade (p = 0.08 for Grade 2 and p = 0.13 for Grade 3-4). Anti-PD(L)1-related deaths were registered in 1 OP and 3 YP (0.5% and 0.7% respectively; NS). The most frequent organs toxicities in OP were skin rash (49%), endocrine (14%), hepatic (10%); it was skin rash (28%), endocrine (25%), digestive (15%) in YP. Median time to

toxicity was similar between the two groups (7 weeks in YP and 6 weeks in OP, $p = 0.31$).

Conclusions: Anti-PD(L)1 immunotherapies are an acceptable treatment option for OPs, by being aware that immune related adverse events are more frequent in this population. Further dedicated studies are warranted to explore prospectively immune-related safety in OPs. Impact: Older patients should be monitored closely as they may be at risk of increased significant immune-related toxicity compared to their younger counterparts.

Legal entity responsible for the study: C. Baldini.

Funding: Has not received any funding.

Disclosure: S. Champiat: Consulting: AstraZeneca, BMS, MSD, Roche, Janssen, Novartis. J-C. Soria: Employee: AstraZeneca Medimmune; Honoraria, Advisory role: Astex, Clovis, GSK, Gammamabs, Lilly, MSD, Merus, Pfizer, Pharmamar, Pierre Fabre, Roche Genentech, Sanofi, Servier, Takeda. C. Massard: Honoraria, Consultancy fees: Sanofi, Janssen, Astellas, Genetech, Orion, Medimmune, Ipsen. A. Marabelle: Honoraria, Consultancy fees: AstraZeneca, BMS, Merck, Sanofi, Janssen, Astellas, Genetech, Orion, Medimmune, Ipsen. All other authors have declared no conflicts of interest.

1207P PD-1 inhibitor-related pneumonitis in patients with minimal interstitial lung shadows before treatment

K. Takahashi, C. Kondo, A. Inukai, G. Asai, M. Okuno, H. Saito

Respiratory Medicine, Aichi Cancer Center Aichi Hospital, Okazaki, Japan

Background: Programmed cell death 1 (PD-1) inhibitors have exhibited significant efficacy in various types of cancer including non-small-cell lung cancer (NSCLC). PD-1 inhibitors are expected to be used increasingly as monotherapy or in combination. Pneumonitis is relatively uncommon but potentially fatal toxicity induced by anti PD-1 therapy. Although patients with apparent interstitial pneumonia are excluded from clinical trials of anti PD-1 therapy, patients with minimal interstitial lung opacity on chest CT scans can be treated with PD-1 inhibitors in the clinical practice. Little is known about the incidence of pneumonitis in such cases.

Methods: Among patients with NSCLC treated with PD-1 inhibitors in our institution, we identified those who developed pneumonitis. We reviewed medical records and chest imaging studies. We investigated association between background factors including lung opacities on chest CT scan before anti PD-1 therapy and development of pneumonitis.

Results: We analyzed a total of 79 patients treated with PD-1 inhibitors. At the baseline CT scan, ground glass opacities and reticular opacities were observed in 20 patients (25%) and 18 patients (23%), respectively. All of these interstitial opacities were very mild, and the case of obvious interstitial pneumonia was not observed. During the anti PD-1 therapy, pneumonitis developed in 16 patients (20%). Of the 20 patients with ground glass opacities, ten patients (50%) developed pneumonitis, and of the 18 patients with reticular opacities, nine patients (50%) developed pneumonitis. Ground glass opacities and reticular opacities at baseline were significantly associated with the incidence of pneumonitis ($p < 0.001$ and $p = 0.001$, respectively). Among the 49 patients who did not have either of these opacities, three patients (6%) developed pneumonitis. There were no association between pneumonitis and other background factors such as presence of radiation pneumonitis or pulmonary emphysema.

Conclusions: Ground glass opacities and reticular opacities on chest CT scan before treatment can be risk factors of pneumonitis, even if they are mild. For the patients without these opacities, anti PD-1 therapy appears relatively safe.

Legal entity responsible for the study: Aichi Cancer Center Aichi Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1208P PD-1 blockade in renal transplant patients with poor prognosis cancer and minimizing risk of organ rejection using comprehensive immune monitoring and screening techniques: A safety study

R. Carroll[1], J.R. Zalcberg[2], H. Tang[3]

[1]Central Northern Adelaide Renal and Transplant Service, Royal Adelaide Hospital RAH Cancer Centre, Adelaide, Australia, [2]Department of Medical Oncology, Alfred Hospital, Melbourne, Australia, [3]Oncology, Royal Adelaide Hospital, Adelaide, Australia

Background: Renal transplant patients have been excluded from studies involving immune checkpoint inhibitors, notwithstanding the fact that these patients develop many of the tumour types that are known to respond to such therapy, for fear of such approaches inducing organ rejection. At the time of initiation of this safety trial there had been 9 case reports of checkpoint inhibitors in organ transplant patients. 4 patients suffered fulminant transplant organ failure. In all of these cases there was prior major reduction in standard immunosuppressive medications.

Methods: Renal transplant and incurable locally advanced or metastatic cancer that has progressed despite first-line standard anti-tumour treatment or defined metastatic solid tumours, will be enrolled onto a Phase 1 trial. Patients will receive Nivolumab as per approved label. Patients are closely monitored for signs of early rejection and for evidence of safety/toxicity and any anti-tumour effect. Standard inclusion/exclusion criteria for oncological trials were used with the addition of the following: serum creatinine <180 umol/l; absence of Human Leukocyte Antigen (HLA) donor specific antibodies; patients willing to accept potential development of renal transplant failure. All patients were counselled by both a transplant physician and oncologist before signing an ethically approved patient information sheet. Patients were allowed to have minimization of immunosuppression but no medication was completely stopped.

Results: Four patients with metastatic cancer (renal cell, melanoma, SCC head and neck, bladder) were treated with 1, 2, 3 and 9 infusions of nivolumab. One patient has a sustained partial response (after 9 infusions) of their tumour but suffered likely interstitial nephritis which resolved with oral steroid. 3 patients died of progressive cancer after 1,2 and 3 cycles but did not suffer any rejection episodes.

Conclusions: Selected renal transplant patients on low dose immunosuppressive regimens, without significant donor specific allo antibodies, can be treated with nivolumab without rejection episodes and some can have sustained anti tumour responses.

Legal entity responsible for the study: Royal Adelaide Hospital.

Funding: Bristol Myers Squibb.

Disclosure: All authors have declared no conflicts of interest.

1209P Immunotherapy in the immunodeficient: A treatment paradox?

N.J. Campbell[1], J. Longley[1], A. Pascalis[2], J. Bennett[3], M. Remer[1], R. Stone[1], D. Muller[1], I. Karydis[1], O. Donnelly[4], M. Wheater[1], C. Ottensmeier[1]

[1]Medical Oncology, Southampton General Hospital Southampton University Hospitals NHS Trust, Southampton, UK, [2]Medical Oncology, Institute of Cancer Research, London, UK, [3]Southampton Experimental Cancer Medicine Centre, University of Southampton, Southampton, UK, [4]Clinical Oncology Department, Southampton General Hospital Southampton University Hospitals NHS Trust, Southampton, UK

Background: Patients with immunodeficiency are typically excluded from trials involving Immunotherapy, however they are at increased risk of developing malignancy. There is currently a lack of evidence to guide clinicians making difficult decisions in this cohort who have a theoretical risk of being unable to mount an adequate immune response.

Methods: Patients diagnosed with Metastatic Melanoma treated with either single or dual immunotherapy regimes at University Hospital Southampton NHS Foundation Trust were identified through our electronic chemotherapy prescribing system. Those with a background of immunosuppressive states were analysed including high intensity chemotherapy or stem cell transplant for prior malignancy and HIV.

Results: A total of 124 patients received Pembrolizumab monotherapy and 47 patients received Iplimumab with Nivolumab. Six patients were considered immunodeficient, including three patients treated with curative intent with intensive chemotherapy for prior lymphoma, one patient with HIV with undetectable viral load, one patient continuing on Ibrutinib treatment for Small Lymphocytic Lymphoma and one patient under a watch and wait approach for Chronic Lymphocytic Leukaemia. All patients in this group had any grade treatment related toxicity, with five experiencing severe grade 3-4 toxicity requiring hospitalisation. With a median follow up of 16.5 months no patients had reactivation of previous malignancy. Four out of six patients have had a complete radiological response and two patients had disease progression.

Conclusions: In our cohort the majority of patients had a significant response to immunotherapy with toxicity managed without any long-term comorbidity. These patients were able to mount an anti-tumour immune response despite concurrent immunodeficiency and experienced an increased incidence of toxicity when compared with other patients treated at our centre. Despite the limitations of a small retrospective series our data would support offering immunotherapy even in the context of apparent immunodeficient states.

Legal entity responsible for the study: University Hospitals Southampton.

Funding: Has not received any funding.

Disclosure: J. Longley: ESMO Travel Grant. I. Karydis: Travel, accommodations, expenses: Delcath Systems. M. Wheater: Consulting or advisory role: Roche, Novartis, MSD, Healthcare at Home; Travel, accommodations, expenses: MSD, Bayer, Bristol-Myers Squibb; Honoraria: Bristol-Myers Squibb, MSD Oncology, Pfizer, GlaxoSmithKline, Novartis, Delcath Systems; Research funding: Roche, GlaxoSmithKline, Novartis, MSD, Aveo, Bristol-Myers Squibb, Verastem, Merck Sharp & Dohme, Inovio Pharmaceuticals, BioNTech AG, Serametrix, Touchlight Genetics, Delcath Systems. C. Ottensmeier: Consulting or advisory role: Bristol-Myers Squibb, Merck Sharp & Dohme, Immatics; Travel, accommodations, expenses: Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Delcath Systems; Research funding: Bristol-Myers Squibb, Verastem, Merck Sharp & Dohme, Inovio Pharmaceuticals, BioNTech AG, Serametrix, Touchlight Genetics, Delcath Systems. All other authors have declared no conflicts of interest.

1211P Hyperprogression during immuno-checkpoint inhibitors (ICIs): A clinically significant problem?

E. Farè[1], S. Sdao[2], S. Damian[1], S. Cresta[1], M. Del Vecchio[1], M. Di Bartolomeo[1], L.A. Di Guardo[1], M. Duca[1], A. Indini[1], A. Necchi[1], M. Niger[1], M. Prisciandaro[1], G. Procopio[1], D. Raggi[1], E. Verzoni[1], G. Pruneri[3], M. Di Nicola[1], F.G.M. de Braud[1]

[1]Medical Oncology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [2]Radiology and Imaging Diagnostics, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Department of Pathology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

Background: ICIs can overcome immune-suppression and activate effective immune responses against cancer cells. Therapy with ICIs have led to a clinically-meaningful extension in overall survival across several solid tumors, being endowed with long term disease control-rate in a part of responding patients (pts). However, an acceleration of the tumor growth rate (TGR) during ICI, defined as hyperprogressive disease (HPD), has been reported in 9-29% of pts. Mechanisms underlying HPD are unknown, yet murine double minute 2 (MDM2) family amplification was found in some of these pts.

Methods: We retrospectively identified a series of 334 pts with miscellaneous advanced solid tumors treated with anti-PD1/PD-L1-containing ICI (mono or combo therapy) at our Institution. Inclusion criteria included imaging assessment at 3 timepoints: during reference period (from 3 months to 2 weeks before ICI baseline scan), before ICI therapy start (baseline scan, performed within 28 days) and during ICI treatment. Patients were considered HPD if they showed progressive disease (PD) by RECIST 1.1 at first radiological evaluation and a $\geq$ 2-fold increase of the TGR during ICI therapy compared to reference period. FISH analysis to evaluate MDM2 family genes amplification was performed in HPD cases whose paraffin embedded tumor material was available.

Results: 73 cases were initially excluded from our analysis due to lack of tumor assessment during ICI. Of the remaining pts, 109 reported PD at first evaluation. Of them, only 45 were suitable for the analyses, having all requested radiological examinations available. Seven cases met HPD criteria: 3,5% of evaluable pts (7/197) and 6.4% of all the PD. No correlation with histology, age, serum biomarkers and type of ICI was found. FISH test for MDM2 family has been performed on 3 cases: one case showed amplification MDM4 gene (mean of signals $>$ 8); other cases showed only increased MDM4 ratio score of unknown significance.

Conclusions: Despite the limits of a retrospective analysis and small numbers, in our series HPD is a rare but clinically relevant event. The role of MDM2 family alteration as predictive biomarker is promising and deserves more investigations. Prospective studies including genomic and biological analysis are warranted.

Legal entity responsible for the study: Elena Farè.

Funding: Has not received any funding.

Disclosure: F.G.M. de Braud: Advisor: BMS, Ignyta, MSD, Novartis, Pfizer, Amgen, Roche, Merck Serono, Servier. All other authors have declared no conflicts of interest.

1212P Pathogenesis, clinical evolution and outcomes of patients with immune checkpoint inhibitor induced acute liver injury: A multicentre study

L. Au[1], R. Nathwani[2], L. Possamai[2], C. Barlow[3], T. Tillett[4], R. Bowen[5], L. Spain[6], J. Thomas[1], M. Backhouse[4], A. Gurung[3], R. Morrison[7], T. Cross[8], C. Herbert[9], R. Goldin[2], M.E. Gore[10], J. Larkin[11], C. Antoniades[2], S. Turajlic[1]

[1]Skin and Renal Unit, Royal Marsden Hospital NHS Foundation Trust, London, UK, [2]Gastroenterology, Imperial College London, London, UK, [3]Medical Oncology, Musgrove Park Hospital, Somerset, UK, [4]Medical Oncology, Royal United Hospitals Bath NHS, Avon, UK, [5]Medical Oncology, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK, [6]Skin, Renal & Gynaecological Cancers Unit, Royal Marsden Hospital NHS Foundation Trust, London, UK, [7]Histopathology, Imperial College London, London, UK, [8]Gastroenterology, Royal Liverpool University Hospital, Liverpool, UK, [9]Medical Oncology, University Hospitals Bristol NHS Trust Bristol Haematology and Oncology Centre, Bristol, UK, [10]Medicine, Royal Marsden Hospital NHS Foundation Trust, London, UK, [11]Department of Medical Oncology, Royal Marsden NHS Foundation Trust, London, UK

Background: Immune checkpoint inhibitor (CPI) induced acute liver injury (ALI) is a frequently encountered toxicity occurring in up to 30% patients (pts). There is a lack of systemic evaluation of CPI induced ALI pathogenesis, clinical evolution and outcome of patients (pts).

Methods: Retrospective analysis was performed on pts with CPI induced ALI presenting to 6 UK oncology centres between 2013-17. Indices of ALI, therapy complications and outcome were recorded. ALI grading was based on Common Terminology Criteria for Adverse Events.

Results: 65% (36/57) pts received ipilimumab+nivolumab (N) or pembrolizumab (P) (combo group) and 35% (21/57) P or N alone (mono group). Median therapy duration to ALI onset was 96 days in the mono and 22 days in the combo group. At presentation, all pts had acute elevations in transaminases (ALT, median 325U/L [range 155-543], ALP 111U/L [72-250]). Immunogolulins and autoantibodies were normal. One pt developed acute synthetic dysfunction without encephalopathy (Bilirubin 64umol/L, INR 1.5). 79% received steriods (mean dose 1.3mg/kg); 34% MMF. Steroid refractory ALI was treated with anti-thymocyte globulin (ATG) in 4 pts. Pathological findings (n = 6 liver biopsies) revealed lobular hepatitis and myelo-lymphoid cell infiltrate/aggregates (CD3+,CD8+,CD68+). Pts with severe, refractory (G4) ALI had significant reductions in circulating lymphocytes/monocytes. 63% (n = 35) had a temporal association between recent infection and ALI. 15% (n = 8) also received anti-TNF-a therapy for colitis. This was not associated with more severe ALI, and ALI resolved in all cases. 21% (n = 11) developed bacterial infections. Fungal sepsis (aspergillus) occurred in all ATG (n = 4) treated patients. Overall no deaths were due to liver failure. 14 pts died with 13 due to disease progression and 1 due to immunotherapy related neuropathy. All deaths due to progressive disease were in pts whose ALI peaked at G3-4. Acturial median survival was significantly lower in G3-4 (14.5 months) vs G1-2 (25 months) liver injury.

Conclusions: Our data report on the largest cohort of CPI induced ALI identifying disease evolution, markers of disease severity and strong correlation with increased morbidity and mortality.

Legal entity responsible for the study: The Royal Marsden Hospital.

Funding: The Royal Marsden Hospital & Imperial College London.

Disclosure: J. Larkin: Institutional research support: BMS, MSD, Novartis, Pfizer Consultancy: Elsai, BMS, MSD, GSK, Kymab, Pfizer, Novartis, Roche/Genetech, Secarna, Pierre Fabre, EUSA Pharma; Support: NIHR RM/ICR Biomedical Research Centre for Cancer. All other authors have declared no conflicts of interest.

1214P Establishing the need for immuno-oncology (IO) therapy (tx) in second-line (2L) small cell lung cancer (SCLC)

L. Schwartzberg[1], J.R. Penrod[2], Y. Yuan[2], T. Gu[2], T.K. Le[3], P. Abraham[2], B. Korytowsky[2], G. Selvaggi[2]

[1]Oncology, West Cancer Center, Germantown, TN, USA, [2]Worldwide Health Economics & Outcomes Research, Bristol-Myers Squibb, Princeton, NJ, USA, [3]Center for Observational Research & Data Sciences, Bristol-Myers Squibb, Princeton, NJ, USA

Background: 2L tx for SCLC is heavily dependent on 1L platinum (PT) response. NCCN guidelines recommend PT retreatment if recurrence is $>$ 3-6 months post 1L PT; while alternative options should be considered for rapid relapse (topotecan [TOP] in 2L PT-resistant). In 2016, nivolumab (NIVO) +/- ipilimumab (IPI), were added to 2L NCCN guidelines. This study evaluates 2L SCLC patterns of care and outcomes and attempts to contextualize CheckMate 032 data by creating a matched real-world comparator.

Methods: Adult SCLC pts receiving systemic tx from the Flatiron Health database were selected (01Jan2011-30Sep2017). Index date was SCLC diagnosis (dx). Pts were included if: not on clinical trial; no secondary malignancy within 3 years (y); no IO use; and $\geq$2 months (mo) of medical data on/after dx. PT sensitivity was based on a 90 day gap. Median, 1-y and 2-y overall survival (OS) by Kaplan-Meier was calculated from 2L initiation to death. Median duration of therapy (mDoT) was assessed. A matched 2L cohort was constructed using CheckMate 032 Inclusion/Exclusion criteria (I/E).

Results: 2,056 pts initiated 1L tx (full cohort), of which 628 pts went on to 2L; 42% received TOP and 58% other txs. Within 2L, mean age was 65y; 69% were white, 51% were female, 98% had a smoking history and 95% were treated in the community. Of 2L pts, 68% had extensive and 27% had limited disease at dx. 372 were PT-sensitive and 231 pts were PT-resistant. Upon matching for CheckMate 032 I/E, 903 pts were identified of whom 254 initiated 2L. For the full and matched cohorts respectively, 2L mDoT for TOP was 2.0 mo (SD = 2.5) and 2.2 mo (SD = 2.7) and for other tx was 2.6 mo (SD = 2.2) and 2.8 mo (2.4). Median, 1-y and 2-y OS results for the full/ matched cohorts and CheckMate 032 are shown (Table).

Table: 1214P Overall survival from diagnosis and 2L initiation in Flatiron Health and CheckMate 032

	median OS, months [95%CI]	1-year / 2-year survival (%)
FULL COHORT		
From Diagnosis		
All (N = 2056)	11.6 [11.1,12.3]	48.6/ 22.0
Limited disease (n = 680)	19.6 [18.0,21.5]	71.9/ 42.3
Extensive disease (n = 1,263)	9.4 [8.9,9.9]	35.2/ 10.5
From Initiation of 2L		
All (n = 628)	4.2 [3.7,4.7]	13.3/ 3.3
PT-sensitive (n = 372)	5.4 [4.4,6.2]	15.9/ 4.2
PT-refractory (n = 231)	3.0 [2.6,3.6]	9.1/ 2.9
MATCHED COHORT		
From Diagnosis		
All (N = 903)	12.5 [11.5,14.3]	47.0/ 26.4
Limited disease (n = 348)	23.8 [20.0,29.5]	72.0/ 49.5
Extensive disease (n = 507)	9.8 [8.9,10.6]	37.9/ 12.1

Continued

Table: 1214P *Continued*

	median OS, months [95%CI]	1-year / 2-year survival (%)
From Initiation of 2L		
All (n = 254)	4.9 [4.0,6.2]	14.6/ 3.8
PT-sensitive (n = 158)	6.3 [5.6,7.5]	18.4/ 6.0
PT-refractory (n = 90)	2.7 [2.1,3.3]	5.6/ 1.9
CHECKMATE 032		
NIVO 3 mg/kg cohort (n = 98)	4.4 [3.0–9.3]	33/ NR
NIVO 1 mg/kg + IPI 3 mg/kg (n = 61)	7.7 [3.6–18.0]	43/ NR
NIVO 3 mg/kg + IPI 1 mg/kg (n = 54)	6.0 [3.6–11.0]	35/ NR

*NR=not reported; PT=platinum; NIVO=nivolumab; IPI=ipilimumab

Conclusions: This large retrospective data set highlighting 2L SCLC outcomes demonstrates poor survival in this setting underscoring the need for novel tx. Results from CheckMate 032 present IO as a potential option for SCLC pts.

Editorial acknowledgement: This study was funded by Bristol-Myers Squibb, Inc. All authors contributed to and approved the presentation. Editorial assistance was provided by PAREXEL, funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: L. Schwartzberg: Consultant: Bristol-Myers Squibb, Merck, Pfizer, Astra Zeneca, Amgen. J.R. Penrod, Y. Yuan, T. Gu, T.K. Le, P. Abraham, B. Korytowsky, G. Selvaggi: Employee, Stock ownership: Bristol-Myers Squibb.

1215P Sequential blockade of PD-1 and PD-L1 causes fulminant cardiotoxicity: From case report to mice model validation

Y-J. Chen[1], W-C. Huang[2], S-Y. Liu[3], C-C. Ko[3]

[1]Department of Radiation Oncology, Mackay Memorial Hospital, Taipei City, Taiwan, [2]Department of Surgery, Mackay Memorial Hospital, Taipei City, Taiwan, [3]Department of Medical Research, Mackay Memorial Hospital, Taipei City, Taiwan

Background: In clinical practice, the sequential use of shifting from a programmed cell death 1 (PD-1) inhibitor to its ligand 1 (PD-L1) inhibitors in consideration of ineffectiveness or toxicity is becoming more common due to prolonged survival. We report a patient in whom fatal myocarditis developed after sequential use of PD-1 and PD-L1 inhibitors. To validate this finding, a syngeneic tumor-bearing mice model was used.

Methods: A 61-year-old woman with metastatic lung adenocarcinoma, who had received 5 doses of nivolumab (3 mg/kg) and then 1 dose of atezolimumab (1200 mg), complained of chest tightness and dyspnea 4 weeks later. The workup revealed sinus tachycardia, a normal Troponin I level (< 0.01 ng/mL), an elevated creatine kinase-myocardial band (CK-MB) level (10 ng/mL), and an elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) level (2960 ng/mL). Serial echocardiograms revealed left ventricular ejection fractions declining from 66.3 to 59.2 %. Under a diagnosis of myocarditis, she was treated with intravenous methylprednisolone at 5 mg/kg/day and oral mycophenolate mofetil at 1000 mg/day. The progressive clinical deterioration was noted with serial elevation of Troponin I, CK-MB and NT-proBNP levels up to 1.3, 24 and 15738 ng/mL, respectively. Cardiac arrest was noted later. The Balb/c mice bearing lung metastasis of CT26 colon cancer cells were treated with PD-1 and PD-L1 inhibitors for pathological and immuohistochemical studies.

Results: The pathology shows that the combination of anti-PD-1 and anti-PD-L1, either sequentially or simultaneously administered, caused myocarditis lesions with myocyte injury and patchy mononuclear infiltrates in the myocardium in all combination group mice (n = 3 for each). The myocarditis lesions were not seen in mice treated with anti-PD-1 or anti-PD-L1 alone. Marked expression of PD-L1 in infiltrating lymphocytes and expression of PD-1 in myocytes was noted only in mice with combination blockade, implying a possible role for pathogenesis of myocarditis.

Conclusions: The combinatory use of PD-1 and PD-L1 blockade, either sequentially or concurrently, may cause fulminant cardiotoxicity, and such usage should be cautious.

Legal entity responsible for the study: Mackay Memorial Hospital, Taipei, Taiwan.

Funding: Mackay Memorial Hospital, Taipei, Taiwan.

Disclosure: All authors have declared no conflicts of interest.

1216P Impact of anti-infectious and corticosteroids on immunotherapy: Nivolumab and pembrolizumab follow-up in a French study

J-P. Metges[1], E. Michaud[2], D. Deniel Lagadec[3], F. Marhuenda[4], A. Chaslerie[2], F. Grude[4]

[1]Oncology and Hematology Institute, C.H.U. Brest - Hôpital Morvan, Brest, France, [2]Medical Department, Regional Health Insurance, Nantes, France, [3]Cancer Observatory, CHRU Brest, Brest, France, [4]Cancer Observatory, ICO Paul Papin, Angers, France

Background: Immunotherapy is a new paradigm with EMA approval in melanoma and lung cancer. However, B Routy and al has recently published a decrease of efficacy of immunotherapy via gut microbiome antiobiotics influence and potential drug interactions between antiobiotics/corticoids and immunotherapy associated with decrease of overall survival have been underlined too. The Observatory of Drugs, Medical Device and Therapeutic Innovations (OMEDIT) Bretagne/ Pays de la Loire (B-PL), in collaboration with French Regional Health Insurance System (FRHIS), wanted to carry out a study about the impact of these treatments on the efficacy of immunotherapy.

Methods: FRHIS (PL) has made an extract in its database for patients who initiated treatment with Nivolumab/Opdivo® and Pembrolizumab/Keytruda® between January 2016 and end of June 2017. Dispensing of antibiotics, corticoids and antifungals 60 days before initiation of immunotherapy and after the beginning of treatment (within 30 or 150 days after). The patient's clinical data (age, sex; diagnosis, indication, grade III/IV side-effects, response rate, survival) would be crossed with the use or not of anti-infectious drug treatment in order to define the impact of taking these drugs on the treatment of immunotherapy.

Results: 798 patients were identified including 377 in 2016 and 421 in the first half of 2017: 148 with malignant melanoma and 650 with lung cancer. 763 were treated with nivolumab and 35 with pembrolizumab. Before the beginning of immunotherapy, 14% of these patients received an antibiotic, 17% a corticoid and 2% an antifungal. After the beginning of immunotherapy (within 30 days after), 8% received a corticoid, 6% an antibiotic and 2% an antifungal. Response to treatment, Progression Free Survival and Overall Survival (PFS and OS) in correlation with the use or not of these drugs for Bretagne and PL areas would be presented at the meeting.

Conclusions: The good use of immunotherapy was crucial to optimize the response rate and to increase OS. Use of anti-infectious and corticosteroids was usual in routine. Antibiotics were found to be prescribed in 20% of the patients receiving immunotherapy. Results about their impact in term of response, PFS and OS would be shown at the meeting.

Legal entity responsible for the study: Cancer Observatoire BPL, OMEDIT B and PL.

Funding: Has not received any funding.

Disclosure: J-P. Metges: Trial coordination without remuneration: MSD. All other authors have declared no conflicts of interest.

1217P Real-world safety of nivolumab in patients with non-small cell lung cancer (NSCLC) in Japan: Interim summary of post-marketing all-case surveillance

Y. Ohe[1], A. Gemma[2], K. Nakagawa[3], N. Yamamoto[4], T. Saito[5], A. Akamatsu[5], K. Kuwano[6], Y. Nakanishi[7]

[1]Pulmonary Medicine, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan, [3]Department of Internal Medicine, Kindai University Faculty of Medicine, Osaka, Japan, [4]Pulmonary Medicine, Wakayama Medical University, Wakayama, Japan, [5]Pharmacovigilance Division, Ono Pharmaceutical Co., Ltd., Osaka, Japan, [6]Pulmonary Medicine, The Jikei University School of Medicine, Tokyo, Japan, [7]Research Institute for Diseases of the Chest, Kyushu University Hospital, Fukuoka, Fukuoka, Japan

Background: Nivolumab, a fully humanized anti-PD-1 antibody, was approved in December 2015 in Japan for the treatment of previously-treated, unresectable, advanced or recurrent NSCLC. A post-marketing all-case surveillance was imposed as a condition for approval, to accumulate real-world safety data for nivolumab, because clinical trial data were limited.

Methods: This all-case surveillance is an ongoing mandatory observational register, searching for new treatment-related safety issues. All NSCLC patients treated with nivolumab between 17 December 2015 and 31 March 2016 were registered and monitored for one year. Safety data were accumulated using case report forms (CRFs) in accordance with Good Post-Marketing Study Practice Ministerial Ordinance in Japan. This interim summary is based on data collected and summarized from patients whose CRFs were available by 3 January 2018.

Results: Overall, 3681 patients were enrolled from 17 December 2015 to 31 March 2016, with 3303 CRFs collected by 3 January 2018. The safety analysis set included 3297 of 3303 patients. Background characteristics of patients: median age was 67 years; 74% of patients were current or former smokers; 77% of patients had an ECOG performance status score of 0 (24%) or 1 (53%); 66% and 28% of patients had adenocarcinoma or squamous cell carcinoma, respectively. The frequency of adverse drug reactions of any grade was 45%. The most frequent (5% or higher) adverse events of special interest were interstitial lung disease (ILD, 9.1%; grade ≥ 3, 3.9%), thyroid dysfunction (8.7%; grade ≥ 3, 0.3%), hepatic function disorder (7.8%; grade ≥ 3, 2.0%), infusion reaction (5.4%; grade ≥ 3, 0.3%) and colitis/severe diarrhea (5.3%; grade ≥ 3, 1.3%). The overall survival rate at 1 year was 37% (95% CI, 35.2 to 38.6). We will report updated data along with estimated risk factors for ILD.

Conclusions: Among Japanese patients with previously-treated, unresectable, advanced or recurrent NSCLC, nivolumab showed an almost consistent safety profile with clinical trial data except for frequency of ILD. The benefit-risk profiles should continuously be monitored.

Editorial acknowledgement: Content Ed Net.

Legal entity responsible for the study: Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb.

Funding: Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb.

Disclosure: Y. Ohe: Grants, Personal fees: AstraZeneca, Chugai, Lilly, Taiho, Pfizer, MSD, Novartis, ONO, BMS; Grants: Kyorin, Dainippon-Sumitomo, Ignyta; Personal fees: Daiichi-Sankyo, Boehringer Ingelheim, Bayer. A. Gemma: Honoraria: Ono Pharmaceutical, Bristol-Myers Squibb, Chugai Pharmaceutical. K. Nakagawa: Grants: AstraZeneca, NichiIko, Astellas, ClinicalTrial, MSD, Taiho, Ono, BMS, Nippon Boehringer,Eli Lilly, Novartis, SymBio, Pfizer, Chugai, NikkeiBusiness, Reno, A2Healthcare, inVentiv, DaiichiSankyo, AbbVie, Quintiles, ICON, Takeda, EP-CRSU, GRITSONE, Linical, Eisai, Parexel. N. Yamamoto: Honoraria: Ono Pharmaceutical, Bristol-Myers Squibb, Chugai Pharmaceutical, MSD, Novartis, AstraZeneca, Boehringer Ingelheim, Maruho. T. Saito, A. Akamatsu: Employee: Ono Pharmaceutical Co., Ltd. K. Kuwano: Honoraria: Ono Pharmaceutical, Bristol-Myers Squibb, Chugai Pharmaceutical, Asteras, GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Teijin, Kyourin, Pfizer, Daiichi Sankyou, and Meiji Seika Farma. Y. Nakanishi: Honoraria: Ono Pharmaceutical, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Pfizer; Research funds: Ono Pharmaceutical, Chugai Pharmaceutical, Astellas Pharma, Taiho Pharmaceutical, Asahi Kasei Pharma.

1218P Immune-related adverse events: Comparison of melanoma and non-small cell lung cancer patients treated with anti-PD1 therapy

N. Duma[1], A-G. Azzouqa[2], S. Yadav[1], K. Hoversten[3], C. Reed[3], A.N. Sitek[3], Y. Lou[2], J. Molina[1], T. Halfdanarson[1], K. Leventakos[1], R.W. Joseph[2], R. Manochakian[2], R. Dronca[2]

[1]Medical Oncology, Mayo Clinic, Rochester, NY, USA, [2]Medical Oncology, Mayo Clinic, Jacksonville, FL, USA, [3]Internal Medicine, Mayo Clinic, Rochester, NY, USA

Background: Immune-related adverse events (IRAEs) represent a clinical challenge, potentially limiting the clinical benefits of immunotherapy. Data suggests nivolumab and pembrolizumab IRAEs rates are similar but no comparisons across tumor types exist. Therefore, we studied IRAEs in patients (pts) with metastatic melanoma and non-small cell lung cancer (NSCLC) treated with anti-PD1 therapy.

Methods: All pts with metastatic melanoma and NSCLC seen at the Mayo Clinic Rochester and Florida from 2015 to 2018 were reviewed. Patients that received prior immunotherapies or thoracic radiation were excluded. Chi-square test was used to estimate differences in categorical data.

Results: Out of 510 pts, 266 (52%) had melanoma and 244 (48%) NSCLC. Baseline characteristics were similar across groups, except for sex (NSCLC: 51% women; melanoma: 40% women). 80% of the pts with NSCLC received chemotherapy prior to immunotherapy compared to 14% of the pts with melanoma. 75% (200) of melanoma pts received pembrolizumab and 66% (161) of NSCLC pts received nivolumab. Higher rates of IRAEs were observed in the melanoma pts (55% vs. 41%, <0.001) (Table). No difference in grade ≥3 IRAEs was observed. Melanoma pts were more likely to develop diarrhea/colitis and endocrinopathies compared to the NSCLC pts (19% vs. 7%, $p < 0.008$; 33% vs. 18%, $p < 0.01$, respectively). Contrarily, pts with NSCLC had higher rates of pneumonitis (14% vs. 6%, $p < 0.007$). Most pts resumed the anti-PD1 agent after developing IRAEs (60% and 57%, respectively). In 31% of the pts experiencing IRAEs the anti-PD1 agent was permanently discontinue due to toxicity.

Table: 1218P

	Melanoma % (n)	NSCLC % (n)	p value
IRAEs	55 (146)	41 (99)	<0.001
Grade ≥2 IRAEs	76 (110)	75 (76)	0.98
Grade ≥3 IRAEs	34 (49)	36 (36)	0.68
Prescribed systemic steroids	66 (97)	60 (59)	0.26
Required intravenous steroids	25 (37)	27 (27)	0.75
IRAEs: Subtype (all grades)			
Diarrhea/Colitis	19 (28)	7 (7)	0.008
Dermatologic Toxicities	19 (28)	22 (22)	0.62
Endocrinopathies	33 (48)	18 (18)	0.01
Pneumonitis	6 (8)	14 (14)	0.007
Transaminitis	14 (21)	9 (9)	0.24
Immunotherapy was restarted	60 (88)	57 (56)	0.60
Immunotherapy DC due to toxicity	31 (45)	31 (31)	0.99

Conclusions: Patients with metastatic melanoma were more likely to develop IRAEs with anti-PD1 therapy. We observed differences in the IRAEs developed across groups. These associations could be attributed to intrinsic tumor characteristics or differences between anti-PD1 agents. Larger studies are needed to enhance our understanding of these differences.

Legal entity responsible for the study: N. Duma.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1219P Evaluation of a possible link between immunotherapy (IO) and acute vascular events

J. Bar[1], K. Shulman[2], T. Kuznetsov[3], G. Markel[4], S. Daher[3], R. Berger[3], T. Golan[3], D. Urban[3], T. Sela[3], E. Shacham Shmueli[3], R. Klempfner[5], A. Talianski[3], A. Onn[6], E. Dudnik[7]

[1]Institute of Oncology, Affiliated to the Sackler Faculty of Medicine, TAU, Chaim Sheba Medical Center, Ramat Gan, Israel, [2]Oncology, Hillel Yaffe Medical Center, Hadera, Israel, [3]Institute of Oncology, Chaim Sheba Medical Center, Ramat Gan, Israel, [4]Ella Institute, Chaim Sheba Medical Center, Ramat Gan, Israel, [5]Institute of Cardiology, Chaim Sheba Medical Center, Ramat Gan, Israel, [6]Institute of Pulmonology, Chaim Sheba Medical Center, Ramat Gan, Israel, [7]Thoracic Cancer Unit, Davidoff Cancer Institute, affiliated to the Sackler Faculty of Medicine, Rabin Medical Center, Petah Tikva, Israel

Background: IO has become one of the major pillars of anti-cancer therapy. A range of immune-related adverse events (IRAE) are recognized within various organs. Acute vascular events (AVE) are generally not considered IRAE. Considering the role of inflammation in acute ischemic cardiovascular events, we assumed such events can be triggered by IO. We aimed to evaluate the frequency and nature of AVEs occurring shortly after the initiation of IO.

Methods: Computerized search of Sheba medical center (SMC) electronic medical records was done for patients (pts) that received IO (any of: pembrolizumab, nivolumab, atezolizumab, ipilimumab). Out of those, we searched for cases with a diagnosis of AVE within 1 month after initiation of IO. Search was for the diagnoses: cerebrovascular accident (CVA), transient ischemic attack (TIA), myocardial infarct (MI), non-ST-elevation MI, ST-elevation MI, embolic event, pulmonary emboli (PE) and deep vein thrombosis (DVT). We excluded cases with AVE within a year prior to the initiation of therapy, concomitant chemotherapy, and cases of a single-site DVT.

Results: Between 1st January 2015 and 14th March 2018, 1396 pts received IO in SMC. 14 pts were identified in the computerized search. Excluded: 4 with a single site DVT, 1 with a prior cardiovascular event within a year prior to initiation of IO, 1 with concomitant chemotherapy, 3 excluded due to AVE not definitely diagnosed, leaving 5 pts not excluded. 8 additional pts were identified by reports of physicians aware of this project, of these 2 were also identified by the computerized search, thus a total of 11 pts fit our study criteria. Events were: multiple CVA (3), PE (2), sudden cardiac death (2), bilateral DVT (1), CVA (1), TIA (1), MI (1). In one pt marantic endocarditis was suspected. 7 pts had diabetes, 7 pts had hypertension, 2 pts had a body mass index > 30, 3 were smoking within < 10 years ago, none had a family history of cardiovascular disease. 9 of the pts were treated in SMC, constituting a frequency of 0.6%.

Conclusions: AVEs occur at a low frequency shortly after initiation of IO. Initiation of IO may be the trigerring event of those events. Further retrospective studies and analyses of clinical trials data are required to evaluate whether this is a random association or a true IRAE.

Legal entity responsible for the study: Sheba Medical Center, Tel Hashomer, Israel.

Funding: Sheba Medical Center.

Disclosure: J. Bar: Consultant fees: Roche, Boehringer Ingelheim, Novartis, BMS, MSD, Pfizer, AstraZeneca, VBL, Takeda; Grant support: Boehringer Ingelheim, Novartis, AstraZeneca, MSD, Pfizer. All other authors have declared no conflicts of interest.

1220P Real-world experience of pembrolizumab in patients with advanced melanoma: A large retrospective observational study

F.X. Liu[1], W. Ou[2], S.J. Diede[3], E.D. Whitman[4]

[1]CORE, Merck & Co Inc, Kenilworth, NJ, USA, [2]CORE, Merck & Co., Inc., Kenilworth, NJ, USA, [3]Clinical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [4]Atlantic Melanoma Center, Carol G. Simon Cancer Center, Morristown, NJ, USA

Background: Pembrolizumab (PEM), a humanized antibody targeting programmed death-1 receptor, has been approved by FDA for the treatment of patients (pts) with advanced melanoma (AM) in the US for over 3 years. The study examined the real-world (RW) use of PEM and associated patient (pt) outcomes in the US Oncology Clinical Practices.

Methods: Flatiron Health longitudinal database was used to identify adult pts with AM who received ≥1 dose of PEM between September 4, 2014 and December 31, 2016. These pts were followed up to December 31, 2017. Pts in clinical trials were excluded. Pt demographic, treatment, and clinical characteristics were described. Time on treatment (ToT) and overall survival (OS) were analyzed using the Kaplan Meier (KM) method, with the first dose of any PEM as the starting point.

Results: Five hundred and thirty-two patients were included in the analysis. Of the 532 patients, 315 in first line (1L), 152 second line (2L), and 65 third line or beyond (3L+). Overall, median age at PEM initiation was 68 years (range, 18-84); most were male (66.4%) and Caucasian (93.5%). 32.9% of pts are confirmed BRAF mutant, 53.6% BRAF wildtype, and 13.5% unknown. When data were available, 21.2% had an elevated lactate dehydrogenase (>ULN), 18.0% had brain metastases, and 23.3% had an ECOG performance status of > 1. At the time of analysis, pts were followed for a median of 12.9 months (mo, range, 0.03 – 39.7). The overall median ToT was 4.4 mo (95% CI, 3.5-5.2), with 4.2, 4.7, 4.2 mo in 1L, 2L, and 3L+, respectively. The overall median OS was 21.9 mo (95% CI, 15.5-29.1), not reached for 1L, and 13.3 and 12.5 mo for 2L and 3L+ respectively. The 1-year and 2-year survival, using the KM method, was 60.9% (95% CI, 56.5-65.0; 1L, 64.9%; 2L, 55.3%; 3L+, 54.6%) and 48.1% (95% CI, 43.2-52.8; 1L, 53.4%; 2L, 41.5%; 3L+, 39.0%) respectively.

Conclusions: The study reports RW use of PEM in a large cohort of pts with AM in US Oncology Clinical Practices. The study pt population is more heterogeneous than that of clinical trials (KEYNOTE-002 and KEYNOTE-006). The findings of ToT and 2-year OS based on RW clinical decision making were consistent with those reported in PEM clinical trials, supporting the RW effectiveness of PEM in pts with AM.

Legal entity responsible for the study: Merck & Co, Inc., Kenilworth, NJ, USA.

Funding: Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosure: F.X. Liu, W. Ou, S.J. Diede: Employee, Stock owner: Merck & Co., Inc., Kenilworth, NJ, USA. E.D. Whitman: Consultant, Advisory boards, Speaker's bureau: Merck, BMS, Genentech, GSK, Novartis, Amgen, Castle Biosciences.

1221P Sites of metastasis and association with clinical outcome (CO) in advanced stage cancer patients (pts) treated with immunotherapy (IO)

M.A. Bilen[1], J.M. Shabto[2], D.J. Martini[2], Y. Liu[3], C. Lewis[1], H.H. Collins[1], M. Akce[1], H. Kissick[4], B.C. Carthon[1], W.L. Shaib[1], O.B. Alese[1], C.E. Steuer[1], C. Wu[1], D.H. Lawson[1], R. Kudchadkar[1], V. Master[4], B. El-Rayes[1], S.S. Ramalingam[1], T.K. Owonikoko[1], R.D. Harvey[1]

[1]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA, [2]Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA, [3]Departments of Biostatistics and Bioinformatics, Emory University, Atlanta, GA, USA, [4]Department of Urology, Emory University, Atlanta, GA, USA

Background: Selecting the appropriate pts to receive IO remains a challenge due to the lack of optimal biomarkers. We investigated the association between sites of metastatic disease and CO in pts enrolled on IO-based phase 1 clinical trials.

Methods: We conducted a retrospective review of 90 pts treated on IO-based phase 1 clinical trials at Winship Cancer Institute of Emory University between 2009-2017, including sites of metastasis. Overall survival (OS) and progression-free survival (PFS) were measured from the first dose of IO to date of death or clinical or radiographic progression, respectively. Clinical benefit (CB) was defined as a complete response (CR), partial response (PR), or stable disease (SD). Univariate analysis (UVA) and multivariate analysis (MVA) was carried out using Cox proportional hazard model or logistic regression model.

Results: The median age was 63 years and 53% of pts were men. The most common histologies were melanoma (33%) and gastrointestinal cancers (22%). Sites of metastasis were lymph node (N = 58), liver (N = 40), lung (N = 37), bone (N = 24), and brain (N = 8). Most pts (81%) were Royal Marsden Hospital (RMH) good risk. Liver metastases were associated with significantly shorter OS, PFS, and lower rate of CB (Table).

Conclusions: Liver metastases are a poor prognostic factor in pts treated on IO-based phase 1 clinical trials. These findings should be validated in a larger study. Equal Contribution: MAB, JMS, DJM.

Legal entity responsible for the study: Emory University IRB.

Funding: Research reported in this publication was supported in part by the Biostatistics and Bioinformatics Shared Resource of the Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure: M.A. Bilen: Consulting/advisory role: Exelixis, Sanofi; Research funding: Bayer, Bristol-Myers Squibb, Genentech/Roche, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Peleton, Pfizer. B.C. Carthon: Consulting/advisory role: Astellas Medivation, Pfizer, Blue Earth Diagnostics; Travel accommodations: Bristol-Myers Squibb. W.L. Shaib: Research funding: ArQule, Lilly. C. Wu: Honorarium: BioTheranostics; Research funding: Amgen, Bristol-Myers Squibb, Vaccinex, Boston Biomedical. R. Kudchadkar: Consulting/advisory role: Bristol-Myers Squibb, Novartis, Array BioPharma; Honorarium: Bristol-Myers Squibb; Research funding: Merck. B. El-Rayes: Consulting/advisory role: Merrimack, BTG, Bayer, Loxo, RTI Health Solutions; Member of the speakers' bureau: Lexicon, Bristol-Myers Squibb; Honorarium: from Lexicon, RTI Health Solutions, Bayer; Research funding: Taiho Pharmaceutical, Bristol-Myers Squibb, Boston Biomedical, Cleave Biosciences, Genentech, AVEO, Pfizer, Novartis, Hoosier Cancer Research Network, Five Prime Therapeutics, PPD Inc., Merck, ICON Clinical Research. S.S. Ramalingam: Consulting/advisory role: Amgen, Boehringer Ingelheim, Celgene, Genetech/Roche, Lilly/ImClone, Bristol-Myers Squibb, AstraZeneca, Abbvie, Merck, Takeda; Travel accommodations: EMD Serono, Pfizer, AstraZeneca. T.K. Owonikoko: Consulting/advisory role: Novartis, Celgene, Lilly, Sandoz, Abbvie, Eisai, G1 Therapeutics, Takeda, Seattle Genetics, Bristol-Myers Squibb, MedImmune; Intellectual property of the following: "Overcoming acquired resistance to chemotherapy treatments through suppression of STAT3" and "Selective chemotherapy treatments and diagnostic methods related thereto"; Research funding: Novartis, Astellas Pharma, Celgene, Bayer, Stem CentRx, Regeneron, AstraZeneca/MedImmune, Abbvie, G1 Therapeutics, and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1222P Clinical outcome of immune related hepatitis (IrHep) in patients with advanced melanoma (AM) treated with single agent or combination immune checkpoint inhibitors (ICIs)

N. Shah[1], J. Puthiamadathil[1], M.T. Serzan[1], A. Belouali[1], W.J. Kelly[1], B. MA[1], M. blackburn[1], A. Knoedler[1], S. OchoaGonzaelz[1], M. Janni[1], S. Madhavan[1], G.T. Gibney[2], M.B. Atkins[2]

[1]Medicine, Lombardi Cancer Center Georgetown University, Washington DC, USA, [2]Oncology & Medicine, Georgetown-Lombardi Comprehensive Cancer Center, Washington DC, USA

Background: Immune related adverse events with single agent or combination ICIs are well described in patients (pts) with AM, but comprehensive clinical characterization of IrHep is still lacking. Here we report retrospectively collected clinical outcomes of IrHep in pts with AM treated with ICIs at Medstar Health Network hospitals.

Methods: Pts with AM treated with ICIs (n = 189): ipilimumab (ipi) (n = 73), nivolumab (n = 17) or pembrolizumab (n = 48) (anti-PD1), or combination nivolumab plus ipilimumab (combo) (n = 51) were identified by pharmacy records. IrHep was defined as any elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and graded in accordance with CTCAE v4.03. Pts with grade >2 ALT/AST elevation at baseline or rise attributed to causes other than IrHep were excluded. Highest grade ALT/AST was reported for each pt. Median time to resolution (MTR) to baseline

Table: 1221P UVA and MVA† of liver metastases with CO

	OS				PFS				CB			
	UVA		MVA		UVA		MVA		UVA		MVA	
	HR (CI)	p-value	HR (CI)	p-value	HR (CI)	p-value	HR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
No liver metastases (n = 50)	0.42 (0.23-0.78)	0.006*	0.38 (0.17-0.84)	0.017*	0.60 (0.39-0.93)	0.024*	0.73 (0.42-1.26)	0.255	2.64 (1.11-6.28)	0.028*	1.09 (0.27-4.44)	0.903
	Median: 21.9 months 12 month survival: 60%				Median: 3.6 months 12 month survival: 13%				Rate: 56% (6 PR, 22 SD, 17 PD, 5 NE)			
Liver metastases (n = 40)	Median: 8.1 months 12 month survival: 19%				Median: 1.8 mos 12 month survival: 5%				Rate: 33% (1 CR, 1 PR, 11 SD, 24 PD, 3 NE)			

†Covariates included in MVA were age, whether IO is indicated for the pts histology, ECOG PS, RMH risk group, number of metastatic sites and histology
*statistically significant PD: Progressive disease, NE: Not evaluable

was analyzed by KM analysis. Steroid use was captured from its initiation to for IrHep, till their discontinuation.

Results: IrHep any grade was identified in 80 (42%) pts (19 (26%) ipi; 24 (37%) anti-PD-1; 37 (73%) combo). Median time to highest grade IrHep for ipi, anti-PD1, and combo groups was 8.78, 9.65 and 6.15 weeks respectively. IrHep grade $\geq$3 occurred in 3 (4%), 2 (3%) and 14 (27%) combo pts respectively. For IrHep grade $\geq$3 (n = 18), MTR was 5 weeks, median starting systemic steroid dose was 1mg/kg and median duration of steroid treatment was 5 weeks. For irHep grade 2 (n = 22), 32% (n = 7) pts were treated with systemic steroid (2 progressed to grade 3 and 5 resolved), 22.7% (n = 5) pts progress to grade 3-4 with treatment interruption, 22.7% resolved with treatment interruption and 22.7% resolved without treatment interruption. TTF failure for pts with/without IrHep was 5.1/12.4, 12.9/12.5 and NR/24.7 months with ipi, PD1 and combo pts respectively.

Conclusions: In our real-world experience, IrHep was identified more frequently than in past AM studies, particularly in pts treated with combo. Pts with grade 3 $\geq$irHep resolved within 5 weeks with systemic steroids at starting dose of 1mg/kg. Pts with grade 2 irHep, one should not proceed with treatment unless they resolved to grade $\leq$1.

Legal entity responsible for the study: Neil J Shah MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1223P Potential drug cost impact of dual agent immunotherapy (DAIO) with nivolumab (N) plus ipilimumab (I) in patients with DNA mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) in Canada

K. Virik[1], R.B. Wilson[2]

[1]Oncology, Queen's University, CCSEO, Kingston, ON, Canada, [2]Surgery, University of NSW, Liverpool, Australia

Background: The overall 5-year survival for mCRC remains poor (14%) despite the use of current chemotherapeutic and biologic agents. Immunotherapy (IO) is a promising treatment option in tumors with a high mutational burden. This includes mCRC DNA dMMR tumors which have upregulation of immune checkpoints and a poorer prognosis. The CheckMate 142 phase II trial in pretreated dMMR mCRC patients using DAIO with N and I showed improved responses and disease control compared to N alone. The use of this DAIO has an anticipated budgetary impact on health care systems within the context of this potentially funded utilization of IO.

Methods: An estimation of the drug acquisition cost for N and I for new cases diagnosed in 2017 and treated upon relapse in Canada was undertaken. A cost estimate for N and I treatment in the first line of dMMR mCRC in relapses and de novo was undertaken should this be a future option. N and I drug costs per patient were calculated based on treatment indication, median number of cycles, standard dose/schedule as per the CheckMate 142 trial. The analysis was performed in Canadian dollars ($) and assumed complete drug delivery and uncomplicated cycles. The cost of N and I was obtained from the pan Canadian Oncology Drug Review (pCODR) costings for N in lung cancer and I in melanoma respectively. The number of target patients and N and I utilization was derived from constructed schema to give a budget impact estimate.

Results: Estimated DAIO drug costs per treated patient are $131,040. Assuming 65% patients received first line chemotherapy, the cost of DAIO second line and third line in mCRC respectively ranges from $32.9 Million (M) – $50.7M and $17.8M – $24.7M. For 1st line DAIO in 65% of patients: the cost of treating early stage dMMR CRC which subsequently recurs would be $45.7M and the cost for treatment of dMMR de novo mCRC would be $22.8M. A sensitivity analysis was performed.

Conclusions: DAIO drug costs in dMMR mCRC potentially add a substantial cost burden to the publically funded Canadian healthcare system. As data evolves, longer duration of therapy and potential first line use will add further to the estimated budgetary impact.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1224P Q-TWiST analysis to assess benefit-risk of pembrolizumab in patients with PD-L1-positive advanced or metastatic NSCLC

M. Huang[1], M.C. Pietanza[2], A. Samkari[3], J. Pellissier[1], T. Burke[4], S. Chandwani[4], F. Kong[5], A.S. Pickard[6]

[1]Economic and Data Sciences, Merck & Co Inc, North Wales, PA, USA, [2]Clinical Research, Merck & Co, Kenilworth, NJ, USA, [3]Clinical Research, Merck & Co Inc, North Wales, PA, USA, [4]Center for Observational and Real World Evidence, Merck & Co, Rahway, NJ, USA, [5]Stat Programming, Merck & Co Inc, North Wales, PA, USA, [6]Outcomes Research, Second City Outcomes Research, LLC, Oak Park, IL, USA

Background: Pembrolizumab monotherapy showed significantly longer progression-free survival and overall survival (OS), and fewer treatment-related adverse events (AEs) compared to chemotherapy in patients with metastatic non-small cell lung cancer (mNSCLC) with PD-L1 positive tumors in the first-line setting (KEYNOTE-024 (KN024)) and in those previously treated (KEYNOTE-010 (KN010)). The objective of this analysis is to assess the benefit-risk of pembrolizumab in terms of quality-adjusted survival amongst patients in these trials.

Methods: The Quality-adjusted Time without Symptoms of disease progression or Toxicity of treatment (Q-TWiST) analysis was used to compare the trial arms. Survival time of each patient was partitioned into three health states: with toxicity before disease progression, without toxicity before disease progression, and disease progression until death. Toxicities considered were grade 3+ AEs. Mean utility scores for the three health states were estimated using EQ-5D-3L data collected in the trials. Q-TWiST was calculated as the utility-weighted sum of the mean health state durations. KN024 and KN010 have undergone several interim analyses. Data from each of these analyses were examined. The published criterion [Revicki 2006] for a 'clearly clinically important' improvement in Q-TWiST is 15% of mean OS in a study.

Results: Based on the most recent analysis of KN024 from July 10, 2017 and KN010 from March 24, 2017, patients randomized to pembrolizumab had 3.25 months (about 20% of mean OS) greater Q-TWiST ($P < 0.001$) compared to those randomized to platinum-based chemotherapy in KN024, and 3.11 months (about 25% of mean OS) greater Q-TWiST ($P < 0.001$) compared to docetaxel in KN010. Results across KN024 and KN010 trial analyses showed an increase in trend for the Q-TWiST improvement of pembrolizumab over time.

Conclusions: Pembrolizumab showed statistically significant and clinically meaningful improvement in quality-adjusted survival using the Q-TWiST analysis compared to chemotherapy in mNSCLC in both previously untreated and treated patients. The benefits continued to accrue over the trial follow-up period with extended survival.

Legal entity responsible for the study: Merck & Co. Inc.

Funding: Merck & Co. Inc.

Disclosure: M. Huang, M.C. Pietanza, A. Samkari, J. Pellissier, T. Burke, S. Chandwani, F. Kong: Employee: Merck & Co., Inc. A.S. Pickard: Consulting fees: Merck, Eli Lilly, Bristol-Myers Squibb, Novartis/Avexis.

1225P Impact of immune-checkpoint inhibitors (ICPIs) as treatment of patients (pts) with metastatic primary uveal melanoma (UM): Results of a single-institution database

C.L. Lee[1], G. Gullo[1], N. Horgan[2], D. Smith[1], M. Moran[1], J.P. Crown[1]

[1]Medical Oncology, St Vincents University Hospital, Dublin, Ireland, [2]Surgery, Royal Victoria Eye & Ear Hospital, Dublin, Ireland

Background: Metastatic primary UM (MUM) is a rare cancer with a poor prognosis and a median overall survival (OS) of about 6 months in historical datasets. Despite the significant improvements produced by ICPIs in metastatic cutaneous melanoma, pts with MUM have been excluded from most trials of ICPIs thus causing an almost complete lack of prospective clinical data.

Methods: An analysis of all pts with MUM included in our institutional prospectively accrued database of all primary UM pts. OS was calculated from date of first diagnosis of metastatic disease to date of death or last follow up.

Results: Out of 169 pts registered between April 2008 and April 2018, 39 pts had MUM. Pts characteristics: males 20 (51%), median age 63 years (range 34-85), median tumour thickness at diagnosis 9mm (range 2-22), tumour location: choroidal 19 (49%) ciliochoroidal 8 (20%), undefined/unknown 12 (31%). Primary therapy (PTx): enucleation 22 (56%), brachytherapy 15 (38%), both 2 (5%). Sites of metastases: liver only 29 (74%), liver + other sites 7 (18%), extra-hepatic only 3 (8%). Median follow-up is 37.9mos. 11 pts had resectable disease at diagnosis and underwent primary metastatectomies, 28 patients underwent: immunotherapy (15), other systemic therapies (5), locoregional Tx (3), best supportive care (5). Median OS is 14.25 mos. At the database lock-out (April 30th 2018), 27 pts (70%) have died of MUM. Pts without hepatic involvement tend to have longer median OS (25.9mos) vs those with liver only disease (16.6mos) or liver + other sites (OS 8.9 mos). Overall, 32/39 pts (82%) received ICPIs during the course of their disease: ipilimumab 13 (40%), single agent anti-PD1 5 (16%), sequential/concomitant ipilimumab and anti-PD1 14 (44%). Median OS is 23.7 mos (sequential Ipilimumab and anti-PD1) vs and single-agent ipilimumab (13.8mos) vs single-agent PD-1 (14.7mos).

Conclusions: In our single-institution experience of nonresectable MUM pts, sequential/concomitant ICPIs produced a longer median OS than single-agent ipilimumab or anti-PD1 and should be considered the preferred treatment option. A more indolent disease could have contributed to more prolonged OS in a subgroup of pts without hepatic involvement.

Legal entity responsible for the study: St Vincents' Hospitals, Dublin, Ireland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1226P Anti-PD1 inhibitors: Assessment of proper use, efficacy and economic impact in daily practice

M. Valery
Hôpital de la Salpêtrière, Paris, France

Background: Nivolumab and pembrolizumab have been approved in France in treatment of several metastatic cancers, with an approximate monthly processing cost of €5,550 per patient. The objective of our study was to evaluate efficacy and correct use of these anti-PD1 antibodies in daily practice since its approvals.

Methods: We retrospectively collected data from patients treated with nivolumab or pembrolizumab for solid tumor since July 2015. Data included the correct use of anti-PD1 according to the Summary of Product Characteristics, requiring compliance with indications, a WHO status < 2 and a limit of 20 mg per day of corticosteroids. Progression-free survival (PFS) and overall survival (OS) were analyzed for the global population and according to the correct use of anti-PD1 (C+ group) or not (C- group).

Results: 129 patients were treated with nivolumab or pembrolizumab: 108 (83%) patients for lung cancer, 11 (9%) for clear cell renal cancer and 10 (8%) for melanoma. At the cut-off analysis, with a median follow-up of 9,6 months (0,03 – 31,9), 89 patients (69%) had a progressive disease, 64 patients (50 %) were still alive with 18 patients (14%) still receiving anti-PD1, 44 patients (34 %) were deceased and 21 patients (16%) were lost to follow-up. The correct use of anti-PD1 was observed in 85 patients (65%), 29 (21%) patients had a WHO status of 2, 7 (5%) patients had a WHO status of 3, and 12 patients received corticosteroids. The poor utilization of treatment for these 44 patients (34%) totaled 338 injections, costing about €470,000 for a total of €3,000,000 of expenditures using this treatment. Median PFS were respectively 6,7 m (CI 95% 3,9 - 11,7) in the C+ group and 2,5 m (CI 95% 1,6- 5,1) in the C- group (p = 0,03). Median OS were respectively 22,3m (CI 95% 13,6- NR) in the C+ group and 8,4 m (CI 95% 3,9-11,8) in the C- group (p < 0,001). Response rate were respectively 34 % in the C+ group and 25% in the C- group.

Conclusions: In our retrospective study, 34% patients were not meeting the SPC criteria with a WHO status, costing for 25% of the total expenditures. These results reflect the willingness of oncologists to give patients access to innovative and promising treatments but should be balanced with the high cost and the poor outcomes in the C- group.

Legal entity responsible for the study: Pitié-Salpétrière Hospital.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1227P Immune-related adverse events (irAEs) predict therapeutic efficacy of an anti-PD-1 antibody in cancer patients

J. Rogado[1], N. Romero Laorden[1], J.M. Sanchez Torres[1], A.I. Ballesteros Garcia[1], V.E. Pacheco-Barcia[1], R. Arranz[2], R. Mondéjar Solís[1], P. Gullón[3], A. Lorenzo[4], R. Colomer Bosch[1]

[1]Medical Oncology, Hospital Universitario de La Princesa, Madrid, Spain, [2]Hematology, Hospital Universitario de La Princesa, Madrid, Spain, [3]Social and Cardiovascular Epidemiology Research Group, Universidad de Alcalá, Madrid, Spain, [4]Hematology, Hospital Universitario de Mostoles, Mostoles, Spain

Background: In addition to inducing clinical responses, cancer immunetherapy may awaken autoimmune disorders. We have attempted to establish if the incidence of any irAE after Nivolumab used in advanced malignant diseases is associated with anti-PD-1 treatment efficacy.

Methods: We studied all advanced cancer patients treated with Nivolumab between January 2016 and September 2017 at our institution. IrAEs were identified according to CTCAE-4.0. Efficacy was evaluated with objective response rate (ORR, immune RECIST criteria) and progression free survival (PFS). Odds Ratio tests were performed to determine the association between irAEs and ORR.

Results: Finally, 64 patients were included. Primary tumor diagnosis were: lung cancer (n = 47), squamous cell carcinoma of head and neck (n = 5), melanoma (n = 4), clear cell renal carcinoma (n = 4), Hodgkińs lymphoma (n = 2), and urothelial bladder carcinoma and gallbladder adenocarcinoma (n = 1, each one). IrAEs were observed in 27 patients (42.2%), and included hypothyroidism (n = 15), nephritis (n = 5) and hyperthyroidism (n = 4) as more frequent. ORR was observed in 28 patients (43.7%). Median PFS was 6 months (1-25). 21 of the 27 patients with irAEs had objective response (77.7%) vs 7 of the 37 cases without irAEs (18.9%) (OR 15.0, p < 0.000001). PFS in patients with irAEs vs non-irAEs was 7 vs 5 months (HR 2.2, p = 0.016). These results were independent of cancer type, age, sex, histology, ECOG performance status, smoking habit or prior lines of therapy.

Conclusions: In advanced cancer patients treated with an anti-PD-1 antibody, the incidence of irAEs after Nivolumab is associated with a dramatically improved ORR and PFS. Future studies of anti-PD-1 cancer immunotherapy will need to address this association of toxicity and efficacy in order to reveal the underlying biological mechanisms.

Legal entity responsible for the study: Instituto de Investigación Sanitaria Princesa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 1227P Descriptions of patients who developed irAEs

irAE Category	TOTAL patients N. (% Total Patients)	irAEs Grade 1-2 N.	irAEs Grade 3-4
Hypothyroidism	12 (18.9%)	9	3
Hypothyroidism + Hypophysitis + Panhypopituitarism + Suprarrenal Insufficiency + Hepatits + Pneumonitis	1 (1.5%)	1 (Hypophysitis + Panhypopituitarism + Suprarrenal Insufficiency + Hepatits + Pneumonitis)	1 (Hypothyroidism)
Hypothyroidism + Hyperthyroidism + Ketoacidotic Diabetes	1 (1.5%)	1 (Hypothyroidism + Hyperthyroidism)	1 (Ketoacidotic Diabetes)
Hypothyroidism + Hyperthyroidism	1 (1.5%)	1	0
Hypothyroidism + Nephritis	2 (3.2%)	2	1 (Nephritis in one of the patients)
Nephritis	2 (3.2%)	1	1
Nephritis + Arthritis	1 (1.5%)	1 (Arthritis)	1 (Nephritis)
Rash	2 (3.2%)	1	0
Rash + Encephalitis	1 (1.5%)	1 (Rash)	1 (Encephalitis)
Pneumonitis	2 (3.2%)	2	0
Colitis	1 (1.5%)	0	1
Arthritis	1 (1.5%)	0	1
Total patients irAEs	27 (42.2%)	20 irAEs in grade 1-2	11 irAEs in grade 2-3
Patients without irAEs	37 (57.8%)	-	-

1228P Previous immunotherapy treatments may improve tumor responses with subsequent chemotherapy regimens

I. Baraibar Argota[1], P. Martin-Romano[2], M.F. Sanmamed[1], M. Rodriguez-Ruiz[1], J.L. Pérez-Gracia[1], I. Gil-Bazo[1], I. Melero[3], L. Resano[1], A. Chopitea Ortega[1], J. Rodriguez[1], J.M. Aramendia[1], I. Gardeazabal[1], L. Ceniceros[1], P. Sala Elarre[1], M. Ponz-Sarvisé[1], E. Castanon Alvarez[1]

[1]Department of Oncology, Clinica Universidad de Navarra, Pamplona, Spain, [2]Drug Development, Institut Gustave Roussy, Villejuif, France, [3]Laboratory of Immunology, Clinica Universitaria de Navarra, Pamplona, Spain

Background: First line therapies usually induce the longest progression free survival (PFS) in advanced/metastatic cancer as compared to subsequent lines of treatment. However, immunotherapy (IT) due to its mechanisms of action could influence sensitivity to conventional cancer therapy (CCT) after progression to IT and thereby, influence both tumor growth rate (TGR) and progression free survival (PFS). We have studied TGR and PFS before and after participation in phase I IT trials.

Methods: We retrospectively studied 173 patients who were enrolled in Phase I IT trials at our institution between January 2012 and September 2017. Patients should have received at least one line of CCT before and after IT. Baseline characteristics (sex, age, tumor type, presence of liver disease, number of CCT lines prior to IT, type of CCT and IT) were recorded. PFS before and after IT was calculated. A ratio of PFS after/before IT (PFS_{aftIT} /PFS_{beffT}) over 1.2 was considered clinically significant. TGR was calculated based on the formulas: TGR = 100 (exp(TG)−1), TG = 3 Log(Dt/D0)/t.

Results: 37 patients met inclusion criteria. Baseline characteristics are shown in the table. Nine of 37 patients (6 CRC, 3 renal cancer) presented a PFS_{aftIT}/PFS_{beffT} rate over 1.2. Regarding TGR, of 16 patients in whom TGRpre and TGRpost were available, 3

patients (2 CRC, 1 NSCLC) presented a decrease in TGR greater than 15% when given treatment after IT therapy.

Table: 1228P

Characteristics	N = 37
Female	17
Median (M) age at diagnosis (range)	55 (31-79)
M lines prior to IT (range)	2 (1-5)
Primary tumor Gastrointestinal	19 7 5 4 1 1
Genitourinary Gynecological NSCLC	
Head and neck Breast cancer	
Presence of liver disease (pre/IT/pro)	15/18/31
CCT class (pre/post IT) Platinum derivatives	14/18 0/3 14/21 3/0 13/7
Other alkylating agents (a)	5/4 17/19 1/3 4/1 4/3
Antimetabolites a Anthracyclines	
Topoisomerase inhibitors (i)	
Antimicrotubules a Antiangiogenic a	
Signal transduction i Immunotherapy	
Others	
Combined/monotherapy during IT	22/15

Conclusions: Our data suggest a better outcome on ensuing systemic therapies after IT. Further prospective investigations are needed to select the subset of patients who are more prone to a re-sensitization to CCT and to understand the mechanisms underlying.

Legal entity responsible for the study: Clínica Universidad de Navarra.

Funding: Has not received any funding.

Disclosure: I. Melero: Advisory: BMS, Roche, AstraZeneca, Genmab, Alligator, Tusk, Bioncotech, Merck/Serono. All other authors have declared no conflicts of interest.

1229P Real world incidence, severity and timing of adverse events (AEs) among patients with metastatic non-small cell lung cancer (NSCLC) receiving second-line (2L) immuno-oncology (IO) therapy vs chemotherapy (C)

M.E. Gutierrez[1], A.D. Norden[2], D.C. Lane[3], B.F. Canavan[4], E.D. Nwokeji[3], Y. Xu[5], S. Kaur[2], S.L. Goldberg[2], L. Noh[2], L. Siegartel[3], J. Whittington[6], K. Tuell[7], B. Korytowsky[3]

[1]Medical Oncology, The John Theurer Cancer Center, Hackensack, NJ, USA, [2]Cota, Inc, New York, NY, USA, [3]US HOER Oncology, Bristol-Myers Squibb, Lawrenceville, NJ, USA, [4]Medical Oncology, Regional Cancer Care Associates, Edison, NJ, USA, [5]US HOER Strategy, Bristol-Myers Squibb, Lawrenceville, NJ, USA, [6]US Pharmaceuticals, Medical Oncology, Bristol-Myers Squibb, Lawrenceville, NJ, USA, [7]US HOER Emerging Health Sectors, Bristol-Myers Squibb, Lawrenceville, NJ, USA

Background: Randomized clinical trials (RCTs) in metastatic NSCLC have demonstrated superior responses and lower rates of AEs with 2L IO compared with 2L C. Real-world data (RWD) are lacking to confirm tolerability of IO reported in the controlled environment of RCTs. This study examines RWD on AEs among patients (pts) with metastatic NSCLC receiving either 2L IO or C.

Methods: Cota database electronic health records (EHR) of 55 oncologists at 13 US centers (2 academic; 11 community) were reviewed to identify pts with stage IV NSCLC who received 2L therapy following prior first-line C (March 2015 - December 2017). EHR documented AEs were graded per CTCAE v4 criteria by trained oncology nurses.

Results: Of 206 pts identified, 152 received 2L IO and 54 2L C. No differences were noted between cohorts in age (median [years]; IO: 70; C: 65; $p = 0.21$), sex (IO: 55% male, C: 41%; $p = 0.08$), or age-adjusted Charlson comorbidity index (IO: 4; C: 4; $p = 0.92$); more IO pts had squamous cell histology (IO: 23%; C: 9%; $p = 0.03$). Median duration of 2L therapy [mo (range)] was 2.3 (0-19.1) with IO and 1.7 (0-21.6) with C. AEs of grade 3-4 or any grade resulting in treatment change or discontinuation occurred in 39 (19%) pts; less frequently with IO (13%) vs C (35%; $p < 0.01$); with 87% of AEs occurring by 3 mo. Cumulative % of pts experiencing AEs by 1, 2, 3, and 4 mo of treatment was significantly lower ($p < 0.05$) at all time-points with IO vs. C (5.3, 8.6, 10.5, 10.5 vs. 25.9, 25.9, 33.3, 35.2, respectively). Unadjusted survival data were similar.

Conclusions: This retrospective study of RWD shows 2L therapy with IO, compared with C, is associated with a lower frequency of AEs of grade 3-4 or any grade leading to treatment discontinuation, over 1 to 4 months of therapy. A limitation is that spontaneous reporting of AEs in RWD likely captures fewer AEs compared with RCTs.

Legal entity responsible for the study: Cota.

Table: 1229P Frequency of adverse events during initial 3 months of treatment

Adverse Events	IO Cohort (n = 152) Grade 2 with treatment discontinued	IO Cohort (n = 152) Grade 3-4	C Cohort (n = 54) Grade 2 with treatment discontinued	C Cohort (n = 54) Grade 3-4	p-value Grades 3-4
Blood and Lymphatic					
–Anemia	1 (0.7%)	4 (2.6%)	5 (9.3%)	5 (9.3%)	0.05
–Neutropenia	0 (0%)	0 (0%)	1 (1.8%)	3 (5.6%)	0.02
Thrombocytopenia	0 (0%)	0 (0%)	2 (3.7%)	2 (3.7%)	0.07
Cardiac disorders	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)	0.26
Endocrine	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	1.00
Gastrointestinal	0 (0%)	1 (0.7%)	3 (5.6%)	0 (0%)	1.00
Infectious	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)	0.26
Metabolism	0 (0%)	1 (0.7%)	3 (5.6%)	0 (0%)	1.00
Musculoskeletal	1 (0.7%)	1 (0.7%)	0 (0%)	2 (3.7%)	0.17
Other	1 (0.7%)	3 (2.0%)	2 (3.7%)	3 (5.6%)	0.19
Neurologic	1 (0.7%)	1 (0.7%)	2 (3.7%)	1 (1.8%)	0.46
Respiratory	2 (1.3%)	2 (1.3%)	1 (1.8%)	1 (1.8%)	1.00
Vascular	0 (0%)	0 (0%)	0 (0%)	3 (5.6%)	0.02

Funding: Bristol Myers Squibb.

Disclosure: M.E. Gutierrez: Personal fees: Bristol-Myers Squibb, Merck, Eli Lilly, Guardant 360, Esanex, Foundation Medicine, AstraZeneca. A.D. Norden, S. Kaur, L. Noh: Employee: Cota. D.C. Lane, L. Siegartel, B. Korytowsky: Employee, Stock ownership: BMS. E.D. Nwokeji, Y. Xu, J. Whittington, K. Tuell: Employee: BMS. S.L. Goldberg: Employee, Stock ownership: Cota. All other authors have declared no conflicts of interest.

1230P Anti-PD-1 therapy combined with chemotherapy or target therapy in patients with advanced biliary tract cancer in real-world clinical setting

D. Sun[1], J. Ma[1], C. Han[1], J. Wang[1], Y. Qian[1], G. Chen[1], X. Li[1], J. Zhang[1], J. Song[2], X. Zhao[2], S. Cai[2], Y. Hu[1]

[1]Department of Medical Oncology, Chinese PLA General Hospital, Beijing, China, [2]The Medicine Department, 3D Medicines Inc., Shanghai, China

Background: Biliary tract cancer (BTC) is associated with poor prognosis and lack of effective treatment. As the deregulation of the immune system playing a key role in the pathogenesis of BTC, immunotherapy has emerged as a promising treatment. However, the objective response rate (ORR) of pembrolizumab monotherapy is only 17.4% in programmed death ligand-1 (PD-L1) positive advanced BTSs. Immune checkpoint inhibitors combined with other treatment may be a potential way to improve efficacy, but related evidence is limited. We aimed to evaluate the efficacy and safety of nivolumab/pembrolizumab with chemotherapy or target therapy compared with monotherapy in advanced BTCs.

Methods: Advanced BTCs patients treated with PD-1 inhibitors alone or plus chemotherapy or target therapy from Dec 2015 to Oct 2017 were retrospectively screened for eligibility. Patients previously treated with any agent targeting T-cell co-stimulation or checkpoint pathways were excluded. The primary outcome was overall survival (OS). Secondary outcome were progression-free survival (PFS), ORR and safety.

Results: In total, 37 patients were included (monotherapy, n = 15; combination, n = 22). Combination group represented significantly longer OS (median, 8.2 vs 3.6 months, HR 0.47 [0.20-1.10], p = 0.011) and longer PFS (median, 3.9 vs 2.0 months, HR 0.58 [0.28-1.19], p = 0.034) than monotherapy group. The ORR was 22.7% (5/22) in combination group and 6.7% (1/15) in monotherapy group (p = 0.368) though no significant difference was observed. No significant difference in the incidence of grade 3-4 treatment-related adverse events (TRAEs) were detected between groups (p > 0.05). Most common grade 3-4 adverse events were thrombocytopenia (13.6%) and leukopenia (9.1%) in combination group, and thrombocytopenia (6.7%) in monotherapy group.

Conclusions: Combination of anti-PD-1 plus chemotherapy or target therapy is effective and tolerable as first-line or beyond for advanced BTCs. Prospective study with larger sample size is needed in the future to further confirm our results.

Legal entity responsible for the study: Chinese PLA General Hospital.

Funding: The National Natural Science Foundation of China (81402552 to YH)

Disclosure: All authors have declared no conflicts of interest.

1231P The efficacy and safety of solid tumors combination therapy with immune checkpoint inhibitor: A systematic review and meta-analysis

M. Peng[1], Y. Weng[2], Y. Yao[1], Q. Song[2]

[1]Oncology, Renmin Hospital of Wuhan University, Wuhan, China, [2]Cancer Center, Renmin Hospital of Wuhan University, Wuhan, China

Background: The value of combination therapy with immune checkpoint inhibitor (ICI) for patients with solid tumors remains unclear. Following the completion of several large phase III clinical trials, the role of combination ICI therapy in solid tumors should be redefined.

Methods: Pub-med, EMBASE, Cochrane Library and ClinicalTrials.gov website were searched for eligible randomized controlled trials (RCTs). The selection criteria were defined according to the PICO question: In patients with solid tumors (population), is there any difference of efficacy and safety (outcome) between combination ICI therapy (intervention) and traditional monotherapy (comparison)?

Results: 17 RCTs with 6,616 patients were included in this meta-analysis. The combination therapy of ICI was signifcantly associated with improvement of overall response rate (ORR) (RR = 1.56 [95% CI 1.24, 1.96], P = 0.0001), progression free survival (PFS) (HR = 0.69 [95% CI 0.59, 0.81], P < 0.00001) and overall survival (OS) (HR = 0.76 [95% CI 0.67, 0.87], P < 0.0001) in solid tumor. In subgroup analyses, combination ICI therapy obviously prolonged OS in melanoma patients (HR = 0.64 [95% CI 0.57, 0.72], P < 0.00001), but not in SCLC (HR = 0.94 [95% CI 0.82, 1.08], P = 0.40) and NSCLC (HR = 0.92 [95% CI 0.79, 1.07], P = 0.26) patients. As for toxicity, there was an increased risk of fatigue, rash, diarrhoea and increased transaminases with combination ICI therapy.

Conclusions: In conclusion, our meta-analysis found that combination ICI therapy showed significant benefits in ORR, PFS and OS for patients with solid tumors. Both of combination of ICI with chemoradiotherapy and dual ICI were effective and relatively safe. Melanoma patients got definite survival benefit from combinaiton ICI therapy. Combination ICI therapy should be taken into account in clinical practice and future study designs for melanoma patients. There was also a tendency of improvement of survival for SCLC and NSCLC patients. However, the current data of our analyses didn't support the large-scale clinical application of combination ICI therapy in NSCLC and SCLC patients. Furthermore, numerous RCTs assessing the efficacy and safety of combination therapy with ICI are ongoing.

Legal entity responsible for the study: M. Peng.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1232P Model-based assessment of benefit-risk profile of nivolumab (NIVO) flat dosing schedules (Q2W and Q4W) across multiple tumor types

X. Zhao[1], J. Shen[1], M. Gopalakrishnan[2], Y. Feng[1], B.J. Schmidt[1], P. Statkevich[1], T. Kelleher[3], M. Rashford[4], V. Ivaturi[2], J.V.S. Gobburu[2], S. Agrawal[1], A. Bello[1], A. Roy[1]

[1]Clinical Pharmacology and Pharmacometrics, Bristol-Myers Squibb, Princeton, NJ, USA, [2]Center for Translational Medicine, School of Pharmacy, University of Maryland, Baltimore, MD, USA, [3]Global Biometric Sciences, Bristol-Myers Squibb, Wallingford, CT, USA, [4]Oncology Clinical Development, Bristol-Myers Squibb, Princeton, NJ, USA

Background: Flat dosing regimens of NIVO 240 mg every 2 weeks (Q2W) and 480 mg every 4 weeks (Q4W) were approved in the US across indications (not including 480 Q4W in MSI-H or dMMR CRC) and the EU across indications (240 mg Q2W) and in melanoma and renal cell carcinoma (480 mg Q4W) to provide flexible and convenient treatment options than the initially approved 3 mg/kg Q2W weight-based regimen. These changes were supported by model-based bridging of available efficacy and safety data.

Methods: NIVO exposures with flat dosing regimens were predicted and compared with 3 mg/kg Q2W dosing for 3817 patients with melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, classical Hodgkin's lymphoma, small cell lung cancer, hepatocellular carcinoma, colorectal carcinoma, and gastric carcinoma. The impact on differences in time-varying exposure on safety were assessed by time-to-event models of Grade (Gr)2+ immune-mediated adverse events (IMAEs) and treatment-related AEs (TRAEs). The impact of differences in early (month 1) exposure on efficacy was assessed by models of tumor growth dynamics and overall survival (OS). Additionally, the potential impact of time-varying exposure on efficacy was assessed by predicting intratumoral programmed cell death 1 (PD-1) receptor occupancy (RO).

Results: The predicted time-averaged concentration at steady-state for 240 mg Q2W and 480 mg Q4W was similar to 3 mg/kg Q2W (<6% difference), whereas the peak and time-averaged concentration after the first dose were higher with 480 mg Q4W. The predicted cumulative probability of experiencing Gr2+ IMAEs or TRAEs with NIVO 240 mg Q2W and 480 mg Q4W were similar to 3 mg/kg Q2W (<1% difference at 2 years). The exposure–response relationship of tumor shrinkage and growth rates were flat. Hazard ratios of OS with NIVO 240 mg Q2W and 480 mg Q4W relative to standard-of-care were predicted to be similar to 3 mg/kg Q2W. The median trough intratumoral RO at steady state was predicted to be maintained above 90% for all 3 dosing regimens.

Conclusions: The benefit-risk of NIVO 240 mg Q2W and 480 mg Q4W regimens are expected to be similar to 3 mg/kg Q2W, with the added convenience and flexibility for patients and providers.

Editorial acknowledgement: Medical writing assistance was provided by Eric Rabinovsky, PhD, of Spark Medica Inc. (US), funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: X. Zhao J. Shen, B.J. Schmidt, P. Statkevich, T. Kelleher: Employee: BMS. Y. Feng: Owned BMS stock. M. Rashford, S. Agrawal, A. Roy, A. Bello: Employee, Stockholder: BMS. All other authors have declared no conflicts of interest.

1233P Imunotherapy in clinical practice: Real world multicentric Brazilian experience

J. Cé Coelho[1], A.C. Zimmer Gelatti[1], E. Mascarenhas[2], C. Dutra[3], T. Rebelato[4], R. D'Avila[5], F. Zaffaroni Caorsí[6], B.M. Rocha Garcia[3], A.C. de Mirandae Figueiredo[3], M. Souto[2], A. Baldasso Zanon[1], N. Balzan[1], G. Werutsky[5], S. Jobim de Azevedo[1]

[1]UPCO - Unidade de Pesquisa Clinica em Oncologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [2]Oncology, Nucleo de Oncologia da Bahia, Salvador, Brazil, [3]Oncology, CEPON - Centro de Pesquisas Oncológicas, Florianópolis, Brazil, [4]Oncology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [5]Oncology, Hospital São Lucas da PUCRS, Porto Alegre, Brazil, [6]Oncology, Latin American Oncology Group, Porto Alegre, Brazil

Background: Immunotherapy is a new standard of care for metastatic NSCLC patients. Approval of this therapy was based on randomized phase 3 trials. Clinical trials employees' strict patient selection criteria, and this may not represent the 'real-world' population.

Methods: From January 2011 to December 2017, all patients with metastatic NSCLC referred for first oncological evaluation at 4 Hospitals in Brazil were identified by electronic database and included in the analysis. Main eligibility criteria used in first-line phase 3 immunotherapy trials were selected to be evaluated. OS was estimated by Kaplan-Meier curves. Cox proportional hazards model was performed to identify factors associated with survival. All statistical analyses were performed using SAS 9.4.

Results: 537 patients were included in this analysis. Mean age was 62.73 ± 10.47 years, 57.3% male and 67.0% had adenocarcinoma. 332 (61.8%) patients didn't meet one or more eligible criteria. Patients with ECOG PS ≥ 2 and/or active brain metastasis accounted alone for 78.3% of non-eligibility cases. The median OS after the diagnosis of metastatic disease was 7.56 (95% CI: 6.37 to 9.59) months in the non-eligible group and 14.55 (95% CI: 12.16 to 18.23) in the eligible group. Logrank test detected a statistically significant difference between the survival curves in both groups ($p = 0.0001$). The hazard ratio (HR) of 1.778 (95% CI: 1.425 - 2.217) to mortality reflects worse prognostic features in non-eligible group. Also, Logrank test detected a statistically significant difference between the survival curves of ECOG 0-1 and ECOG 2-4 (HR 2.313 95% CI: 1.839 – 2.909 $p < 0.0001$) and histology, with a HR of 1.479 (95% CI: 1.135 – 1.927 $p = 0.0036$) in favor of adenocarcinoma. Median OS in ECOG 0-1 group was 13.17 months (95% CI: 11.89 – 15.05) and in ECOG 2-4 was 6.05 months (95% CI: 4.67 – 6.77). Median OS in Adenocarcinoma group was 12.48 months (95% CI: 9.63 – 13.83) and in Squamous cell was 6.51 months (95% CI: 5.29 – 11.17).

Conclusions: A significant part of real life Brazilian NSCLC population doesn't fit the strict selection criteria specified by clinical trials. As soon as the experience and safety with this treatment improves, is desirable that future trials admits patiets more representative of real world NSCLC population.

Legal entity responsible for the study: J. Cé Coelho.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1234P Correlation, in a real-world setting, between clinical-disease characteristics and compliance with immunotherapy in solid metastatic tumors: First results of an Italian CORE-IMMUNO study

C. Masini[1], A. Berselli[1], M. Banzi[1], C. Bonelli[1], A. Romagnani[1], M. Pagano[1], A. Damato[1], G. Prati[2], E. Gasparini[3], G. Moretti[1], I.T. Lorenzetti[1], F. Zanelli[1], F. Iachetta[1], C. Pinto[1]

[1]Oncology Unit, AUSL di Reggio Emilia-IRCCS, Reggio Emilia, Italy, [2]Oncology, Day Hospital Oncology, Ospedale Civile di Guastalla, Guastalla, Italy, [3]Medical Oncology, Day Hospital Oncology, Ospedale Magati di Scandiano, AUSL Reggio Emilia, Reggio Emilia, Italy

Background: Nivolumab, Pembrolizumab and Ipilimumab monotherapy has shown survival benefits in patients (pts) with melanoma, kidney, lung and head-neck cancer. The aim of this study is to evaluate safety and treatment compliance in terms of delays in the administration or withdrawal of drugs due to toxicity, according to disease and clinical characteristics of pts in clinical practice.

Methods: In this retrospective study, data were evaluated on pts in the Reggio Emilia Provincial Oncology Network who were treated for solid metastatic tumors with Nivolumab, Pembrolizumab and Ipilimumab monotherapy in clinical practice. The pts included in the study had received at least 1 dose of therapy by December 2017 and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events (v. 4.1).

Results: A total of 92 pts were analyzed, of which 42 with lung cancer, 35 with melanoma, 12 with kidney cancer and 3 with head-neck cancer. Sixty-five pts (71%) were treated with Nivolumab, 17% with Pembrolizumab and 12% with Ipilimumab. Overall, 36 pts (39%) experienced an immunorelated adverse event (iAE) of any grade; 33/92 pts (36%) presented a G1-2 iAEs, while only 7% had a G3-4. Out of the 92 pts, the immunotherapy of 17% was delayed due to toxicity, but only 5% of pts discontinued treatment due to iAEs. No statistically significant differences in PFS (9.5 vs. 5.9 months, $p = 0.12$) and OS (21.9 vs. 12.2 months, $p = 0.15$) were found between pts who experienced iAEs and those who did not. Cox regression was performed for PFS and OS using sex, performance status (PS), comorbidities, presence of brain metastases, number of previous lines of therapy, number of metastatic sites and age as covariates. For both, only PS (1-2) significantly correlates with poor PFS and OS with respect to PS 0 ($p < 0.001$).

Conclusions: The data supports the use of immune checkpoint-inhibitors in pts treated in clinical practice with different solid tumors. These treatments are suitable for elderly pts with multiple comorbidities, pts with brain metastases and heavily pretreated pts. However, the use of these drugs should be evaluated with caution in pts with poor PS.

Legal entity responsible for the study: Oncology Unit, AUSL IRCCS Reggio Emilia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1235P Safety of immunotherapy in elderly patients: A retrospective analysis of a phase I unit

E. Ferraro, G. Viale, B. Achutti Duso, C. Belli, C. Criscitiello, L. Mazzarella, A. Esposito, S. Morganti, D. Trapani, P. Tarantino, P. D'Amico, C. Busacca, M.A. Massaro, G. Curigliano

Division of Early Drug Development for Innovative Therapies and Department of Oncology and Hemato-Oncology, European Institute of Oncology and University of Milan, Milan, Italy

Background: Cancer immunotherapy has been used in patients over 70 years old with controversial results. Several age-associated changes including the dysregulation of the immune system could be involved. The main goal of our study is to retrospectively investigate the safety of immunotherapy in elderly patients enrolled in early phase studies regardless tumor type.

Methods: We retrospectively reviewed all cases of patients ≥70 years old enrolled in early phase trials with different immunotherapeutics between January 2016 and March 2018. Eligible patients have received at least one cycle of single agent or a combination of first and/or second generation immune-modulating drugs. The primary aim of the study was to evaluate the safety of such an approach in the elderly population. Toxicity has been graded using the NCI CTCAE v 4.0. Secondary objective was disease control rate (DCR). Fisher test was used to perform the comparison analysis.

Results: We identified 29 patients, of those 21 were eligible and 8 were screening failures. Patients included in the analysis had an ECOG performance status 0-1. Twelve patients were treated with combo regimens (including a backbone of an anti-PD1 in combination with a new generation immune-checkpoint inhibitor) and 9 with monotherapy. Only 2 patients, one treated with combo and one with monotherapy, experienced a grade 3 immuno-related toxicity leading to treatment discontinuation: an autoimmune thyroiditis in one case and an autoimmune hepatitis, histologically proved, in the other one. The most common adverse event (AE) was G1-G2 fatigue that occurred in 33% of patients. Immuno-related AEs of any grade were observed in 22% of patients treated with monotherapy compared to 33% in the combo group. Three out of 9 patients treated with monotherapy had a partial response or a stable disease with a DCR of 33%, whereas in the combo group the observed DCR was 66%. Differences were not statistically significant between the two groups for neither toxicity nor efficacy (p value 0.65 and 0.19, respectively). No complete response was observed.

Conclusions: Our results suggest that immunotherapy is an effective and well tolerated treatment for older patients with solid tumors.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1236TiP The safety and efficacy of durvalumab in combination with paclitaxel for the treatment of metastatic triple negative breast cancer

H. Ghebeh[1], A.N. Alsayed[2], K. Suleman[2], T. Al-Tweigeri[2]

[1]Stem Cell & Tissue Re-engineering Program, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [2]Oncology Centre, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: Metastatic triple negative breast cancer has poor prognosis and limited treatment options. Immunotherapy with anti-PD-L1 monoclonal antibodies has shown promising results in several types of cancer including triple negative breast cancer. We have initiated a clinical trial to test the safety and efficacy of a combination of the investigational anti-PD-L1 monoclonal antibody durvalumab and paclitaxel for the treatment of metastatic breast cancer. The rationale behind this trial is that treatment with paclitaxel correlates with development of tumor infiltrating lymphocytes (Demaria et al. 2001; Sardella et al. 2006), and the upregulation of PD-L1 on tumor cells. On the other hand, response to targeted anti-PD-L1 therapy correlates with the level of expression of PD-L1 on tumor cells and the pre-existing tumor immunity like CD8+ infiltrating cells and type I helper CD4+ activated lymphocytes (Herbst, Soria et al. 2014). In addition, PD-L1 has anti-apoptotic function that its blockade will synergize with the apoptotic effect of chemotherapeutic agents like paclitaxel. Therefore, the combination of these two agents is likely to be synergistic.

Trial design: The treatment is designed to start with one cycle of paclitaxel alone to enhance the immunogenicity and immune cell infiltration followed by the combination of the two agents. Paclitaxel will be delivered weekly on days 1, 8 and 15 of each 28 days cycle while Durvalumab will be given every two weeks (Days 1 and 15 of each cycle). Paclitaxel is given for 6 cycles only while Durvalumab is given until disease progression, or unacceptable toxicity. The primary endpoint of the study is to measure safety and tolerability of the combination while the secondary endpoints include efficacy monitoring.

Legal entity responsible for the study: T. Al-Tweigeri, M.D.

Funding: This clinical trial is an investigator-initiated trial sponsored partially by AstraZeneca as an externally sponsored research (ESR 14 10649).

Disclosure: All authors have declared no conflicts of interest.

1237TiP VSV-IFNβ-NIS intratumoral (IT) injection: A first-in-human (FIH), phase I study of an innovative oncolytic virotherapy, alone and with an anti-PD-L1 antibody, in patients with refractory solid tumors

S.F. Powell[1], M.R. Patel[2], J. Merchan[3], J. Strauss[4], T.P. Cripe[5], M.O. Old[6], R.M. Diaz[7], M. Reckner[8], B. Brunton[9], N. Packiriswamy[9], D. Upreti[9], L. Suksanpaisan[10], R. Vandergaast[10], R. Khan[9], S.J. Russell[11], K.W. Peng[12], A.S. Bexon[13]

[1]Sanford Cancer Center, Sanford Health, Sioux Falls, SD, USA, [2]Minnesota Medical School, Minneapolis, MN, USA, [3]Miami School of Medicine, Miami, FL, USA, [4]Medical Oncology, Mary Crowley Medical Research Center, Dallas, TX, USA, [5]Hematology/Oncology/BMT, Nationwide Children's Hospital, Columbus, OH, USA, [6]Arthur James Cancer Hospital, The Ohio State University, Columbus, OH, USA, [7]Regulatory and Clinical Affairs, Vyriad, Rochester, MN, USA, [8]Clinical Development, Bexon Clinical Consulting, Montclair, NJ, USA, [9]Molecular Medicine, Mayo Clinic, Rochester, NY, USA, [10]Diagnostics, Imanis Life Sciences, Rochester, NY, USA, [11]Vyriad, Rochester, NY, USA, [12]CTO, Vyriad, Rochester, NY, USA, [13]CMO, Vyriad, Rochester, NY, USA

Background: VSV-IFNβ-NIS (Voyager V1; VV1) is derived from VSV, a bullet-shaped, negative-sense RNA virus with low human seroprevalence; it is engineered to replicate selectively in and kill human cancer cells. VV1 encodes hIFNβ to increase antitumoral immune response and tumor specificity, plus the thyroidal sodium iodide symporter NIS to allow imaging of virus. VV1 is synergistic with different anti-PD-(L)1 antibodies in several tumor models. Three phase 1 clinical studies of VV1 are ongoing (IV and IT). The IT trial described here includes a monotherapy and a combination arm with an anti-PD-L1.

Trial design: The study uses two 2-part, open-label, phase 1, parallel, staggered escalations to determine safety, PK and tumor/biomarker response, after a single VV1 IT dose into 1 target lesion. VV1 is given alone in the 1st arm and in combination with IV anti-PD-L1 in the 2nd arm. Each arm has 2 parts: a single ascending VV1 dose escalation all comers (alone or in combination with anti-PD-L1 until PD) followed by a dose expansion at the RP2D in patients with metastatic colorectal cancer. Virus is injected under radiological guidance. The VV1 dose is escalated from 3×10^6 to 3×10^9 $TCID_{50}$ (dose infecting 50% of cells in culture). The primary objective is to identify MTD/RP2D alone and in combination. Endpoints include PK by RT- PCR for viral genomes, serum IFNβ levels, Tc-99m SPECT/CT imaging of virus infection in injected lesions, peripheral blood immunophenotyping with 11-color flow cytometry for activation markers on T cells, T- regs, NK cells, and MDSCs, and serial biopsies to assess the tumor microenvironment. IHC is performed on tumor biopsies for CD3, CD8, CD4, FoxP3, CD68, CD45, PD-1 and PD-L1 pre- and post-treatment (~day 29) in non-injected and injected lesions. All patients must have $\geq$1 measurable lesion per RECIST 1.1 amenable for a single IT injection and at least one patient per cohort is required to have $\geq$2 measurable lesions, one for injection and one to assess abscopal effects. The study started in 2017 and monotherapy escalation should be near completion, with combination underway, by October 2018.

Clinical trial identification: NCT02923466.

Legal entity responsible for the study: Vyriad.

Funding: Vyriad.

Disclosure: J. Merchan: Consultant: Exelexis. R.M. Diaz: Employee and paid consultant: Vyria. M. Reckner: Consultant: Vyriad. L. Suksanpaisan, R. Vandergaast: Employee: Imanis Life Sciences. S.J. Russell: CEO, stock, board of directors: Vyriad; Employee: Mayo Clinic. K.W. Peng: CTO, stock: Vyriad; Management: Imanis Life Sciences; Employee: Mayo Clinic. A.S. Bexon: CMO, paid consultant: Vyriad. All other authors have declared no conflicts of interest.

1238TiP A first-in-human phase I/II clinical trial assessing novel mRNA-lipoplex nanoparticles encoding shared tumor antigens for immunotherapy of malignant melanoma

R.A. Jabulowsky[1], C. Loquai[2], E. Derhovanessian[3], H. Mitzel-Rink[2], J. Utikal[4], J. Hassel[5], R. Kaufmann[6], A. Pinter[6], M. Diken[7], M. Gold[8], L. Heesen[1], K.H. Schreeb[9], D. Schwarck-Kokarakis[9], S. Kreiter[7], M.R. Gaiser[4], D. Jäger[10], S. Grabbe[2], Ö. Türeci[11], U. Sahin[12]

[1]BioNTech AG, Mainz, Germany, [2]Department of Dermatology, Universitätsmedizin Mainz, Mainz, Germany, [3]GxP Analytics, BioNTech AG, Mainz, Germany, [4]Department of Dermatology, Venereology and Allergology, Universitätsklinikum Mannheim, Mannheim, Germany, [5]Department of Dermatology, University Hospital Heidelberg, Heidelberg, Germany, [6]Department of Dermatology, Venereology, and Allergology, University of Frankfurt, Frankfurt, Germany, [7]Immunotherapies & Preclinical Research, BioNTech AG, Mainz, Germany, [8]Data Science & Biomarker Analysis, BioNTech AG, Mainz, Germany, [9]Clincal Research, BioNTech AG, Mainz, Germany, [10]Medical Oncology, Nationales Zentrum für Tumorerkrankungen (NCT), Heidelberg, Germany, [11]Cluster for Individualized Immune Intervention, Mainz, Germany, [12]BioNTech AG, Mainz, Germany

Background: Local therapeutic vaccination with tumor antigen-encoding mRNAs is being investigated in various clinical trials. We have developed a novel class of RNA-lipoplex ($RNA_{(LIP)}$) immunotherapeutics for intravenous application allowing systemic targeting of antigen-presenting cells (APCs). $RNA_{(LIP)}$ is a novel nanoparticulate formulation of lipid-complexed mRNA which selectively delivers the functional mRNA to APCs in lymphoid compartments body-wide for efficient mRNA uptake and expression of the encoded antigen by APCs. Moreover, this formulation has intrinsically strong adjuvant activity, mimics a systemic viral infection, and induces synchronized activation of potent adaptive as well as type-I-IFN-mediated innate immune responses (Kranz et al., Nature 2016).

Trial design: The first-in-human phase I/II dose escalation Lipo-MERIT trial (NCT02410733) is the first clinical trial to investigate the intravenous administration of a RNA-based cancer vaccine. The trial assesses the safety and tolerability of systemic $RNA_{(LIP)}$ immunotherapy in patients with stage IIIB/C and IV melanoma in four German study centers. Patients are treated with repeated dosing of the tetravalent Lipo-MERIT vaccine composed of $RNA_{(LIP)}$ products encoding the shared melanoma-associated antigens NY-ESO-1, tyrosinase, MAGE-A3, and TPTE based on the expression of at least one of these antigens in routinely collected patients tumor samples. Patients in dose escalation cohorts (classical 3 + 3 design) follow a step-up dosing towards different target doses. Pharmacodynamic activity and immunogenicity of the vaccine is investigated by concerted immune monitoring and correlative biomarker studies. Clinical activity is assessed following imaging according to irRECIST1.1.

Clinical trial identification: EudraCT: 2013-001646-33.

Legal entity responsible for the study: BioNTech RNA Pharmaceuticals GmbH.

Funding: Has not received any funding.

Disclosure: R.A. Jabulowsky, E. Derhovanessian, M. Diken, M. Gold, K.H. Schreeb, D. Schwarck-Kokarakis, S. Kreiter: Employee: BioNTech; Patent ownership, patent applications, stock ownership. C. Loquai: Roche, Novartis, Pierre Fabre, MSD, BMS, Leo, Amgen, Biontech. J. Utikal: Amgen, Biontech, BMS, GSK, MSD, Novartis, Roche, Rheacell, Evalys. J. Hassel: Consulting or advisory role: BioNTech AG, BMS, Roche, Novartis, Pierre Fabre, Philogen, Amgen, ImmunoCore. R. Kaufmann: Merz, Roche, Regeneron, Novartis, Amgen, BMS, Icon, Actelion, Abbvie, Allmiral, Biogen, Idec, Boehringer, Celgene, GSK, Lily, Galderma, LEO, Medac, Merck, Mitsubishi, MSD, Pfizer, TigerCat, Sandoz, Shering, UCB. A. Pinter: AbbVie, AstraZeneca, Biogen, Boehringer Ingelheim, BMS, Celgene, GSK, Janssen-Cilag, LEO Pharma, Lilly Pharma, Novartis, MSD, Regeneron, Roche, Tigercat, UCB. L. Heesen: Employee: BioNTech. D. Jäger: Amgen, Bayer, BMS, Curevac, MSD, Roche. S. Grabbe: Roche, Novartis, MSD, BMS. Ö. Türeci: BioNTech, patent ownership, patent applications, stock ownership. U. Sahin: Founder, patent ownership, patent applications, stock ownership: BioNTech. All other authors have declared no conflicts of interest.

1239TiP MORPHEUS: A phase Ib/II umbrella study platform evaluating the safety and efficacy of multiple cancer immunotherapy (CIT)-based combinations in different tumour types

I. Chau[1], G.M. Haag[2], O.E. Rahma[3], T.M. Macarulla[4], S.L. McCune[5], D.A. Yardley[6], B.J. Solomon[7], M. Johnson[6], G.A. Vidal[8], P. Schmid[9], G. Argiles[4], K. Dimick[10], S. Mahrus[10], H. Abdullah[10], X. He[10], P. Sayyed[11], H. Barak[10], C. Bleul[11], E. Cha[10], A. Drakaki[12]

[1]Department of Medicine, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK, [2]National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany, [3]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [4]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital (HUVH), Barcelona, Spain, [5]Marietta Cancer Center, Northwest Georgia Oncology Centers, Marietta, GA, USA, [6]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA, [7]Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia, [8]Medical Oncology, University of Tennessee West Cancer Center, Germantown, TN, USA, [9]Barts Cancer Institute, Queen Mary University London, London, UK, [10]PD Oncology, Genentech, Inc., South San Francisco, CA, USA, [11]PD Oncology, F. Hoffmann-La Roche, Ltd, Basel, Switzerland, [12]Medicine, UCLA Medical Center, Los Angeles, CA, USA

Background: Significant survival benefit has been achieved with CIT across multiple tumour types, but only subsets of patients (pts) experience durable response with CIT monotherapy. Efficacious CIT combinations targeting multiple cancer immune escape mechanisms need to be identified to extend clinical benefit to more pts. The MORPHEUS platform includes multiple Phase Ib/II trials designed to identify early signals of safety and activity of CIT combinations. Using a randomised trial design, multiple CIT combination arms are compared with a single standard-of-care control arm. We present 7 tumour type–specific MORPHEUS trials, each evaluating various CIT combinations that simultaneously enhance immune-cell priming and activation, tumour infiltration and/or recognition of tumour cells for elimination.

Trial design: The MORPHEUS trials described here are global, open-label, randomised, Phase Ib/II trials enrolling pts with 1 of the following cancers: pancreatic ductal adenocarcinoma (PDAC), gastric or gastro-oesophageal junction cancers (GC/GEJ), hormone receptor-positive or triple-negative breast cancers (HR+/TNBC), non-small cell lung cancer (NSCLC), or colorectal cancer (CRC) (Table). These trials have the flexibility to open new treatment arms with novel CIT combinations as they become available and to close arms that show minimal activity or unacceptable toxicity. Pts experiencing loss of clinical benefit or unacceptable toxicity may be eligible to switch to a different CIT combination arm. Eligibility requires measurable disease per RECIST v1.1. Further eligibility criteria will be provided. Primary endpoints are safety and investigator-assessed ORR per RECIST v1.1. Secondary endpoints include PFS, OS, DCR and DOR. Exploratory biomarkers will also be examined.

Clinical trial identification: NCT03193190, NCT03281369, NCT03280563, NCT03424005, NCT03337698.

Editorial acknowledgement: Medical writing assistance for this abstract was provided by Steffen Biechele, PhD, of Health Interactions.

Legal entity responsible for the study: F. Hoffmann-La Roche AG.

Funding: F. Hoffmann-La Roche AG.

Disclosure: I. Chau: Honoraria: Amgen, Gilead Sciences, Lilly, Pfizer, Taiho Pharmaceutical; Consulting or advisory role: Bayer, Bristol-Myers Squibb, Five Prime Therapeutics, Lilly, MSD Oncology, Roche/Genentech, Sanofi; Research funding: Janssen-Cilag (Inst), Lilly (Inst), Merck Serono (Inst), Sanofi (Inst); Travel, accommodations, expenses: Bristol-Myers Squibb, Lilly, Merck Serono, MSD, Sanofi. G.M. Haag: Advisory role: BMS, Taiho, Nordic, Lilly, MSD; Honoraria: Roche, Pfizer; Travel grant: Amgen, Ipsen, BMS; Research funding: Nordic, Taiho Pharmaceuticals. O.E. Rahma: Consulting or advisory role: Celgene, Alcimed, Gfk, Merck, Five Prime Therapeutics, Putnam Associates; Travel, accommodations, expenses: Merck, Clinical Care Options; Honoraria: Merck, Company: Clinical Care Options, MI Bioresearch; Research Funding: Amgen, Merck. D.A. Yardley: Speaker's bureau, Advisory boards: Genentech. B.J. Solomon: Advisory boards: AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Roche/Genentech, Novartis; Honoraria: Bristol-Myers Squibb, AstraZeneca; Grant/research support: Pfizer; Royalty, IP Rights/Patent Holder: Veristrat (Biodesix). Consulting/advisory role (inst): Genentech/Roche, Celgene, Boehringer Ingelheim, AstraZeneca, OncoMed, BerGenBio, Lilly, EMD Serono, Kadmon, Janssen, Mirati Therapeutics, Genmab, Pfizer, AstraZeneca, Sten CentRx, Novartis, Checkpoint Therapeutics, Array BioPharma, Regeneron, Merck, Hengrui Pharmaceutical, Lycera, BeiGene, Tarveda Therapeutics, Loxo, AbbvieBoehringer Ingelheim, Guardant Health, Foundation Medicine, Daiichi Sankyo, Danofi; Research funding to institution: Mersana; Immediate family member: Contract lobbyist: Astellas Pharma, Otsuka. G.A. Vidal: Advisory board: Genentech, Eli Lily, Immunomedics; Sponsored research: PUMA and Celcuit; Speaker: PUMA, AstraZeneca, Novartis, Lilly, Pfizer. P. Schmid: Honoraria: AstraZeneca, Bayer, Boehringer, Celgene, Eisai, Novartis, Pfizer, Puma, Roche/Genentech; Research support/funding: Astellas, AstraZeneca, Medivation, Novartis, Oncogenex, Roche/Genentech (all to instituation). Spouse: Employee: Roche. K. Dimick, S. Mahrus, C. Bleul: Employee: Roche/Genentech. P. Sayyed: Employee and stock: Roche. H. Barak: Employee and stock: Roche/Genentech; Previously employed: Baxalta. E. Cha: Employee and stock: Roche/Genentech. A. Drakaki: Consulting: BMS; Research funds: Kite. All other authors have declared no conflicts of interest.

1240TiP Phase II study of cemiplimab, a human monoclonal anti-PD-1, in patients with advanced basal cell carcinoma (BCC) who experienced progression of disease on, or were intolerant of prior hedgehog pathway inhibitor (HHI) therapy

K.D. Lewis[1], M.G. Fury[2], E. Stankevich[3], M. Mathias[2], K.K. Mohan[2], S. Li[4], K. Nunnink[2], C. Perry[2], A. Narwal[3]

[1]School of Medicine, University of Colorado Hospital, Denver, CO, USA, [2]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [3]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA, [4]Biostatistics & Data Management, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA

Background: BCC is the most common cancer worldwide. There is no approved agent to treat advanced BCC in patients who experience disease progression on, or who are intolerant of HHIs. Cemiplimab (REGN2810), an anti-PD-1 has demonstrated encouraging efficacy and favourable tolerability in a phase 1 study of patients with advanced malignancies (NCT02383212).

Trial design: We are conducting a phase 2, non-randomised, 2-group, multi-centre study of cemiplimab in patients with advanced BCC who experienced disease progression or are intolerant to HHI therapy (NCT03132636). Group 1 will enrol patients with both nodal and distant metastatic BCC. Group 2 will enrol patients with locally advanced BCC who are not candidates for surgery. Cemiplimab will be administered intravenously every 3 weeks in all patients. The primary objective of the study is to evaluate overall response rate (ORR) as determined by central review. The ORR will be assessed separately for patients in Group 1 or Group 2 (by RECIST 1.1 for radiology, and modified WHO for photography). Up to 137 patients will be enrolled. For Group 1, 50 patients are required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of 5% if the true ORR is 34%. For Group 2, 80 patients are required to provide at least 85% power to reject a null hypothesis of an ORR of 20% at a 2-sided significance level of 5% if the true ORR is 35%. An additional 5% in sample size will account for patient withdrawals. This study is ongoing.

Clinical trial identification: NCT03132636.

Editorial acknowledgement: Medical writing support under the direction of the authors was provided by Emmanuel Ogunnowo, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc. and Sanofi according to Good Publication Practice guidelines (http://annals.org/aim/article/2424869/good-publication-practice-communicating-company-sponsored-medical-research-gpp3).

Legal entity responsible for the study: Regeneron Pharmaceutical, Inc. and Sanofi.

Funding: Regeneron Pharmaceutical, Inc. and Sanofi.

Disclosure: K.D. Lewis: Research funding: Regeneron Pharmaceuticals, Inc. M.G. Fury: Shareholder, employee, patents, royalties, other intellectual property: Regeneron Pharmaceuticals, Inc. E. Stankevich: Shareholder, employee: Regeneron Pharmaceuticals, Inc.; Shareholder: Celgene, Bristol-Myers Squibb, Merck. M. Mathias, K.K. Mohan, S. Li, K. Nunnink, C. Perry, A. Narwal: Shareholder, employee: Regeneron Pharmaceuticals, Inc.

Table: 1239TiP

Summary of Cancer-Type Specific MORPHEUS Trials

Cancer Type	Cohort	No. of Experimental Arms[a]	Countries Currently Targeted for Enrolment
PDAC	2L	3	Germany, South Korea, Spain, United States
GC and GEJ	1L	2	Germany, South Korea, Spain, Taiwan, United Kingdom, United States
	2L	4	
HR+ BC	2L	4	France, South Korea, Spain, United Kingdom, United States
TNBC	2L	5	Australia, France, Germany, South Korea, Spain, United Kingdom, United States
NSCLC	1L	2	Australia, France, South Korea, Spain, United Kingdom, United States
	2L+[b]	5	
CRC	3L	2	Australia, France, South Korea, Spain, United Kingdom, United States

[a]Not all experimental arms may be open at the same time.

[b]Patients who have progressed on prior platinum chemotherapy and anti–PD-L1/PD-1 treatment given concurrently or sequentially. CIT, cancer immunotherapy; CRC, colorectal cancer; GC, gastric cancer; GEJ, gastro-oesophageal junction cancer; HR+ BC, hormone receptor–positive breast cancer; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; TNBC, triple-negative breast cancer.

1241TiP JAVELIN PARP medley: A phase Ib/II study of avelumab (anti–PD-L1) plus talazoparib in locally advanced or metastatic solid tumors

T.A. Yap[1], J.T. Beck[2], R.A. Stewart[3], S.C. Dahm[3], C. Chappey[4], R. Cesari[5], A. Scheuber[6], M.D. Galsky[7], D. Wise[8]

[1]Investigational Cancer Therapeutics, University of Texas MD Anderson Cancer Center, Houston, Surrey, TX, USA, [2]Medical Oncology and Hematology, Highlands Oncology Group, Fayetteville, AZ, USA, [3]Oncology, Pfizer, San Diego, CA, USA, [4]Oncology, Pfizer, San Francisco, CA, USA, [5]Oncology, Pfizer, Milan, Italy, [6]Oncology, Pfizer, Philadelphia, PA, USA, [7]Medicine, Hematology, and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [8]Medicine, NYU Laura and Isaac Perlmutter Cancer Center, New York, NY, USA

Background: Avelumab, a human anti–PD-L1 IgG1 monoclonal antibody, is approved for the treatment of metastatic Merkel cell carcinoma in various countries and advanced urothelial carcinoma after progression on platinum therapy in the United States and Canada. Talazoparib is a potent, orally bioavailable PARP inhibitor with a dual mechanism (PARP enzyme inhibition and PARP trapping). Preclinical studies suggest that the combination of an immune checkpoint inhibitor and PARP inhibitor may have additive antitumor activity, and initial clinical studies support evaluation of this combination.

Trial design: JAVELIN PARP Medley (NCT03330405) is an open-label, multicohort, phase 1b/2 trial investigating avelumab plus talazoparib in ≈316 patients with selected solid tumors. Eligible adult patients have locally advanced (primary/recurrent) or metastatic solid tumors that are not amenable for treatment with curative intent, including non-small cell lung cancer with no EGFR mutations, triple-negative breast cancer, hormone receptor–positive and HER2-negative breast cancer, recurrent platinum-sensitive ovarian cancer, urothelial carcinoma, castration-resistant prostate cancer (CRPC), or advanced solid tumors with BRCA/ATM defects. Requirements for prior anticancer therapy and platinum exposure vary between phases 1b and 2 and between tumor types. Prior treatment with a PARP inhibitor or immunotherapy is not permitted. Different daily oral doses of talazoparib plus avelumab 800 mg IV Q2W will be administered in phase 1b to define the recommended phase 2 dose for the combination before enrolling patients in phase 2. The primary endpoint in phase 1b is first-cycle dose-limiting toxicity, and in phase 2, it is objective response according to RECIST 1.1 (also according to Prostate Cancer Working Group 3 [PCWG3] for patients with CRPC). Other endpoints include duration of response and progression-free survival according to RECIST 1.1 (plus PCWG3 for CRPC), overall survival, adverse events, laboratory abnormalities, pharmacokinetic parameters, and tumor tissue biomarkers. Enrollment in phase 2 of the study is expected to begin in Q3 2018.

Clinical trial identification: B9991025 (NCT03330405).

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking Inc, Hamilton, NJ, USA.

Legal entity responsible for the study: Pfizer.

Funding: This trial was sponsored by Pfizer and is part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.

Disclosure: T.A. Yap: Research funding: AstraZeneca, Vertex Pharmaceuticals; Board membership/Advisory committee: AstraZeneca, Janssen, Clovis, Pfizer, EMD Serono, Bristol-Myers Squibb, Roche, Ignyta, Atrin, Aduro, Almac; Travel support: AstraZeneca, Bristol-Myers Squibb, MSD, Vertex Pharmaceuticals, GlaxoSmithKline, EMD Serono. J.T. Beck: Consulting or advisory role: Novartis; Research funding (institution): AstraZeneca, Novartis, Genentech, Lilly, Amgen, Abbvie. R.A. Stewart, S.C. Dahm, C. Chappey, R. Cesari: Employee: Pfizer. A. Scheuber: Employee, Stocks: Pfizer. M.D. Galsky: Consultant, Advisory board: Merck, Pfizer, Merck-Serono, Genentech; Other research support: Merck, Bristol-Myers Squibb, Novartis. All other authors have declared no conflicts of interest.

1242TiP Study of TBI-1301 (NY-ESO-1 specific TCR gene transduced autologous T lymphocytes) in patients with solid tumors

M.O. Butler[1], H. Majeed[1], M. Nelles[2], S. Saibil[1], L. Bonilla[1], S. Boross-Harmer[1], V. Sotov[2], S. Elston[2], K. Ross[2], B. van As[2], M. Le[2], M. Fyrsta[2], C. Lo[2], J. Yam[2], J. Nie[2], L. Scheid[2], P. Ohashi[3], L. Nguyen[2], S. Tanaka[4], N. Hirano[1]

[1]Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [2]Tumor Immunotherapy Program, Princess Margaret Cancer Centre, Toronto, ON, Canada, [3]Immunology, Campbell Family Institute for Cancer Research, University Health Network, Toronto, ON, Canada, [4]Immunotherapy, Takara Bio Inc, Kusatsu, Japan

Background: The use of cell based immune therapies involving infusion of autologous T-lymphocytes with anti-tumor activity targeting tumor-associated antigens is a rapidly evolving area of research. One approach involves the use of peripheral blood as a source of lymphocytes that are then used in the generation of cytotoxic tumor-specific T cells via introducing a tumor-specific TCR gene into T lymphocytes. NY-ESO-1 is a cancer testis antigen expressed in numerous cancers yet absent in most adult normal tissues apart from high expression in adult testes – thereby making it an ideal target for immunotherapy.

Trial design: TB1-1301 is a gene-modified T cell product that contains a NY-ESO-1 specific TCR introduced with the MS3II-NY-ESO1-SiTCR retroviral vector. This vector encodes for TCR α and β chains that recognize an NY-ESO-1 derived epitope (amino acids 157-165: SLLMWITQC) that is presented in the context of HLA-A*02:01 and HLA-A*02:06 molecules. The vector also encodes for siRNA (small interfering RNA) that are homologous to the constant region sequence of the endogenous, but not transduced TCR α and β chain mRNAs – these siRNAs in turn increase expression of the transduced TCR. Pre-clinical murine studies demonstrated safety, persistence, and efficacy of transduced T cells. This study represents a Phase 1b study of TBI-1301 in patients with advanced solid tumors, which express NY-ESO-1 (synovial sarcoma, ovarian cancer, and melanoma). A pre-conditioning lymphodepletion regimen of cyclophosphamide 750 mg/m^2 will be used on Day -3 and Day -2 prior to infusion of cell product. The objectives of this study include assessing the safety profile of TBI-1301, determining the RP2D dose, and evaluating the efficacy of TBI-1301 via RECIST v1.1.

Clinical trial identification: NCT02869217.

Legal entity responsible for the study: Tumor Immunotherapy Program, Princess Margaret Cancer Centre.

Funding: Takara Bio Inc.

Disclosure: M.O. Butler: Advisory boards: Merck Canada, BMS, Novartis, Immunocore, Immunovaccine, GSK; Research support: Takara Bio Inc. conducting this clinical trial. S. Tanaka: Employee: Takara Bio Inc. N. Hirano: Research support: Takara Bio Inc. All other authors have declared no conflicts of interest.

1243TiP Phase I study of BI 754111 (anti-LAG-3) plus BI 754091(anti-PD-1) in patients (pts) with advanced solid cancers, followed by expansion in pts with microsatellite stable metastatic colorectal cancer (mCRC), anti-PD-(L)1-pretreated non-small cell lung cancer (NSCLC) and other solid tumors

M.L. Johnson[1], M.R. Patel[2], S.V. Ulahannan[3], A. Hansen[4], B. George[5], Q.S-C. Chu[6], M. Elgadi[7], M. Ge[8], C. Duffy[8], R. Graeser[9], S. Khedkar[10], S.F. Jones[11], H. Burris[1]

[1]Medical Oncology, Sarah Cannon/Tennessee Oncology, Nashville, TN, USA, [2]Medical Oncology, Sarah Cannon/Florida Cancer Specialists, Sarasota, FL, USA, [3]Medical Oncology, Sarah Cannon/Stephenson Cancer Center, Oklahoma City, OK, USA, [4]Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [5]Medical Oncology, Medical College of Wisconsin, Milwaukee, WI, USA, [6]Medical Oncology, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, [7]Oncology, Boehringer Ingelheim (Canada) Ltd, Burlington, ON, Canada, [8]Oncology, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA, [9]Transl. Medicine + Clin. Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Rhein, Germany, [10]Pharmacovigilance, Sarah Cannon Development Innovations, Nashville, TN, USA, [11]Oncology, Sarah Cannon, Nashville, TN, USA

Background: Lymphocyte-activation gene 3 (LAG-3) is a negative regulator of immune response implicated in T cell exhaustion and tumor immune escape. Available data demonstrate that tumor-derived T cells frequently co-express the PD-1 and LAG-3 co-inhibitory receptors and that dual blockade of the LAG-3 and PD-1 pathways results in more potent reactivation of T-cell function and anti-tumor immune response than blockade of the individual pathway. BI 754091 and BI 754111 are monoclonal IgG4Pro antibodies (mAbs) against PD-1 and LAG-3, respectively. In this Phase I study, we investigate the safety, tolerability, PK, and preliminary efficacy of the combination of these 2 mAbs.

Trial design: This 2-part, open-labeled, non-randomized ongoing study consists of dose escalation in pts with advanced solid tumors followed by expansion cohorts in pts with NSCLC, microsatellite stable (MSS) mCRC, or any PD-1/PD-L1 pretreated solid tumor with high tumor mutational burden (TMB-H) and/or high microsatellite instability and/or DNA mismatch repair deficiency (MSI-H/MMRd). Dose escalation in pts with solid tumors started at 4mg q3w BI 754111 and was guided by Bayesian Logistic Regression Method. All dose levels of BI 754111 were co-administered with 240 mg q3w BI 754091 (the BI 754091 RPIID selected from 1381.1 phase I [Johnson, et al. ASCO-SITC 2017 abstract 212]). Enrollment in the solid tumor dose escalation portion is nearly complete. The expansion phase will use a combination dose selected from the solid tumor dose escalation. Primary endpoints in the dose escalation are the number of pts with dose-limiting toxicities and the combination MTD. The primary endpoint of the dose expansion portion is the objective response rate.

Clinical trial identification: NCT03156114.

Legal entity responsible for the study: Boehringer Ingelheim Pharmaceuticals, Inc.

Funding: Boehringer Ingelheim Pharmaceuticals, Inc.

Disclosure: M. Elgadi: Employee: Boehringer Ingelheim (Canada) Ltd./Ltee. M. Ge, C. Duffy: Employee: Boehringer Ingelheim Pharmaceuticals, Inc. R. Graeser: Employee: Boehringer Ingelheim Pharma GmbH & Co. KG. All other authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii442–viii466, 2018
doi:10.1093/annonc/mdy289

MELANOMA AND OTHER SKIN TUMOURS

1244O KEYNOTE-022 Part 3: Phase II randomized study of 1L dabrafenib (D) and trametinib (T) plus pembrolizumab (Pembro) or placebo (PBO) for BRAF-mutant advanced melanoma

P.A. Ascierto[1], P.F. Ferrucci[2], R. Stephens[3], M. Del Vecchio[4], V. Atkinson[5], H. Schmidt[6], J. Schachter[7], P. Queirolo[8], G.V. Long[9], A.M. Di Giacomo[10], I. Svane[11], M. Lotem[12], G. Bar-Sela[13], F. Couture[14], B.P. Mookerjee[15], R. Ghori[16], N. Ibrahim[16], B. Homet Moreno[16], A. Ribas[17]

[1]Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy, [2]Oncology, Istituto Europeo di Oncologia, Milan, Italy, [3]Medical Oncology, Auckland City Hospital, Auckland, New Zealand, [4]Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [5]Medical Oncology, Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Brisbane, Australia, [6]Oncology, Aarhus University Hospital, Aarhus, Denmark, [7]Oncology, Ella Lemelbaum Institute for Melanoma, Sheba Medical Center at Tel HaShomer, Cancer Center (Oncology Institute), Ramat Gan, Israel, [8]Oncologia Medica, IRCCS San Martino-IST, Genoa, Italy, [9]Medical Oncology, Melanoma Institute Australia, University of Sydney, North Sydney, Australia, [10]Medical Oncology, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy, [11]Oncology, Herlev Hospital, University of Copenhagen, Herlev, Denmark, [12]Medical Oncology, Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel, [13]Oncology, Rambam Health Care Campus, Haifa, Israel, [14]Hematology, Centre Hospitalier Universitaire de Québec Research Center, Laval University, Québec, QC, Canada, [15]Oncology Clinical Development, Novartis, East Hanover, NJ, USA, [16]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [17]Medical Oncology, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA

1245PD Intratumoral (IT) Injection of the TLR9 agonist tilsotolimod (IMO-2125) in combination with ipilimumab (ipi) triggers durable responses in PD-1 inhibitor refractory metastatic melanoma (rMM): Results from a multicenter, phase I/II study

A. Diab[1], C. Haymaker[2], C. Bernatchez[2], R.H.I. Andtbacka[3], M. Shaheen[4], D. Johnson[5], J. Markowitz[6], I. Puzanov[7], R. Murthy[8], D.H. Johnson[1], M. James[1], S. Chunduru[9], J. Geib[10], S. Swann[11], S. Rahimian[12], P. Hwu[13]

[1]Melanoma, MD Anderson Cancer Center, Houston, TX, USA, [2]Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Surgical Oncology, Huntsman Cancer Institute, Salt Lake City, UT, USA, [4]Medicine, University of Arizona Cancer Center North, Tucson, AZ, USA, [5]Medical Oncology, Vanderbilt University, Nashville, TN, USA, [6]Medical Oncology, Moffitt Cancer Center, Tampa, FL, USA, [7]Melanoma, Roswell Park Cancer Center, Buffalo, NY, USA, [8]Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA, [9]Translational Biology, Idera Pharmaceuticals, Exton, PA, USA, [10]Oncology Clinical Development, Idera Pharmaceuticals, Exton, PA, USA, [11]Biometrics, Idera Pharmaceuticals, Exton, PA, USA, [12]Oncology, Idera Pharmaceuticals, Exton, PA, USA, [13]Melanoma, MD Anderson Cancer Center, Houston, TX, USA

1246PD **Talimogene laherparepvec (T-VEC) treatment increases intratumoral effector T-cell and natural killer (NK) cell density in noninjected tumors in patients (pts) with stage IIIB–IVM1c melanoma: Evidence for systemic effects in a phase II, single-arm study**

H. Gogas[1], I. Samoylenko[2], D. Schadendorf[3], R. Gutzmer[4], J.J. Grob[5], J.J. Sacco[6], K. Gorski[7], A. Anderson[7], C. Liu[8], J. Malvehy[9]

[1]First Department of Medicine, Laiko General Hospital of Athens, Athens, Greece, [2]Tumor Biotherapy, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation, [3]Department of Dermatology, University of Duisburg-Essen and German Cancer Consortium (DKTK), Essen, Germany, [4]Skin Cancer Center, Hannover Medical School, Hannover, Germany, [5]Service de Dermatologie, Aix Marseille University and APHM University Hospital Timone, Marseille, France, [6]Medical Oncology, Clatterbridge Cancer Center, Wirral, UK, [7]Clinical Biomarkers, Amgen Inc., Thousand Oaks, CA, USA, [8]Biostatistics, Amgen Inc., Thousand Oaks, CA, USA, [9]Dermatology Department and IDIBAPS, Hospital Clinic of Barcelona, Barcelona, Spain

1247PD **Phase II multicenter, single arm, open label study of nivolumab in combination with ipilimumab in untreated patients with metastatic uveal melanoma (GEM1402.NCT02626962)**

J.M. Piulats Rodriguez[1], L. De La Cruz Merino[2], E. Espinosa[3], L. Alonso Carrión[4], S. Martin Algarra[5], R. López-Castro[6], M.T. Curiel García[7], D. Rodriguez Abreu[8], A.J. Rullan Iriarte[9], A. Berrocal Jaime[10]

[1]Medical Oncology, Institut Catala d'Oncologia (ICO), Barcelona, Spain, [2]Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, [3]Oncology, Hospital Universitario La Paz, Madrid, Spain, [4]Oncology, Universidad de Málaga, Malaga, Spain, [5]Oncology, Clínica Universitaria de Navarra, Navarra, Spain, [6]Medical Oncology, Hospital Universitario Clínico de Valladolid, Valladolid, Spain, [7]Oncology, Hospital Universitario Clínico de Santiago, Santiago De Compostela, Spain, [8]Oncology, Hospital Insular de Canarias, Las Palmas de Gran Canarias, Spain, [9]Oncology, Institut Catala de Oncologia, Barcelona, Spain, [10]Medical Oncology, Hospital General Universitario Valencia, Valencia, Spain

1248PD **Efficacy of pembrolizumab (Pembro) in patients (Pts) with advanced melanoma with stable brain metastases (BM) at baseline: A pooled retrospective analysis**

O. Hamid[1], A. Ribas[2], A. Daud[3], M.O. Butler[4], M.S. Carlino[5], W-J. Hwu[6], G.V. Long[7], K. Ancell[8], F.S. Hodi[9], N.I. Khushalani[10], C.U. Blank[11], C. Loquai[12], J. Lin[13], S.J. Diede[13], C. Robert[14]

[1]Medical Oncology and Hematology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA, [2]Medical Oncology, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA, [3]Medicine, University of California, San Francisco, CA, USA, [4]Medical Oncology, UHN Princess Margaret Cancer Centre, Toronto, ON, Canada, [5]Medical Oncology, Westmead Hospital, Westmead, Australia, [6]Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [7]Medical Oncology, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia, [8]Medical Oncology, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA, [9]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [10]Cutaneous Oncology Program, Moffitt Cancer Center, Tampa, FL, USA, [11]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [12]Dermatology, University Medical Center Mainz, Mainz, Germany, [13]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [14]Medical Oncology, Gustave Roussy, Villejuif, France

1249PD **Concomitant radiotherapy in melanoma brain metastases using the propensity score matching within the French cohort, MelBase**

C. Allayous[1], B. Oriano[2], S. Dalle[3], L. Mortier[4], M-T. Leccia[5], B. Guillot[6], G. Jeudy[7], C. Dutriaux[8], J-P. Lacour[9], P. Saiag[10], F. Brunet-Possenti[11], J. De Quatrebarbes[12], P-E. Stoebner[13], D. Legoupil[14], M. Beylot-Barry[15], T. Lesimple[16], F. Aubin[17], A. Ballon[1], R. Porcher[2], C. Lebbe[1]

[1]Dermatology, AP-HP, Saint-Louis Hospital, Paris, France, [2]Biostatistics, AP-HP, Hotel-Dieu Hospital, Paris, France, [3]Dermatology, Lyon Sud Hospital, Pierre Bénite, France, [4]Dermatology, Lille Hospital, Lille, France, [5]Dermatology, Grenoble Hospital, La Tronche, France, [6]Dermatology, Montpellier Hospital, Montpellier, France, [7]Department of Dermatology, Dijon University Hospital, Dijon, France, [8]Dermatology, Bordeaux St. André Hospital, Bordeaux, France, [9]Dermatology, Nice Hospital, Nice, France, [10]Dermatology, AP-HP Ambroise Paré Hospital, Boulogne-Billancourt, France, [11]Dermatology, AP-HP Bichat Hospital, Paris, France, [12]Dermatology, Annecy Genevois Hospital, Annecy, France, [13]Dermatology, Nimes Hospital, Nimes, France, [14]Dermatology, Brest Hospital, Brest, France, [15]Dermatology, Bordeaux Saint-André Hospital, Bordeaux, France, [16]Department of Medical Oncology, Eugene Marquis Center, Rennes, France, [17]Dermatology, Besançon Hospital, Besançon, France

Table: 1250P Stratified Cox regression model for RFS (N/n[a] = 870/845)

Covariate	Effect Tested	HR (95% CI)	P Value
Sex	Male/female	1.25 (1.02-1.53)	.030
T stage	1/4 2/4 3/4	0.49 (0.34-0.70)	< .001 .071 .377
		0.76 (0.56-1.02)	
		0.89 (0.69-1.15)	
Tumor ulceration	Yes/no	0.94 (0.74-1.20)	.630
N stage	1/3 2/3	0.67 (0.49-0.93)	.017 .109
		0.78 (0.58-1.06)	
In-transit metastases	Yes/no	1.05 (0.76-1.47)	.753
Melanoma subtype	Superficial spreading/other	0.73 (0.57-0.93)	.010 .321
	Nodular/other	0.88 (0.68-1.13)	

[a]N/n = total population/patients with data available for all covariates.

1250P Estimate of long-term relapse-free survival (RFS) and analysis of baseline factors associated with RFS in the COMBI-AD trial

R. Dummer[1], D. Schadendorf[2], A. Hauschild[3], M. Santinami[4], V.G. Atkinson[5], M. Mandala[6], V. Chiarion Sileni[7], J. Larkin[8], M.S. Nyakas[9], C. Dutriaux[10], A. Haydon[11], L. Mortier[12], C. Robert[13], J. Schachter[14], X. Feng[15], E. de Jong[16], B. Mookerjee[15], R. Kefford[17], J.M. Kirkwood[18], G.V. Long[19]

[1]Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zurich, Switzerland, [2]Department of Dermatology, University Hospital Essen, Essen, Germany, [3]Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany, [4]Melanomi e Sarcomi, Fondazione Istituto Nazionale Tumori, Milan, Italy, [5]Division of Cancer Services, Princess Alexandra Hospital, Gallipoli Medical Research Foundation, University of Queensland, Queensland, Australia, [6]Division of Oncology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy, [7]Melanoma Oncology Unit, Veneto Oncology Institute, Padua, Italy, [8]Department of Medical Oncology, Royal Marsden NHS Foundation Trust, London, UK, [9]Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway, [10]Service de Dermatologie et Dermatologie Pédiatrique, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France, [11]Department of Medical Oncology, The Alfred Hospital, Melbourne, Australia, [12]Service de Dermatologie, Université de Lille, INSERM U 1189, Lille, France, [13]Department of Medicine, Institute Gustave Roussy, Paris, France, [14]Division of Oncology, Ella Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Israel, [15]Global Clinical Program, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [16]Global Medical Affairs Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [17]Department of Medical Oncology, Macquarie University, Melanoma Institute Australia, Westmead Hospital, and The University of Sydney, Sydney, Australia, [18]Melanoma Program, UPMC Hillman Cancer Center, & Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA, [19]Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, North Sydney, Australia

Background: Adjuvant therapy with dabrafenib plus trametinib (D + T) for 12 months significantly reduced the risk of relapse or death vs placebo (Pbo; HR, 0.47; P < .001) in patients (pts) in the COMBI-AD trial with resected BRAF V600–mutant stage III melanoma (NCT01682083), leading to the recent US FDA approval in this indication. We used a cure-rate model to estimate long-term RFS benefit and explore the association of baseline factors with RFS to better characterize pts likely to benefit from adjuvant treatment.

Methods: COMBI-AD randomized pts with completely resected BRAF V600E/K–mutant stage III melanoma to receive adjuvant D (150 mg twice daily) + T (2 mg once daily) or Pbo for 12 months. Long-term RFS (proportion of pts who did not experience an event) was estimated using a Weibull cure-rate model. Baseline covariates were analyzed using a stratified Cox regression model for RFS, with P values calculated using a Wald χ^2 test. AJCC 7th edition criteria were used for pt staging at baseline.

Results: Eight hundred seventy pts were enrolled (D + T, n = 438; Pbo, n = 432). The median follow-up was 2.8 years. Estimation of long-term RFS using a cure-rate model showed a 55% (95% CI, 49%-61%) long-term RFS rate in the D + T arm vs 38% (95% CI, 33%-43%) in the Pbo arm. Evaluation of the association between baseline disease characteristics and RFS demonstrated that lower T stage, lesser nodal involvement, and a superficial spreading melanoma subtype were independently associated with better RFS (Table). Conversely, tumor ulceration and the presence of in-transit metastases were not associated with RFS. With respect to baseline patient demographics, an association was observed between female sex and RFS benefit (P = .030).

Conclusions: The results of the long-term RFS analysis suggest potential long-term RFS in > 50% of pts treated with D + T. Lower T stage and less nodal involvement at baseline were associated with better RFS.

Clinical trial identification: NCT01682083.

Editorial acknowledgement: Medical writing assistance was provided by Michael Demars, PhD (ArticulateScience LLC), funded by Novartis Pharmaceuticals Corporation.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: R. Dummer: Intermittent, consulting, advisor: Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma outside the submitted work. D. Schadendorf: Personal fees: Amgen, Boehringer Ingelheim, Leo Pharma, Roche, Novartis, Incyte, Regeneron, 4SC, AstraZeneca, Bristol-Myers Squibb, MS, Pierre Fabre, Merck-EMD, Pfizer, Philiogen, Array; Patients' fees to institution: MSD, Roche, Novartis, Regeneron, Brisol-Myers Squibb, Merck-EMD, Philiogen. A. Hauschild: Consultancy: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Philogen, Pierre Fabre, Provectus, Regeneron, Roche, OncoSec; Research funding: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Philogen, Pierre Fabre, Provectus, Regeneron, Roche; Honoraria: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Philogen, Pierre Fabre, Provectus, Roche. V.G. Atkinson: Consulting or advisory role: Bristol-Myers Squibb, MSD, Novartis, Merck Serono, Pierre Fabre; Honoraria: Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Merck Serono; Speakers' bureau: Bristol-Myers Squibb, MSD, Novartis, Roche; Travel, accommodations, expenses: Bristol-Myers Squibb; . M. Mandala: Research funding, Honoraria, Speakers bureau: Novartis, Roche. V. Chiarion Sileni: Consultancy: Bristol-Myers Squibb, MSD, Novartis, Pierre-Fabre, Merck Serono. J. Larkin: Consultancy, Honoraria: Eisai, Bristol-Myers Squibb, MSD, GlaxoSmithKline, Kymab, Pfizer, Novartis, Roche, Genentech, Secarna, Pierre-Fabre, EUSA Pharma; Research funding: Bristol-Myers Squibb, MSD, Novartis, Pfizer. M.S. Nyakas: Honoraria (institution) for advisory board: Novartis, Incyte. C. Dutriaux: Consultancy: Bristol-Myers Squibb, MSD; Membership on board of directors or advisory committee: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD; Clinical trials investigator: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD, Amgen. A. Haydon: Honoraria: Novartis. L. Mortier: Research funding: Novartis. C. Robert: Advisory board participation: Merck, MSD, Novartis, Roche. J. Schachter: Honoraria: Bristol-Myers Squibb, MSD; Travel, accommodations, expenses: Bristol-Myers Squibb. X. Feng, E. de Jong: Employee: Novartis. B. Mookerjee: Employee: Novartis; Stock ownership: Novartis, GlaxoSmithKline, AstraZeneca. R. Kefford: Membership on board of directors or advisory committees: Bristol-Myers Squibb, Amgen, Merck, Novartis, Teva; Conference travel: Bristol-Myers Squibb, Amgen. J.M. Kirkwood: Consultancy: Bristol-Myers Squibb, Novartis, Array Biopharma, Merck, Roche, Amgen, Immunocore, Prometheus; Research funding: Merck. G.V. Long: Consultancy: Amgen, Bristol-Myers Squibb, Merck MSD, Novartis, Roche, Pierre-Fabre, Array; Honoraria: Bristol-Myers Squibb, MSD, Roche, Novartis, Incyte. All other authors have declared no conflicts of interest.

1251P Adverse events (AEs) over time in patients (pts) treated with adjuvant dabrafenib plus trametinib (D + T) or placebo (Pbo) in the COMBI-AD trial

V.G. Atkinson[1], A. Hauschild[2], M. Santinami[3], M. Mandala[4], V. Chiarion Sileni[5], J. Larkin[6], M.S. Nyakas[7], C. Dutriaux[8], A. Haydon[9], L. Mortier[10], C. Robert[11], J. Schachter[12], D. Schadendorf[13], X. Feng[14], E. de Jong[15], B. Mookerjee[14], R. Kefford[16], R. Dummer[17], J.M. Kirkwood[18], G.V. Long[19]

[1]Division of Cancer Services, Princess Alexandra Hospital, Gallipoli Medical Research Foundation, University of Queensland, Queensland, Australia, [2]Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany, [3]Melanomi e Sarcomi, Fondazione Istituto Nazionale Tumori, Milan, Italy, [4]Division of Oncology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy, [5]Melanoma Oncology Unit, Veneto Oncology Institute, Padua, Italy, [6]Department of Medical Oncology, Royal Marsden NHS Foundation Trust, London, UK, [7]Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway, [8]Service de Dermatologie et Dermatologie Pédiatrique, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France, [9]Department of Medical Oncology, The Alfred Hospital, Melbourne, Australia, [10]Service de Dermatologie, Université de Lille, INSERM U 1189, Lille, France, [11]Department of Medicine, Institute Gustave Roussy, Paris, France, [12]Division of Oncology, Ella Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Israel, [13]Department of Dermatology, University Hospital Essen, Essen, Germany, [14]Global Clinical Program, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [15]Global Medical Affairs Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [16]Department of Medical Oncology, Macquarie University, Melanoma Institute Australia, Westmead Hospital, and The University of Sydney, Sydney, Australia, [17]Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zurich, Switzerland, [18]Melanoma Program, UPMC Hillman Cancer Center, & Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA, [19]Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia

Background: In COMBI-AD (NCT01682083), adjuvant D + T led to a significant improvement in relapse-free survival vs Pbo in pts with resected BRAF V600–mutant stage III melanoma supporting recent US FDA approval in this indication. There were no new safety signals; however, a higher rate of permanent discontinuation due to AEs was observed compared with metastatic disease (26% [10% due to grade 3/4 AEs]); pyrexia (9%) and chills (4%) were most common. Here we further characterize AEs in COMBI-AD.

Methods: COMBI-AD was a randomized, double-blind, Pbo-controlled phase III trial comparing 12 mo of adjuvant D (150 mg twice daily) + T (2 mg once daily) vs Pbo in pts with resected BRAF V600E/K–mutant stage III melanoma. AEs were graded according to CTCAE v4.0. To assess AEs over time, exposure-adjusted AE rates (no. of occurrences/pt/3-mo exposure) were calculated over 3-mo intervals.

Results: Although most pts in both arms experienced ≥ 1 AE, the majority of AEs reported were low grade (eg, pyrexia [% of pts in D + T arm]: grade 1 [29%], grade 2 [29%], grade 3 [5%], grade 4 [< 1%]). In the first 3 mo of treatment, the exposure-adjusted AE rate of any event in pts treated with D + T was 6.14 occurrences/pt/3-mo exposure. However, the AE rates declined substantially with increased time on treatment (3 to < 6 mo [2.58]; 6 to < 9 mo [1.80]; 9 to < 12 mo [1.65]). Similar results were observed in pts in the Pbo arm, albeit at lower rates. Adjusted AE rates for the 10 most common AEs observed in COMBI-AD in the D + T arm also declined after the initial 3 mo (Table). Results were similar in pts who completed 12 mo of treatment.

Table: 1251P AE occurrences per patient per 3-month exposure

Preferred Term	Dabrafenib + Trametinib (n = 435)				Placebo (n = 432)			
	0 to < 3 mo	3 to < 6 mo	6 to < 9 mo	9 to < 12 mo	0 to < 3 mo	3 to < 6 mo	6 to < 9 mo	9 to < 12 mo
Pyrexia	1.26	0.65	0.50	0.45	0.08	0.05	0.05	0.02
Fatigue	0.53	0.17	0.10	0.13	0.27	0.09	0.05	0.04
Nausea	0.49	0.14	0.08	0.09	0.20	0.07	0.06	0.05
Headache	0.50	0.17	0.13	0.12	0.27	0.10	0.09	0.07
Chills	0.55	0.29	0.21	0.14	0	0	0	0
Diarrhea	0.32	0.11	0.09	0.10	0.14	0.08	0.06	0.05
Vomiting	0.32	0.13	0.09	0.08	0	0	0	0
Arthralgia	0.30	0.12	0.07	0.07	0.09	0.05	0.06	0.05
Rash	0.26	0.07	0.10	0.08	0.08	0.04	0.03	0.02
Cough	0.14	0.04	0.03	0.01	0	0	0	0

Conclusions: These results show that most AEs with adjuvant D + T occurred during the first 3 mo of treatment and declined thereafter, highlighting the importance of AE management early during treatment to prevent premature discontinuations and allow patients to complete 1 year of adjuvant treatment.

Clinical trial identification: NCT01682083.

Editorial acknowledgement: Medical writing assistance was provided by Michael Demars, PhD (ArticulateScience LLC), funded by Novartis Pharmaceuticals Corporation.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: V.G. Atkinson: Consulting or advisory role: Bristol-Myers Squibb, MSD, Novartis, Merck Serono, Pierre Fabre; Honoraria: Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Merck Serono; Speakers' bureau: Bristol-Myers Squibb, MSD, Novartis, Roche; Travel, accommodations, expenses: Bristol-Myers Squibb. A. Hauschild: Consultancy: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Philogen, Pierre Fabre, Provectus, Regeneron, Roche, OncoSec; Research funding: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Philogen, Pierre Fabre, Provectus, Regeneron, Roche; Honoraria: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Philogen, Pierre Fabre, Provectus, Roche. M. Mandala: Research funding, Honoraria, Speakers bureau: Novartis, Roche. V. Chiarion Sileni: Consultancy: Bristol-Myers Squibb, MSD, Novartis, Pierre-Fabre, Merck Serono. J. Larkin: Consultancy and honoraria: Eisai, Bristol-Myers Squibb, MSD, GlaxoSmithKline, Kymab, Pfizer, Novartis, Roche, Genentech, Secarna, Pierre-Fabre, EUSA Pharma; Research funding: Bristol-Myers Squibb, MSD, Novartis, Pfizer. M.S. Nyakas: Honoraria (institution) for advisory board: Novartis, Incyte. C. Dutriaux: Consultancy: Bristol-Myers Squibb, MSD; Membership on board of directors or advisory committee: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD; Clinical trials investigator: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD, Amgen. A. Haydon: Honoraria: Novartis. L. Mortier: Research funding: Novartis. C. Robert: Advisory board: Merck, MSD, Novartis, Roche. J. Schachter: Honoraria: Bristol-Myers Squibb, MSD; Travel, accommodations, expenses: Bristol-Myers Squibb. D. Schadendorf: Personal fees: Amgen, Boehringer Ingelheim, Leo Pharma, Roche, Novartis, Incyte, Regeneron, 4SC, AstraZeneca, Bristol-Myers Squibb, MS, Pierre Fabre, Merck-EMD, Pfizer, Philiogen, Array; Patients' fees to institution: MSD, Roche, Novartis, Regeneron, Brisol-Myers Squibb, Merck-EMD, Philiogen. X. Feng, E. de Jong: Employee: Novartis. B. Mookerjee: Employment: Novartis; Stock ownership: Novartis, GlaxoSmithKline, AstraZeneca. R. Kefford: Membership on board of directors or advisory committees: Bristol-Myers Squibb, Amgen, Merck, Novartis, Teva; Conference travel: Bristol-Myers Squibb, Amgen. R. Dummer: Intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma outside the submitted work. J.M. Kirkwood: Consultancy: Bristol-Myers Squibb, Novartis, Array Biopharma, Merck, Roche, Amgen, Immunocore, Prometheus; Research funding: Merck. G.V. Long: Consultancy: Amgen, Bristol-Myers Squibb, Merck MSD, Novartis, Roche, Pierre-Fabre, Array; Honoraria: Bristol-Myers Squibb, MSD, Roche, Novartis, Incyte. All other authors have declared no conflicts of interest.

1252P Management of melanoma recurrence following adjuvant anti-PD1 therapy

C. Owen[1], D. Palmieri[2], A. Guminski[3], M.S. Carlino[4], A.M. Menzies[5], G.V. Long[6]

[1]Melanoma Medical Oncology, Melanoma Institute Australia, Sydney, Australia, [2]Medical Oncology, Westmead Hospital, Westmead, Australia, [3]Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, North Sydney, Australia, [4]Medical Oncology, The Crown Princess Mary Cancer Centre, Melanoma Institute Australia, Sydney University, Westmead, Australia, [5]Medical Oncology, Melanoma Institute Australia, University of Sydney, North Sydney, Australia, [6]Medical Oncology, Melanoma Institute Australia, University of Sydney, North Sydney, Australia

Background: Anti-PD1 immunotherapy prolongs recurrence-free survival when used as adjuvant therapy in high-risk resected melanoma. To date, detailed data on nature and management of recurrences following adjuvant anti-PD1 therapy are lacking.

Methods: All patients with resected stage III or IV melanoma who received adjuvant anti-PD1-based therapy (pembrolizumab or nivolumab) at two sites since 2015 and had a melanoma recurrence were included. Disease characteristics prior to adjuvant therapy, adjuvant treatments received, timing and nature of recurrences, and subsequent local and systemic management and their outcomes were examined.

Results: 28 patients (pts) had a melanoma recurrence during or following adjuvant anti-PD1 therapy (including 5 on nivolumab/ipilimumab combination). Prior to adjuvant therapy, 26 patients had stage III (13 IIIB, 12 IIIC, 1 IIID), 2 had resected stage IV melanoma, 16 were male, median age 59 years, and 12 were BRAF V600 mutation positive (11 wildtype, 5 unknown). 22 (79%) recurred during adjuvant therapy, 6 recurred following cessation of therapy (1 after completing 12 months, 4 after ceasing early for toxicity, 1 withdrew consent). Median time to recurrence from surgery was 6.8mo (range 2.8-28.2). 15 recurrences were detected clinically and 13 on 3-monthly imaging. 13 (46%) recurrences were loco-regional only, and 15 distant (2 brain). 12 (43%) patients were treated with surgery at recurrence (10 local, 1 brain and 1 lung metastasis) to no evidence of disease, and 6 have subsequently recurred. Data on systemic therapy after recurrence (either 1st relapse or 2nd after salvage surgery) are in the Table. 3 of 17

(18%) treated with systemic therapy after recurrence have progressed. 1 (4%) patient has died, 9 months after recurrence.

Table: 1252P

Systemic treatment	N	Best RECIST response				
		CR	PR	SD	PD	Not reached first scan
BRAF/MEKi	7	1	3	0	1	2
Anti-PD1	3	0	0	0	2	1
Combination anti-PD1/-CTLA-4	4	1	1	0	0	2
Combination anti-PD1/-LAG-3	2	0	0	0	1	1
MEK+CDK4/6i	1	0	0	0	1	0
Total	17	2	4	0	5	6

Conclusions: These data are the first to demonstrate the utility of salvage therapy for pts who progress early despite adjuvant anti-PD1. Early data suggest that this is a challenging group, likely to require multimodal treatment. Updated analyses will be presented.

Legal entity responsible for the study: Melanoma Institute Australia.

Funding: Has not received any funding.

Disclosure: M.S. Carlino: Consultant advisor: Novartis, BMS, Merck MSD, Amgen, Pierre-Fabre. A.M. Menzies: Consultant advisor: BMS, Merck MSD, Novartis, Pierre-Fabre, Roche. G.V. Long: Consultant advisor: Amgen, Array, BMS, Merck MSD, Novartis, Pierre-Fabre, Roche. All other authors have declared no conflicts of interest.

1253P High response rate with T-VEC in early metastatic melanoma (stage IIIB/C-IVM1a)

V. Franke[1], D.M.S. Berger[2], W.M.C. Klop[2], B. van der Hiel[3], B.A. van de Wiel[4], S. Ter Meulen[1], M. Wouters[1], W. van Houdt[5], A.C.J. van Akkooi[6]

[1]Surgical Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands, [2]Head and Neck Surgery and Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands, [3]Nuclear Medicine, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands, [4]Pathology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands, [5]Surgical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [6]Surgical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: Talimogene laherparepvec (T-VEC) is a modified herpes simplex virus, type 1 (HSV-1), which can be administered intralesionally in patients with stage IIIB/C-IVM1a unresectable melanoma (EMA label). The phase 3 OPTiM registration study showed an overall response rate (ORR) of 26%.

Methods: Since approval of T-VEC in the Netherlands in December 2016, 35 eligible patients started treatment with T-VEC monotherapy at the Netherlands Cancer Institute. We included 23 patients with a follow up time $\geq$6 months. Analysis of overall response rate (ORR), adverse events (AE), prior treatment for melanoma and baseline characteristics, documented in a prospectively maintained database. Besides clinical evaluation, in this study we used PET-CT and histological biopsies for response evaluation.

Results: The median follow-up was 11.3 months. Of 23 patients, 12 (52.2%) had a complete response (CR) as their best response, all except for one ongoing after stopping treatment. As their best response, 7 (30.4%) patients had a partial response (PR), 2 (8.7%) patients had a mixed response and 2 (8.7%) patients showed progressive disease (PD). ORR for the analyzed cohort was 82.6%. Disease Control Rate (DCR) was 91.3%. At baseline, the mean number of lesions was between 5 and 50 lesions. Grade 1-2 AE's occurred in all patients. Mostly, these consisted of fatigue, influenza-like symptoms and injection site pain. 1 patient had to pause treatment due to $\geq$grade 3 AE (colitis). Prior treatment was documented: all 23 patients underwent surgical resection, 13 isolated limb perfusion (56.5%), 1 targeted therapy (4.3%), 2 immunotherapy (8.7%), 2 radiotherapy (8.7%). Prior treatment did not influence response or toxicity of T-VEC. PET-CT and biopsies proved to be a clinically useful tool to evaluate treatment response for T-VEC monotherapy, confirming pCR or PD to stage IV disease requiring systemic treatment.

Conclusions: ORR for T-VEC monotherapy at our institute was 82.6% with 52.2% achieving a CR. This prospective study for T-VEC in early metastatic (stage IIIB/C-IVM1a) melanoma demonstrated superior results to the phase 3 OPTiM study and confirms the role of oncolytic immunotherapy for melanoma.

Legal entity responsible for the study: Alexander C.J. van Akkooi.

Funding: Has not received any funding.

Disclosure: V. Franke: Travel grant, Research funding: Amgen. A.C.J. van Akkooi: Honoraria: Amgen, Novartis, MSD/Merck; Travel cost: Amgen, Novartis, MSD/Merck. All other authors have declared no conflicts of interest.

1254P Neoadjuvant cytoreductive treatment with BRAF/MEK inhibition of prior unresectable regionally advanced melanoma to allow complete surgical resection, REDUCTOR trial

S. Blankenstein[1], M.W. Rohaan[2], W.M.C. Klop[3], B. van der Hiel[4], B. van de Wiel[5], D. Peeper[6], A.C.J. van Akkooi[1], J.B.A.G. Haanen[7]

[1]Surgical oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [2]Medical Oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, [3]Head and Neck Surgery and Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital (NKI-AVL), Amsterdam, Netherlands, [4]Nuclear medicine, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [5]Pathology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [6]Molecular Oncology and Immunology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [7]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: The aim of this trial is to evaluate the potency of short-term neoadjuvant cytoreductive therapy with dabrafenib and trametinib (BRAF and MEK inhibitor respectively) to allow radical surgical resection in patients with unresectable BRAF-mutated, locally advanced stage III or oligometastatic stage IV melanoma.

Methods: A total of 25 patients with BRAF-mutated, unresectable locally advanced stage III or oligometastatic stage IV ($\leq$3 metastases) melanoma will be treated with dabrafenib and trametinib for 8 weeks. Response evaluation by positron emission tomography/computed tomography (PET/CT) will occur at 2 and 8 weeks. If sufficient downsizing occurs, surgical resection will be performed. Biopsies for translational research will be taken at baseline and 2 weeks. The dissection specimen will be stored at 8 weeks.

Results: Currently 17 patients have been included. Of these, 2 patients showed PD upon treatment and did not proceed to surgery. In 14/15 (93%) patients resection was possible after neoadjuvant treatment, of which 13 (93%) were R0 resections. Median follow-up time is 22 months with a median recurrence free survival of 9 months in patients undergoing surgery. The 1-year overall survival (OS) was 88% and 2-year OS 59%. Median OS was not reached. Metabolic response rates (RR) on PET/CT at 8 weeks were: 4 (24%) CR, 11 (65%) PR, 0 (0%) SD, 2 (12%) PD. Pathologic RR differed: 6 (35%) CR, 5 (29%) PR, 3 (19%) SD, 0 (0%) PD and in 3 patients (18%) no pathologic response was measured, since no resection was performed. Most patients (82%) experienced any toxicity, of which the majority (64%) was grade 1 and the most common reported toxicity was fever. Grade 3 toxicity occurred in 2 patients (12%).

Conclusions: Neoadjuvant dabrafenib and trametinib shows to be a potent cytoreductive treatment, allowing radical resection of metastases in 13/17 (76%) patients with prior unresectable locally advanced melanoma. Patients with no recurrence remained disease-free for a prolonged period of time. If there was recurrent disease, this usually occurred within months after surgery and this may present an opportunity for further tailored adjuvant therapy.

Clinical trial identification: EudraCT: 2013-002616-28

Legal entity responsible for the study: Netherlands Cancer Institute, Amsterdam, The Netherlands.

Funding: Netherlands Cancer Institute and Novartis.

Disclosure: D. Peeper: Research support: BMS. A.C.J. van Akkooi: Consulting or advisory role: Amgen, Novartis, MSD Oncology, Merck Research funding: Amgen, Novartis; Travel, accomodations, expenses: Amgen, Novartis, MSD Oncology, Merck. J.B.A.G. Haanen: Compensation to NKI for advisory roles: BMS, Merck, Roche, Neon Therapeutics, Pfizer, Ipsen; Grants to NKI: BMS, Merck, Novartis, Neon Therapeutics. All other authors have declared no conflicts of interest.

1255P Impact of intralesional interleukin 2 (IL2) for in-transit melanoma in two Canadian centres

D.S. Ernst[1], V. Hayward[2], H. McConkey[3], X. Teng[4], E. Saettler[5], T. Cheng[6], C. Temple-Oberle[7], F. Gwadry-Sridhar[8]

[1]Department of Oncology, London Regional Cancer Program, London, ON, Canada, [2]Department of Surgery, University of British Columbia, Kelowna, BC, Canada, [3]Global Melanoma Research Network, London, ON, Canada, [4]Data Science, Pulse Infoframe Inc., London, ON, Canada, [5]Department of Surgery, Western University, London, ON, Canada, [6]Departemnt of Oncology, University of Calgary, Calgary, AB, Canada, [7]Department of Surgery, University of Calgary, Calgary, AB, Canada, [8]Department Computer Science, Western University, London, ON, Canada

Background: In-transit (IT) melanoma is a form of metastatic disease that is associated with high morbidity and is often refractory to treatment. Intralesional (IAL) IL2 has been increasingly utilized to obtain loco-regional control. This study utilizes a national

registry to evaluate response and duration of response of standardized IAL therapy at tertiary centres in 2 provinces.

Methods: Patients (pts) receiving IAL IL2 between 2000 and 2017 were included. Data regarding patient demographics, stage, extent of disease, and all treatments were collected. All pts received a median IL2 dose of 12 million IU given as an IAL injection every 2 to 4 weeks repeated 2 to 8 times to complete a session.

Results: A total of 87 pts aged 21 to 94 (mean: 69 yrs) were included. IT disease was located in the following areas: limbs in 68 pts (79%), head and neck in 13 pts (15%) and trunk in 5 pts (6%). 20% of pts developed IT within 3 months of primary diagnosis, 69% developed IT after 6 months and 11% after 3 years. IT lesions per individual ranged from 1 to 40+; 45% had >10 lesions. Patients had a complete response rate of 32% (28 pts) and a partial response rate of 38% (33 pts). 27 (31%) pts experienced a recurrence after their 1st IL2 session, with a mean of 225 days (median: 204). Of these pts, 15 (56%) pts developed loco-regional recurrences, while 6 (22%) developed distant metastases and 6 (22%) had both distant and loco-regional recurrences. 27 pts (31%) received systemic treatment for metastatic disease. 18 (21%) pts died of disease, while 3% died of other causes while disease was present. 7 (8%) died of other causes with disease status unknown, and 25 (29%) and 34 (39%) are recorded alive with more than a year (1 to 11 yrs) or less than a year follow up, respectively. No grade 3 or 4 toxicity was experienced by pts who received IL2 therapy. On multi-variant analysis, age, extent of disease and prior systemic therapy did not impact overall response (X^2 test, $p > 0.05$).

Conclusions: IAL IL2 appears to be an effective therapeutic option for pts with advanced melanoma and IT disease, with an overall response rate of 70%. With further long-term follow up of these pts, the impact on overall survival can be determined.

Legal entity responsible for the study: Global Melanoma Research Network.

Funding: Global Melanoma Research Network.

Disclosure: All authors have declared no conflicts of interest.

1256P Combined ipilimumab and nivolumab first-line and after BRAF-directed targeted therapies in advanced melanoma patients

H.C. Dearden[1], R. Mason[2], B. Nguyen[3], J.A. Soon[4], J.L. Smith[5], M. Randhawa[6], A. Mant[7], L. Warburton[3], S. Lo[1], T. Meniawy[3], A. Guminski[1], P. Parente[7], S. Ali[6], A. Haydon[4], G.V. Long[1], M.S. Carlino[5], M. Millward[3], V.G. Atkinson[2], A.M. Menzies[1]

[1]Medical Oncology, Melanoma Institute Australia, University of Sydney, North Sydney, Australia, [2]Medical Oncology, Princess Alexandra Hospital, Woolloongabba, Australia, [3]Medical Oncology, Sir Charles Gairdner Hospital, Perth, Australia, [4]Medical Oncology, The Alfred Hospital, Melbourne, Australia, [5]Medical Oncology, Westmead Hospital, Westmead, Australia, [6]Medical Oncology, The Canberra Hospital, Garran, Australia, [7]Medical Oncology, Box Hill Hospital-Eastern health, Box Hill, Australia

Background: Combination ipilimumab and nivolumab is a highly active systemic therapy for metastatic melanoma but can cause significant toxicity. How best to integrate this combination into clinical practice, in real-world patients, and in the setting of BRAF targeted therapy, is not clear. We sought to explore the safety and efficacy of combination ipilimumab and nivolumab in such a population.

Methods: Consecutive patients with unresectable stage IIIC/IV melanoma commenced on ipilimumab and nivolumab via an early access scheme across 10 tertiary melanoma institutions in Australia were identified retrospectively. Data collected included demographics, prior and subsequent systemic treatments, toxicity, RECIST response and survival outcomes.

Results: 152 patients were included for analysis, including 60 (39%) treatment-naïve and 33 (22%) who had failed first-line BRAF/MEK inhibitors and then treated with combination therapy second-line. In the whole cohort, most patients had a high AJCC M stage (63% M1c, 26% M1d) and elevated LDH (55%), with similar distribution of adverse features in the treatment naïve and BRAF/MEK failure subgroups. Treatment-related adverse events occurred in 102 (67%) patients, grade 3-5 in 38% (1 death from immune myocarditis). The objective response rate was 41% in the whole cohort, 57% (17% complete) in treatment naïve, and only 21% (3% complete) in BRAF/MEK failure patients. Median progression-free survival was 4.0 months (95% CI, 3.0 to 6.0) in the whole cohort, 11.0 months (95% CI, 6.0 - NR) in treatment-naïve patients, and 2.0 months (95% CI, 1.4 - 4.6) in BRAF/MEK failure patients.

Conclusions: Combination ipilumumab and nivolumab can be used safely and effectively in a real-world population, including in patients that are heavily pre-treated and those with adverse disease characteristics. While first-line efficacy appears comparable to that seen in trial populations, BRAF-mutant patients who have failed prior BRAF/MEK inhibitors are less likely to respond, supporting first-line use of combination immunotherapy in the majority of newly diagnosed poor prognosis metastatic melanoma patients.

Legal entity responsible for the study: A. Menzies.

Funding: Has not received any funding.

Disclosure: H.C. Dearden: Travel expenses support: MSD. R. Mason: Travel expenses support: Bristol-Myers Squibb. J.A. Soon: Travel expenses support: Pfizer. M. Randhawa: Travel expenses support: Merck. A. Mant: Consultancy: Novartis. L. Warburton: Travel expenses support: MSD. T. Meniawy: Honoraria; Consultancy: AstraZeneca/MedImmune; Research funding: Incyte, BeiGene, AstraZeneca/MedImmune, Regeneron, Bayer, Roche/Genetech, Bristol Myers Squibbs, Merck Serono Ltd; Travel expenses support: Roche/Genetech. A. Guminski: Consultancy for Roche, Regeneron, Eisai, Sun Pharma, Bristol Myers Squibbs; Travel and expenses support: Sun Pharma, Bristol Myers Squibb. S. Ali: Honoraria and consultancy: Bristol Myers Squibb. G.V. Long: Consultancy: Bristol-Myers Squibb, Roche/Genentech, Amgen, Merck, Novartis, Array BioPharma, Pierre Fabre, Incycte; Honoraria: Bristol-Myers Squibb, Merck, Roche, Novartis, Incycte. M.S. Carlino: Consultancy: Bristol-Myers Squibb, MSD, Amgen, Novartis, Pierre Fabre; Honoraria: Bristol-Myers Squibb, MSD, Novartis. M. Millward: Consultancy: AstraZeneca, MSD, Roche, Bristol Myers Squibbs; Travel expenses support: Roche, MSD, Bristol Myers Squibb. V.G. Atkinson: Honoraria; Novartis, Bristol Myers Squibbs; Consultancy: Novartis, Pierre Fabre, Bristol Myers Squibbs, Merck Serono Ltd, MSD; Travel expenses support: Bristol Myers Squibb. A.M. Menzies: Consultancy: MSD, Novartis, Pierre Fabre, Bristol-Myers Squibb, Roche; Travel expenses support: Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1257P KEYNOTE-151: A phase Ib study of second-line pembrolizumab (Pembro) for Chinese patients (pts) with advanced or metastatic melanoma

L. Si[1], X. Zhang[2], Y. Shu[3], H. Pan[4], D. Wu[5], J. Liu[6], F. Lou[4], X. Wang[7], X. Wen[2], Y. Gu[3], L. Zhu[3], S. Lan[3], X. Cai[6], Y. Zhou[8], J. Ge[9], J. Li[9], H. Wu[9], J. Guo[7]

[1]Department of Renal Cancer and Melanoma, Peking University Cancer Hospital-Beijing Cancer Hospital, Beijing, China, [2]Biotherapy Centre, Sun Yat-sen University Cancer Centre, Guangzhou, China, [3]Oncology Department, Jiangsu Province Hospital, NanJing, China, [4]Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China, [5]Cancer Center, The First Hospital of Jilin University, Jilin, China, [6]Oncology, The First Affiliated Hospital of Dalian Medical University, Liaoning Sheng, China, [7]Urology and Melanoma, Beijing Cancer Hospital, Beijing, China, [8]Medical Oncology, MSD China, Shanghai, China, [9]Medical Oncology, MSD China, Beijing, China

Background: Pembro shows robust antitumor activity and a avourable safety profile in metastatic melanoma. Checkpoint inhibition has not been well characterized in Chinese pts. We present the first results of KEYNOTE-151 (NCT02821000), which was conducted to evaluate the safety and efficacy of second-line pembro in Chinese pts with advanced melanoma.

Methods: Chinese pts aged ≥18 y with previously treated advanced melanoma and measurable disease per RECIST v1.1 as assessed by blinded independent central review (BICR) received pembro 2 mg/kg Q3W for 35 cycles (~2 y) or until confirmed disease progression, intolerable toxicity, or pt/investigator decision to discontinue. Primary end points were ORR per RECIST v1.1 assessed by BICR and safety. Objective response was confirmed by repeat radiographic assessment ≥4 wk from first response. Key secondary end points included DOR and PFS per RECIST v1.1 assessed by BICR and OS. Data cutoff was Dec 27, 2017.

Results: 103 pts were enrolled; median age was 52.0 y (range, 22.0-77.0); 42.7% were male; 51.5% had PD-L1–positive tumors; 37.9% had acral melanoma; 14.6% had mucosal melanoma. Median follow-up was 7.9 mo (range, 5.6-13.1). Confirmed CR and PR were achieved in 1 pt and 16 pts, for an ORR of 16.7% (95% CI, 10.0-25.3). 22 (21.6%) pts had SD. DCR was 38.2% (95% CI, 28.8-48.4). ORR was 15.8% (95% CI, 6.0-31.3%) for the acral subtype and 13.3% (95% CI, 1.7-40.5%) for the mucosal subtype. Median DOR for responders was 8.4 mo; 5 (65.6%) pts had a response duration ≥6 mo at data cutoff. Median OS was 12.1 mo (95% CI, 9.6-NR). Estimated OS was 75.7% at 6 mo and 50.6% at 12 mo. Median PFS was 2.8 mo (95% CI, 2.7-3.5). Estimated PFS was 20.4% at 6 mo and 11.9% at 12 mo. Treatment-related AEs (TRAEs) were reported in 87 (84.5%) pts; 9 (8.7%) experienced a grade 3-5 TRAE; 2 (1.9%) discontinued due to a TRAE; no pts died due to a TRAE.

Conclusions: Results demonstrate pembro was well tolerated, with clinically meaningful antitumor activity in Chinese pts with advanced melanoma who were treated in the second-line setting where there is no standard regimen available. The extended Kaplan-Meier curve tail indicates that treatment with pembro can provide long-term survival benefit.

Clinical trial identification: NCT02821000, first posted July 1, 2016.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Trisha Stankiewicz, PhD, of the ApotheCom Merck oncology team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: Y. Zhou, J. Ge, J. Li, H. Wu: Employee, Stockholder: MSD China. J. Guo: Research funding, Advisory board member: Merck. All other authors have declared no conflicts of interest.

1258P Baseline predictive factors for efficacy of anti-PD1 used in first line in melanoma patients: An Italian melanoma intergroup study

R. Marconcini[1], E. Tanda[2], L.A. Di Guardo[3], O. Nigro[4], P. Fava[5], A. Todisco[6], F. Morgese[7], A. Cortellini[8], E. Stroppa[9], G. Gallizzi[10], L. Festino[11], E. Grego[12], S. Quadrini[13], C. Orlandini[1], A. Nuzzo[1], S. Manacorda[1], F. Bloise[1], A. Indini[3], C. Astrua[5], A. Falcone[1]

[1]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Medical Oncology, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, [2]Department of Medical Oncology, IRCCS AOU San Martino-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [3]S.S. Oncologia Medica Melanomi, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [4]U.O. Oncologia Medica, ASST Settelaghi, Ospedale di Circolo di Varese, Varese, Italy, [5]SC Dermatologia U., AOU Città della Salute e della Scienza, Turin, Italy, [6]Medical Oncology Unit, Department of Biomedical Sciences and Clinical Oncology, University of Bari, Bari, Italy, [7]Clinica Oncologica Università Politecnica delle Marche, Azienda Ospedaliero Universitaria Umberto I, Ancona, Italy, [8]Medical Oncology, Ospedale Civile San Salvatore, L'Aquila, Italy, [9]U.O. Oncologia Medica, Ospedale "Guglielmo de Saliceto", Piacenza, Italy, [10]SC Oncologia, Ospedale SS Antonio e Biagio e C. Arrigo, Alessandria, Italy, [11]Melanoma Cancer Immunotherapy and Innovative Therapy Unit, AOU Policlinico Federico II, Naples, Italy, [12]U.O Oncologia Medica, Struttura Ospedaliera S. Chiara, Trento, Italy, [13]Oncologia Medica, Ospedale "Fabrizio Spaziani", Sora, Italy

Background: AntiPD1 Nivolumab (N) or Pembrolizumab (P) are an option for first line treatment in metastatic melanoma (MM) but predictive factors of efficacy are needed to choose between them or other treatment (antiPd1+AntiCTLA4, BRAF+MEK inhibitors (BMEi) for BRAF mutated melanoma). Many studies suggest that LDH, ECOG PS, tumor burden can identify BRAF mutated MM patients (pt) in which BMEi show better outcome. Similar data are not available for N or P in first line. We evaluate pt treated with N or P in first line in order to verify if these factors or other factors can be applyed also to antiPD1.

Methods: A retrospective multicenter study was conducted in 13 Italian Oncology Centers, evaluating MM pt treated with N or P in first line from 2016. Endpoints were OS and PFS, Kaplan Mayer and Cox regression were applied for survival analysis.

Results: 236 pt were analyzed (51% treated with N, 7% BRAF mutated). ECOG PS was 0 in 169 pt, number of metastatic sites (Nu) was less then 3 in 135 pt, in 88 pt there were not visceral metastasis (Vi), LDH was normal in 141 pt, ratio between baseline neutrophils and total leukocytes count (Fr) was less then 0.7 in 152 pt: in univariate analysis, all this factors resulted significantly associated with better OS (all $p < 0.0003$) and PFS (all $p < 0.003$), the only exeption were pt with Nu less then 3 that resulted not signficantly different in PFS then pt with higher Nu (p 0.13). In multivariate analysis all these factors were confirmed as significantly associated with better PFS and OS (all $p < 0.03$), with the exeption of Nu (p 0.22) A score was counted for every pt considering the number of favorable baseline factors present (normal LDH, ECOG PS 0, Vi 0, Fr < 0.7) 18 months-PFS was 69% in pt with all 4 favorable factors vs 41% in pt without favorables factors (p value 0.0029). 18 months-OS was 90% in pt with all four favoreble factors vs 48% in pt without favorables factors (p value<0.0001).

Conclusions: ECOG PS 0, normal LDH, Fr < 0.7, absent Vi are indipendent baseline factors associated with favorable PFS and OS of MM pt treated with N or P in first line (instead of Nu – that was found relevant for BMEi in other study). Subgroup with all these factors has a better prognosis. These data can help first line treatment choice and should be evaluated prospectively.

Legal entity responsible for the study: Italian Melanoma Intergroup I.M.I.

Funding: Has not received any funding.

Disclosure: R. Marconcini: Consultancy, Advisory board, Honoraria for speaking: BMS, MSD, Novartis, Roche. All other authors have declared no conflicts of interest.

1259P Switch to checkpoint inhibition (CPI) after targeted therapy (TT) at time of progression or during ongoing response: A retrospective analysis of patients with advanced BRAF mutated melanoma

I.L.M. Reijers, E.A. Rozeman, H. Mallo, W. Uyterlinde, S. Adriaansz, J. Lijnsvelt, S. Wilgenhof, J.V. van Thienen, J.B.A.G. Haanen, C.U. Blank

Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: The outcome of patients (pts) with BRAFV600 mutated advanced melanoma has dramatically improved by the introduction of TT and CPI. Pts responding on CPI have a high chance of long-term benefit. Pts with fast progressive disease (PD), high LDH and/or symptomatic (brain) metastasis often start with TT to induce a fast response, although most pts will relapse. Short-term TT increases intratumoral T-cell infiltration, which is diminished at PD. In addition, LDH level normalization and improvement of performance status (PS) during response to TT, might also argue for an earlier switch to CPI before PD.

Methods: We retrospectively identified pts that started treatment with TT and switched to subsequent CPI (either anti-PD-1 or anti-PD-1 plus anti-CTLA-4) at our institute. Progression was defined as radiological PD according to RECIST 1.1 or clinical PD defined by treating physician. Progression free survival (PFS) from start CPI (PFS-CPI), start TT (PFS-total) and overall survival (OS) were analyzed by Kaplan Meier methods and hazard ratio's (HR) were calculated by Cox regression analysis.

Results: In total 74 pts were included; 37 pts switched to CPI prior to PD (noPD-switch) and 37 pts switched at PD (PD-switch); 32 vs 51% had brain metastases and 41 vs 49% had an elevated LDH. Median time on TT in the noPD-switch and the PD-switch group was 3.2 and 4.5 months, respectively. PFS-CPI was 2.5 months in the noPD-switch group vs 1.2 months in the PD-switch group ($p = 0.11$). OS was superior in the noPD-switch group with a median of 30.6 vs 14.1 months ($p = 0.01$). After correcting for previous treatment, LDH, PS, brain metastasis and number of metastatic sites, HR for OS was 0.48 (95% CI 0.22–1.01). Subgroup analysis revealed that pts with brain metastasis seem to benefit most from switch prior to PD. In pts that had reinduction of TT after CPI failure, the noPD-switch group benefitted longer from this subsequent TT line, although total time of benefit on TT (before and after CPI) was the same in both groups.

Conclusions: Pts that switch to CPI prior to PD upon TT have an increased OS, which can be attributed to the benefit from CPI and not the total time on TT.

Legal entity responsible for the study: Netherlands Cancer Institute.

Funding: Has not received any funding.

Disclosure: J.V. van Thienen: Travel support: Roche. J.B.A.G. Haanen: Advisory boards: BMS, Merck, Roche, Neon Therapeutics, Pfizer, Ipsen; Grants to NKI from BMS, Merck, Novartis, Neon Therapeutics, outside the submitted work. C.U. Blank: Advisory boards: MSD, BMS, Roche, GSK, Novartis, Pfizer, Lilly; Grants: BMS, Novartis; Stock ownership: Verastem outside the submitted work. All other authors have declared no conflicts of interest.

1260P An open-label, non-randomized, phase IIIb study of trametinib in combination with dabrafenib for patients with unresectable (stage III) or distant metastatic (stage IV) BRAF V600-mutant melanoma

P. Saiag[1], C. Robert[2], J.J. Grob[3], L. Mortier[4], O. Dereure[5], C. Lebbe[6], S. Mansard[7], F. Grange[8], E-M. Neidhardt[9], T. Lesimple[10], L. Machet[11], C. Bedane[12], G. Jeudy[13], F. Aubin[14], B. Dreno[15], A. Szenik[16], A. Denden[16], C. Dutriaux[17]

[1]Department of Dermatology, AP-HP Ambroise Paré Hospital, Boulogne-Billancourt, France, [2]Department of Dermatology, Institut Gustave Roussy, Villejuif, France, [3]Department of Dermatology, Aix Marseille University and APHM University Hospital Timone, Marseille, France, [4]Department of Dermatology, Hopital Claude Huriez, Lille, France, [5]Department of Dermatology, CHU Montpellier, Montpellier, France, [6]Department of Dermatological Oncology, Hôpital Saint Louis, Paris, France, [7]Department of Dermatology, CHU Estaing, Clermont-Ferrand, France, [8]Department of Dermatology, CHU Reims - Hospital Robert-Debré, Reims, France, [9]Department of Medical Oncology, Centre Léon Bérard, Lyon, France, [10]Department of Medical Oncology, Eugene Marquis Center, Rennes, France, [11]Department of Dermatology, CHRU de Tours et Université François Rabelais de Tours, Tours, France, [12]Department of Dermatology, CHU Limoges - Hopital Dupuytren, Limoges, France, [13]Department of Dermatology, Dijon University Hospital, Dijon, France, [14]Department of Dermatology, EA3181, Besancon University Hospital, Besançon, France, [15]Department of Dermatology, Centre Hospitalier Universitaire Nantes, Nantes, France, [16]Department of Medical Oncology, Novartis Pharma - France, Rueil-Malmaison, France, [17]Derpartment of Dermatology, CHU Bordeaux Hopital St. André, Bordeaux, France

Background: Regimens combining BRAF and MEK inhibitors have revolutionized the treatment of patients with unresectable (stage III) or distant metastatic (stage IV) BRAF V600-mutant cutaneous melanoma. As only dabrafenib (D) was available in France, the objective of this study was to provide access to T and to assess, in the French population, the benefits of the combination of T (D+T) previously reported.

Methods: This single arm, open label, multicenter, non-randomized study included patients with histologically confirmed stage III unresectable or IV BRAF V600-mutant melanoma, with or without brain metastases (BM). Patients received D (150 mg twice/day) combined with T (2 mg once/day). Outcomes were overall response rate (ORR), progression-free survival (PFS), and frequencies of adverse events (AEs). Median PFS was estimated using the Kaplan-Meier method.

Results: Between March 2015 and November 2016, 914 patients were screened in 40 French centers and 856 received at least one dose of D+T. The table presents baseline characteristics. Median followup was 5.63 months. ORR was 50.2% in the overall population and 41.5% in patients with BM. Median PFS was 8.02 months (95% CI, [7.33-8.77]) in the overall population and 5.68 months (95% CI, [5.29-6.87]) in patients with BM. The safety profile was consistent with previous reports. Among AEs of special interest, pyrexia/hyperthermia was the most frequent: 38.2% (327/856) all grades; grade (G) 1 29.0%, G2 14.8%, G3 4.0% and G4 0.5%.

Table: 1260P Baseline demographic and disease characteristics

Parameter	Statistics	Total (N = 856)
Age at screening (years)	Mean (SD)	58.5 (14.8)
Sex		
Male	n (%)	474 (55.4)
Female	n (%)	382 (44.6)
ECOG PS scale at screening		
0	n (%)	531 (62.0)
1	n (%)	242 (28.3)
2	n (%)	69 (8.1)
3	n (%)	13 (1.5)
4	n (%)	1 (0.1)
Stage at screening		
II	n (%)	1 (0.1)
III unresectable	n (%)	67 (7.8)
IV	n (%)	788 (92.1)
TNM staging at screening (M) [a]		
M0	n (%)	68 (8.0)
M1a	n (%)	81 (9.5)
M1b	n (%)	88 (10.3)
M1c	n (%)	617 (72.2)
If M1c, brain metastasis [b]		
No	n (%)	342 (55.4)
Yes	n (%)	275 (44.6)
Type of BRAF mutation		
E	n (%)	727 (84.9)
K	n (%)	93 (10.9)
Other	n (%)	36 (4.2)
LDH (IU/L) [c]	Mean (SD)	377.2 (464.8)
LDH (IU/L) in classes [c]		
≤ 400	n (%)	483 (76.9)
]400 ; 800]	n (%)	100 (15.9)
>800	n (%)	45 (7.2)
Sequence of dabrafenib and trametinib		
1st sequence: patient with no prior systemic anti-cancer treatment	n (%)	449 (52.5)
2nd sequence: patient with one prior systemic anti-cancer treatment	n (%)	260 (30.4)
3rd sequence: patient with two prior systemic anti-cancer treatments	n (%)	88 (10.3)
>3rd sequence: patient with three or more prior systemic anti-cancer treatments	n (%)	59 (6.9)

Abbreviations: ECOG= Eastern Cooperative Oncology Group; PS= Performance Status; LDH= Lactate Dehydrogenase; SD= Standard Deviation. Footnotes: [a] Data was missing for 2 patients [b] Percentage based on subjects with M1c stage at screening (N = 617) [c] Based on patients with known LDH at baseline (N = 628)

Conclusions: This is, to date, the largest prospective study worldwide in BRAF V600-mutant cutaneous melanoma patients treated with the D+T combination. It confirms the efficacy and tolerability of D+T in this population, including pts with BM.

Clinical trial identification: NCT02416232.

Editorial acknowledgement: Editorial assistance in the writting of the abstract was provided by Jone Iriondo-Alberdi (PhD) of ITEC Services.

Legal entity responsible for the study: Novartis Pharma S.A.S. (France) Novartis Pharma S.A.S. (France).

Funding: Novartis Pharma S.A.S. (France).

Disclosure: P. Saiag: Advisory board: BMS, MSD, Novartis, GSK, Merck Serono, Roche, Novartis, Pierre Fabre, Amgen. C. Robert: Honoraria, Consulting, Advisory board: Amgen, BMS, Merck, Novartis, Roche, GSK. J.J. Grob: Honoraria: BMS, MSD, Roche, Novartis, Amgen, Merck, Pierre Fabre, Pfizer, Incyte; Consulting or advisory role: BMS, MSD, Roche, Novartis, Amgen, Merck, Pierre Fabre, Pfizer, Incyte; Research funding (self and institution), Travel, accomodation, expenses: BMS, Roche, MSD. L. Mortier: Honoraria: BMS, MSD, Roche, Novartis, Amgen, Merck, Incyte; Consulting or advisory role: BMS, MSD, Roche, Novartis, Amgen, Merck, Incyte; Travel, accomodations, expenses: BMS, Roche, MSD. C. Lebbe: Honoraria: BMS, MSD, Roche, Novartis, Amgen, Merck, Pierre Fabre, Pfizer, Incyte; Consulting or advisory role: BMS; Research funding (self and institution), Travel, accommodation, expenses: BMS, MSD. S. Mansard: Advisory board, Travel expenses: Novartis, BMS, MSD, Roche. E-M. Neidhardt: Advisory board: Novartis, BMS. T. Lesimple: Advisory board: Roche, Novartis, MSD, Incyte. C. Bedane: Advisory board: Novartis; Investigator: Combi I study. A. Szenik, A. Denden: Employee: Novartis. C. Dutriaux: Advisory boards, Investigator: Roche, Amgen, BMS, MSD, Merk Serono, Novartis. All other authors have declared no conflicts of interest.

1261P Loss of HLA class I expression and T-cell infiltration or PD-L1 expression are associated with different response patterns to pembrolizumab in melanoma

A. Degraeuwe[1], N. van Baren[2], F. Cornelis[3], P. van Eeckhout[4], J-F. Baurain[5]

[1]Medical Oncology, Université Catholique Louvain, Bruxelles, Belgium, [2]Institut de Duve, Université Catholique Louvain, Bruxelles, Belgium, [3]Medical Oncology, Cliniques Universitaires St. Luc, Brussels, Belgium, [4]Anatomopathologie, Cliniques Universitaires St. Luc, Bruxelles, Belgium, [5]King Albert 2 Cancer Institute, Cliniques Universitaires St. Luc, Brussels, Belgium

Background: PD-1 blockade monoclonal antibodies, nivolumab and pembrolizumab, increase quality of life and overall survival of metastatic melanoma and are today's first-line treatment of metastatic melanoma. Nevertheless, only 40% of the patients will respond to anti-PD-1 monotherapy. In the era of personalized medicine, an important stake is to identify the patients who will benefit from these treatments, which are also responsible for scare but serious side effects. We have tested several biomarkers to discriminate between responders and non-responders.

Methods: We have retrospectively analysed 18 patients treated by pembrolizumab for metastatic melanoma. Immunohistochemical staining was performed on pre-treatment metastatic tissue for antigens such as MELANA, TYR, GP100, PD-L1, CD3, CD8, IDO1, HLA class I heavy chain and β_2-microglobulin. Two reviewers assessed the staining independently. For PD-L1 testing, the MEL-score was used. For T-cell infiltration, we have quoted the presence of CD3 CD8 T cell and their location.

Results: We found that only PD-L1 expression and the presence of T-cell infiltration were associated with a better response to pembrolizumab: PD-L1 expression ($p = 0,043$), T-cell infiltration ($p = 0,025$) and T-cell location at the periphery of the tumoral nodules ($p = 0,025$). PD-L1 expression and the presence of T lymphocytes were also associated with a longer survival. The median overall survival was 31,5 months for the T-cell rich metastasis and PD-L1 high expression versus 4 months for non T-cell infiltrated tumours and 7 months for PD-L1 negative tumours. Furthermore, 50% of the metastases showed reduced or absent HLA class I expression by the tumour cells. The role of tumoral HLA loss in response and resistance to PD-1 blockade has still to be defined.

Conclusions: Although significant correlations were observed between some biomarkers and the response to anti-PD-1 therapy as described in larger studies, no predictive biomarker has currently been identified in our small series. Recent and future technical progresses will enable new studies aiming to find reliable biomarkers and to clarify the complex mechanisms of response and resistance to immune checkpoint inhibitors.

Legal entity responsible for the study: Cliniques universitaires Saint-Luc.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1262P Soluble PD-L1 as a prognostic factor in advanced acral and mucosal melanoma

X. Wang, C. Cui, J. Yu, Y. Kong, L. Si, Z. Chi, X. Sheng, L. Mao, B. Lian, B. Tang, X. Yan, J. Guo

Renal Cancer and Melanoma, Beijing Cancer Hospital, Beijing, China

Background: Elevated levels of soluble PD-L1 (sPD-L1) have been associated with worse prognosis in renal cell carcinoma and multiple myeloma. However, the regulatory roles and function of sPD-L1 in advanced melanoma are not fully understood. This study was designed to evaluate the association between circulating sPD-L1 expression and prognosis in patients with advanced acral and mucosal melanoma.

Methods: Totally 102 untreated advanced acral and mucosal melanoma patients from Peking University Cancer Hospital between Jan 2012 and Dec 2015 were enrolled in the present study. Peripheral blood samples were obtained from 40 healthy donors as control. Circulating sPD-L1 expression was tested by enzymelinked immunosorbent assay (ELISA).

Results: The advanced melanoma cohort includes 58 acral melanoma and 44 mucosal melanoma. Concentrations of sPD-L1 (2.91ng/mL) were elevated in the plasma of prior to treatment advanced melanoma patients in comparison with healthy donors (0.59ng/mL). The expression of sPD-L1 in serum was found to be highly up-regulated in 39 (38.2%) of 102 cases. The sPD-L1 concentration appeared to be significantly related with subtype (arcal 3.14 vs. mucosal 2.60 ng/mL P = 0.004). No significant association was observed between serum sPD-L1 level and other clinicopathological variables as: BRAF mutation, LDH level, tumor burden and peripheral blood CD4+/CD8+. There were no associations between sPD-L1 and chemotherapy clinical responses in our cohort. But the overall survival rates were statistically estimated with the expression of sPD-L1. The OS in this cohort with high and low up-regulated sPD-L1 expression levels was 8.50 months and 11.64 months, respectively (p = 0.022).

Conclusions: sPD-L1 was elevated in advance acral and mucosal melanoma patients and may play an important role in patients prognosis.

Legal entity responsible for the study: Peking University Cancer Hospital & Research Institute.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1263P The analysis of treatment sequencing and clinical outcomes in BRAF-positive and BRAF-negative unresectable/metastatic melanoma patients treated with systemic therapies in routine practice

A.M. Czarnecka, P. Teterycz, I. Lugowska, P. Rogala, T. Switaj, P.L. Rutkowski

Department of Soft Tissue, Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland

Background: BRAF V600 mutation was considered as a negative prognostic factor in metastatic (stage IV) melanoma patients (pts). Nowadays, two effective systemic treatment modalities - targeted therapy with BRAF+MEK inhibitors and immunotherapy are available for this group of pts contrary to BRAF-wild-type patients where only immunotherapy is used. It is unclear what is the outcome of therapy and treatment sequence in advanced melanoma patients with BRAF-positive and negative patients in the routine practice.

Methods: In this retrospective one-center study, we included 276 (134, 48.6% BRAF V600 mutated) consecutive pts with unresectable/metastatic stage III/IV melanoma treated between 01/2016 and 02/2018. Kaplan-Meier survival probability estimation and Cox's proportional hazards model were used for analysis.

Results: The first line treatment comprised of anti-PD1 antibodies (in 167 cases, i.e. all BRAF-negative and 25 BRAF-mutant pts) and BRAF/MEK inhibitors (in 109 cases BRAF+ pts). The 1-year overall survival (OS) rates were 61.6% (95% confidence interval, CI: 53.4-71.1) in BRAF-negative pts, 61.1% (95%CI: 51.8-72.1) and 77.3% (95%CI: 61.6-97.1) in BRAF-mutated pts who started BRAF/MEK inhibitors or anty-PD1 antibodies as the first line treatment, respectively. In the multivariable model adjusted for age, sex and LDH level BRAF-mutated pts who received anti-PD1 as 1st line treatment had slightly worse first line progression-free survival (HR: 1.91, 95%CI: 1.00-3.63, p = 0.05), but there were no differences in the multivariable model for OS (HR: 0.67, 95%CI: 0.28-1.58, p = 0.35).

Conclusions: The short-term outcomes of advanced melanoma patients treated with modern systemic therapies are similar independently of BRAF V600 mutation status. Numerically, the best survival rates were reached in BRAF-positive pts who received anti-PD1 antibodies as the 1st line treatment, but this effect needs to be confirmed in a larger population study.

Legal entity responsible for the study: Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw, Poland.

Funding: Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw, Poland.

Disclosure: A.M. Czarnecka: Honoraria, Speakers' bureau, Travel expenses reimbursement: Bristol-Myers Squibb, Roche, Novartis, Merck, Pfizer, GlaxoSmithKline. P. Teterycz: Honoraria, Travel expenses reimbursement: Roche, Eli Lilly, Bayer, Novartis. I. Lugowska, P. Rogala, T. Switaj: Honoraria, Speakers' bureau, Travel expenses reimbursement: Bristol-Myers Squibb, Roche, Novartis, Merck, Pfizer, GlaxoSmithKline. P.L. Rutkowski: Honoraria: Bristol-Myers Squibb, Roche, Novartis, Merck, Sharp & Dohme, GlaxoSmithKline; Paid consulting role with Bristol-Myers Squibb, Roche, Merck, Sharp & Dohme, Blueprint Medicines, Amgen; Speakers' bureau: Novartis, Pfizer, Merck, Sharp & Dohme; Institutional research funding: Bristol-Myers Squibb, Novartis; Travel expenses reimbursement: Novartis,Orphan Drugs.

1264P Long-term survivors among patients with metastatic melanoma treated with targeted agents and/or checkpoint inhibitors

H. Linardou, A. Laskarakis, A. Molfeta, K. Sakellariou, A. Tarampikou, E. Soroli, K. Gkiati, D. Bafaloukos

Oncology Department, Metropolitan Hospital, Athens, Greece

Background: Long-term survival for patients with metastatic melanoma (MM) was very rare until the advent of targeted and checkpoint inhibitor therapy. Today clinical trial data provide evidence of encouraging 3-year and even 5-year survival rates, while real-world data are lacking.

Methods: Patient and disease characteristics were collected among MM patients treated in a reference oncology center since 2012 with targeted and/or checkpoint inhibitor agents. We defined long-term survivors as patients with survival >2years from MM diagnosis; biological material was collected for genomic analyses.

Results: From 130 MM patients treated with BRAF/MEK inhibitors and/or anti-CTLA4, anti-PD1 agents in any line, 25 long-term survivors were identified (19,2%), 15 men/ 10 women. Long-term survival was characterized by good prognosis features at initial diagnosis: median PS 0, normal LDH (60%), low disease burden (≤3 metastatic sites, 88%), median Distant Metastasis Free Interval (DMFI) 3 years (range 0-23+ years), 16/25 BRAF mutant MM. All long-term survivors had achieved an objective response (complete/partial) to targeted or immuno- therapy. Objective response was associated with long-term survival regardless of treatment line. Complete responses to targeted or immunotherapy are still ongoing (2 to immunotherapy >3 years, 2 to BRAF/MEKi >5 years). Most patients are alive today (21/25, 84%): 9 patients (36%) survive >5 years from MM diagnosis, with 8 of them (32%) surviving >5 years from new therapy initiation (targeted or immuno). The majority of patients (22/25, 88%) survive >3 years from initial MM diagnosis and 76% survive >3 years from therapy initiation (targeted or immuno-), suggesting that the long-term survival benefit is due to the new therapy. Genomic analysis will complement the clinical characteristics of long-term survival.

Conclusions: A significant number of patients with MM treated in a reference center achieved long-term survival with targeted or immuno-therapy. The specific clinical and genomic characteristics of these long-term survivors can improve our understanding of the biological behaviour of the disease but also assist the optimal choice and use of new therapies.

Legal entity responsible for the study: Oncology Department, Metropolitan Hospital, Athens.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1265P Phase Ib/II study of the combination of SD-101 and pembrolizumab in patients with advanced melanoma who had progressive disease on or after prior anti-PD-1 therapy

A. Ribas[1], I. Mehmi[2], T. Medina[3], C. Lao[4], S. Kummar[5], A. Amin[6], S. Deva[7], A.K. Salama[8], T. Tueting[9], M. Milhem[10], C.J. Hoimes[11], G. Daniels[12], M. Shaheen[13], S. Jang[14], M. Barve[15], A. Powell[16], S. Chandra[17], E.V. Schmidt[18], R. Janssen[19], G.V. Long[20]

[1]Department of Medicine, Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA, USA, [2]Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV, USA, [3]Medicine/Medical Oncology, University of Colorado Cancer Center, Aurora, CO, USA, [4]Medicine, University of Michigan Health System, Ann Arbor, MI, USA, [5]Medical Oncology, Stanford University School of Medicine, Stanford, CA, USA, [6]Medical Oncology, Levine Cancer Institute, Charlotte, NC, USA, [7]Medical Oncology, Auckland City Hospital, Auckland, New Zealand, [8]Oncology, Duke University, Durham, NC, USA, [9]Dermatology, University Hospital Madgeburg, Madgeburg, Germany, [10]Medicine, University of Iowa, Iowa City, IA, USA, [11]Hematology and Oncology, Case Western Reserve University, Cleveland, OH, USA, [12]Medicine, University of California, San Diego, San Diego, CA, USA, [13]Medicine, University of Arizona Cancer Center North, Tucson, AZ, USA, [14]Melanoma and Skin Cancer Center, Inova Schar Cancer Institute, Fairfax, VI, USA, [15]Oncology, Mary Crowley Cancer Research, Dallas, TX, USA, [16]Oncology, Affinity Research, Nedlands, Australia, [17]Medicine, Northwestern University, Chicago, IL, USA, [18]Early Oncology, Clinical Development, Merck & Co Inc, North Wales, PA, USA, [19]Clinical Development, Dynavax Technologies Corporation, Berkeley, CA, USA, [20]Medical Oncology, Melanoma Institute Australia, University of Sydney, North Sydney, Australia

Background: SD-101 is a synthetic CpG-ODN agonist of TLR9. Pembrolizumab is an antibody to PD-1. DV3-MEL-01 (SYNERGY-001) assesses the safety and preliminary efficacy of the combination of SD-101 and pembrolizumab in stage IIIC-IV melanoma.

Methods: Phase 1b evaluated SD-101 at multiple doses injected in a single tumor Q1W x 4 then Q3W x 7 in combination with a fixed dose of pembrolizumab (200 mg IV Q3W). Phase 2 is evaluating SD-101 at 8 mg in 1 lesion and 2 mg/lesion in 1-4 lesions. Patients were eligible if their tumor progressed on or after prior anti-PD-1 therapy. Scans are performed every 64 days. Per-protocol overall responses (ORR) were assessed per investigator using RECIST v1.1/irRECIST. The modified intent-to-treat (mITT) population included all patients except those on study who had not reached the Day 64 scan. PFS rate was calculated using the mITT population. The per-protocol population comprised patients who received at least 1 dose of each drug and had ≥1 post baseline scan.

Results: 38 patients enrolled: median age 64 years; male 74%; ECOG PS 0 58%; Stage IIIC 32%, IVM1a/b 13%, Stage IVM1c/d 50%; LDH > ULN 39%. SD-101 safety profile consists of transient, mild-to-moderate flu-like symptoms and injection-site reactions. Grade 3-4 treatment-related AEs = 32%. Immune-related AEs (irAEs) = 5%. ORR (mITT) = 16% (6/37) (CR 3%/PR 14%/SD 30% [DCR = 46%]/PD 38%/NE 16%). Evaluable ORR =19% (6/31). 7 pts were not evaluable: on study but no Day 64 scan yet (n = 1), AE (n = 1), clinical PD (n = 2), withdrew consent/unknown (n = 3). 2 of 8 patients who began combination therapy within 3 months of starting anti-PD-1 therapy had responses including 1 CR. Median DOR not reached (range 9 weeks, 45 weeks). Median follow up = 13 weeks (range 6, 45 weeks). 6 month PFS rate = 16%. One third

of the patients currently have biomarker assessments demonstrating a broad increase in TILs in patients with responses with ≥ 3 fold increase in T cells.

Conclusions: The combination of SD-101 and pembrolizumab induced responses in some patients who developed progressive disease on or after prior anti-PD-1 therapy. The combination is well tolerated with no evidence of an increased rate of irAEs.

Clinical trial identification: NCT02521870.

Legal entity responsible for the study: Dynavax Technologies Corporation.

Funding: Dynavax Technologies Corporation.

Disclosure: A. Ribas: Consulting fees: Dynavax Technologies. C. Lao: Research funding: Merck. A. Amin: Honoraria, Speaker's bureau: Merck & Co. M. Milhem: Advisory board: Blueprint Medicines GIST. S. Chandra: Membership on advisory boards and/or Speaker's Bureau Member: EMD Serono, Bristol-Myers Squibb, Array BioPharma, Regeneron. E.V. Schmidt: Employee: Merck. R. Janssen: Employee: Dynavax Technologies Corporation; Shareholder: Dynavax and Merck stock. All other authors have declared no conflicts of interest.

1266P Update on the randomised phase Ib/II study of the selective small molecule AXL inhibitor bemcentinib (BGB324) in combination with either dabrafenib/trametinib or pembrolizumab in patients with metastatic melanoma

C. Schuster[1], G. Gausdal[2], B.T. Gjertsen[3], J. Lorens[4], O. Straume[5]

[1]Department of Clinical Science, Centre for Cancer Biomarkers, University of Bergen, Bergen, Norway, [2]BerGenBio ASA, BerGenBio ASA, Bergen, Norway, [3]Department of Internal Medicine, Helse Bergen Haukeland University Hospital, Bergen, Norway, [4]Department of Biomedicine, Centre for Cancer Biomarkers, University of Bergen, Bergen, Norway, [5]Oncology and Medical Physics, Haukeland Universitetssykehus, Bergen, Norway

Background: Upregulation of the receptor tyrosine kinase AXL has been linked with both minor treatment effect of PD-1 blockade and acquired resistance to BRAF inhibitors in melanoma. Bemcentinib is a first-in-class orally bioavailable selective inhibitor of AXL which is currently investigated in several phase II clinical trials. BGBIL006 (NCT02872259) is an open label phase Ib/II trial designed to explore whether combination with bemcentinib improves overall response rates to standard of care therapies in patients (pts) with metastatic melanoma (MM).

Methods: Dose escalation of bemcentinib in combination with 150mg twice daily/2mg daily dabrafenib/trametinib (D/T) in newly diagnosed, BRAF+, MM with high tumour load followed a 3 + 3 design (part 1). In part 2, pts were randomised 2:1 to receive D/T or pembro +/- bemcentinib at RP2D, respectively, based on mutation status and tumour load. Pts were allowed to switch D/T with pembrolizumab and vice versa upon progression (part 3). Tumour responses were assessed per investigator using RECIST v1.1. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in pts pre-dose and at C2D1.

Results: In part 1, 6 pts were enrolled first line (age 34-71, LDH > 1 x ULN 50%). There was 1 dose limiting toxicity (G3 rash) and an RP2D of bemcentinib in combination with D/T of 200mg daily bemcentinib with full dose D/T was confirmed. As of 2 May 18, a further 17 pts have been enrolled into part 2 of the study and four had progressed to part 3. Grade 3 treatment-related adverse events (AEs) were observed in 7 pts (30%). No G4 AEs or treatment related deaths occurred. Biomarkers candidates predicting treatment benefit were explored. Pre/post treatment changes of soluble proteins will be presented.

Conclusions: Bemcentinib RP2D (200 mg daily) is well tolerated in combination with both D/T and pembro without increased toxicity compared to either therapeutic approach alone. Further investigation of safety and efficacy as well as biomarker candidates is ongoing.

Clinical trial identification: NCT02872259.

Legal entity responsible for the study: Department for Oncology and Medical Physics, Haukeland University Hospital Bergen.

Funding: KLINBFORSK governmental funding.

Disclosure: G. Gausdal: Employee: BerGenBio. B.T. Gjertsen: Stock/ownership: Alden Cancer Therapy II, Kinn Therapeutics AS. J. Lorens: Ownership: BerGenBio ASA. All other authors have declared no conflicts of interest.

1267P Topline results from phase II of combination treatment with canerpaturev (HF10), an oncolytic viral immunotherapy, and ipilimumab in patients with unresectable or metastatic melanoma after anti-PD-1 therapy

T. Isei[1], K. Yokota[2], H. Uhara[3], Y. Fujisawa[4], T. Takenouchi[5], Y. Kiyohara[6], H. Uchi[7], H. Saruta[8], H. Ihn[9], T. Inozume[10], D. Watanabe[11], A. Takahashi[12], S. Fukushima[9], M. Tanaka[13], N. Yamazaki[12]

[1]Department of Dermatological Oncology, Osaka International Cancer Institute, Osaka, Japan, [2]Department of Dermatology, Nagoya University Hospital, Nagoya, Japan, [3]Department of Dermatology, Sapporo Medical University Hospital, Sapporo, Japan, [4]Department of Dermatology, University of Tsukuba, Tsukuba, Ibaraki, Japan, [5]Division of Dermatology, Niigata Cancer Center Hospital, Niigata, Japan, [6]Division of Dermatology, Shizuoka Cancer Center Hospital, Shizuoka, Japan, [7]Department of Dermatology, Kyushu University, Graduate School of Medical Sciences, Fukuoka, Japan, [8]Department of Dermatology, Kurume University School of Medicine, Kurume, Japan, [9]Department of Dermatology and Plastic Surgery, Graduate School of Medical Sciences, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan, [10]Department of Dermatology, Faculty of Medicine, University of Yamanashi, Chuo, Japan, [11]Department of Dermatology, Aichi Medical University School of Medicine, Nagakute, Japan, [12]Department of Dermatologic Oncology, National Cancer Center Hospital, Tokyo, Japan, [13]Gene Medicine Business Unit, Takara Bio Inc., Kusatsu, Shiga, Japan

Background: Canerpaturev (C-REV, formerly HF10) is an oncolytic, spontaneous mutant of HSV-1, and is one of immunotherapies that combine direct tumor cell killing with immune modulation. We report the safety and antitumor activity data of Phase II multicenter trial of C-REV in combination with ipilimumab (ipi) in melanoma.

Methods: The Phase II was to determine the efficacy and safety of i.t. C-REV and i.v. ipi. Key entry criteria: age ≥ 20 yrs, ECOG PS ≤ 2, Stage IIIB, IIIC or IV unresectable melanoma, who received prior therapies and had measurable non-visceral lesion(s) suitable for injection. C-REV was injected into each tumor (1×10^7 $TCID_{50}$/mL/dose, up to 5mL); 4 injections q1wk; then up to 15 injections q3wk. Four ipi infusions (3 mg/kg) were administered at q3wk. AEs were graded per CTCAE 4.0. Tumor responses were assessed per irRC and mWHO at 6, 12, 18 and 24 wks. Primary endpoint was Best Overall Response Rate (BORR) by irRC at 24 wks.

Results: Of 28 pts enrolled and treated as of the data cut-off 04 May 2018: 43% men, 31 to 81 yrs, disease stage 7% IIIB, 29% IIIC and 64% IV, and disease type 39% acral lentiginous and 21% mucosal melanoma. All pts were received prior cancer therapies: 89% PD-1 monotherapy, 7% DAVFeron and 11% DTIC. 12% had ≥G3 drug-related AEs; Hepatic function disorder, Malaise, Hyponatraemia, Constipation, Nausea, Toxicoderma, Adrenal insufficiency, and Muscle weakness lower limb. Of 27 efficacy evaluable pts, BORR by irRC at 24 wks was 7% and disease stability rate was 56%. One patient had PR in injected lesions and systemic lesions also showed the response after 6 wks of the combo therapy.

Conclusions: The combination of C-REV with ipi did not show the exacerbate ipi toxicity, and had a favorable benefit/risk profile. The encouraging antitumor activity was observed in Japanese pts who had received prior therapies such as PD-1. It is recently well-known that the response to ipi after anti-PD-1 therapy was unsatisfactory and associated with a high frequency of severe irAEs, in particular Asian populations. From this study, C-REV+ipi therapy has potential to become a new 2nd line treatment for melanoma.

Clinical trial identification: NCT03153085.

Legal entity responsible for the study: Takara Bio Inc.

Funding: Takara Bio Inc.

Disclosure: T. Isei: Honoraria: Novartis, Toray Industries, GlaxoSmithKline, Daiichi Sankyo, Maruho, Pola Pharma, BMS UK, Ono Pharmaceuticals, MSD China; Consulting or advisory role: Novartis, BMS UK, Ono Pharmaceuticals, Merck Serono Ltd, MSD China; Research funding: Nocartis, Takara Bio, Array BioPharma, Amgenm, BMS UK, Ono Pharmaceuticals, MSD China. K. Yokota, H. Uchi, H. Ihn, T. Inozume, S. Fukushima: Research funding: Takara Bio. H. Uhara: Honoraria: MSD, Chugai Pharma, Novartis, Pola Pharma, Maruho, BMS UK, Ono Pharmaceuticals; Consulting or advisory role: Chugai Pharma, Novartis, MSD, Kyowa Hakko Kirin, BMS UK, Ono Pharmaceuticals; Speakers' bureau: Chugai Pharma, Novartis, MSD, Kyowa Hakko Kirin, Mitsubisi Tanabe Pharma, Pola Pharma, BMS UK, Ono Pharmaceuticals, Janssen Inc. Pharmaceuticals; Research funding: Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, Eisai, Abbvie, Maruho, Daiichi Sankyo, Tsumura&Co., Pola Pharma, Mochida Pharmaceutical Co. Ltd., Nihonlayaku, Torii Pharmaceutical, Kaken Pharmaceutical, Takara Bio, Ono Pharmaceuticals, Taiho Pharmaceutical. Y. Fujisawa: Consulting or advisory role: Novartis; Research funding: Maruho, Eisai, Chugai Pharma, Novartis, Toray Industries, Takara Bio, BMS UK, Ono Pharmaceuticals; Patients, Royalities, Other intellectural property: Novartis. T. Takenouchi: Speakers' bureau: MSD, Chugai Pharma, Novartis, BMS UK, Ono Pharmaceuticals; Research Funding: Takara Bio. Y. Kiyohara: Honoraria: MSD, Novartis, Chugai Pharma, Toray Industries, Takara Bio, Amgen, BMS UK, Ono Pharmaceuticals, Boehringer Ingelheim International GmbH, Merck Serono Ltd; Research funding: MSD, Takara Bio, BMS UK, ONO Pharmaceuticals, Merck Serono Ltd; Travel, accommodations, expenses: Ono Pharmaceuticals. H. Saruta: Speakers' bureau: Kyowa Hakko Kirin, Ono Pharmaceuticals; Research funding: Takara Bio, MSD; Travel, accommodations, expenses: Novartis, Minophargen Pharmaceuticals. D. Watanabe: Consulting or advisory role: Maruho, Japan Vaccine; Speakers' Bureau: Maruho; Research funding: Maruho, Sanofi, Nihon Zouki, Daiichi Sankyo, Takara Bio. A. Takahashi: Honoraria: Novartis, BMS UK, Ono Pharmaceuticals; Research funding: Novartis, Takara Bio,

BMS UK, Ono Pharmaceuticals. M. Tanaka: Employee: Takara Bio. N. Yamazaki: Honoraria: Novartis, MSD, BMS UK, Ono Pharmaceuticals; Consulting or advisory role: Novartis, MSD, BMS UK, Ono Pharmaceuticals; Research funding: Novartis, MSD, Takara Bio, BMS UK, Ono Pharmaceuticals.

1268P NCI 9922: Phase II study of ibrutinib in treatment-refractory distant metastatic cutaneous melanoma (DMCM)

S.J. Moschos[1], Z. Eroglu[2], N.I. Khushalani[2], K.L. Kendra[3], G. Ansstas[4], G.K. In[5], P. Wang[6], G. Liu[7], F.A. Collichio[8], C.C. Arrowood[9], J.E. Reed[1], N. Garrett-Mead[9], N.E. Thomas[8], D.W. Ollila[8], S.P. Ivy[10], A. Ivanova[8], E.C. Dees[8], J.L. Abbruzzese[11]

[1]Medicine, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA, [2]Cutaneous Oncology Program, Moffitt Cancer Center, Tampa, FL, USA, [3]Cutaneous Oncology Program, Ohio State University Comprehensive Cancer Center - James, Columbus, OH, USA, [4]Medicine, Washington University School of Medicine in St. Louis, St. Louis, MO, USA, [5]Medicine, Keck School of Medicine at University of Southern California, Los Angeles, CA, USA, [6]Medicine, UK Markey Cancer Center, Lexington, KY, USA, [7]Medicine, University of Wisconsin, Madison, WI, USA, [8]Medicine, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA, [9]Clinical Trials Unit, Duke Cancer Institute, Durham, NC, USA, [10]Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD, USA, [11]Medicine, Duke Cancer Institute, Durham, NC, USA

Background: The IL-2 inducible kinase (ITK) is highly expressed in metastatic melanomas and molecular targeting and/or pharmacologic inhibition of ITK in preclinical melanoma models suppresses cell proliferation without inducing cell death (Carson CCR 2015). Ibrutinib suppresses proliferation of melanoma cell lines in low nM concentrations (Moschos ASCO 2017, TPS9592). We hypothesize that targeting DMCM with ibrutinib will induce antitumor responses, especially in high ITK-expressing melanomas.

Methods: This is an open-label, single-arm, Simon's 2-stage design, multicenter, phase II study for patients (pts) with DMCM refractory to or ineligible for PD-1 and MAPK inhibitors, if BRAFV600-mutant. Given that the IC50 of ibrutinib for ITK is > 10 times than Bruton's tyrosine kinase's, we administered ibrutinib at 840mg qd. We hypothesized that an ineffective drug will have a = <5% response rate and = <18% 6-month PFS rate. We present the results of the first stage.

Results: 18 pts (13 males; median age 63.5, range 37-82; 14 with M1c disease; 4 with BRAFV600 mutation; 12 with performance status 1 or 2; 4 with resistance to 4 treatments; 5 with resistance to = >5 treatments) were enrolled. Median exposure to ibrutinib was 27.5 days (range 4-155). The most frequent all-grade side effects were fatigue (55%), anorexia (50%), gastrointestinal upset (44%), and anemia (39%). 4 grade IV (hyponatremia, sepsis, cytokine release syndrome, and constipation occurred 6% each) and 9 grade III events [hyponatremia (17%); pneumonia, hypertension, anemia, hypoalbuminemia, dehydration, lymphopenia occurred 6% each] were seen. No antitumor responses were seen. At a median follow-up of 5 months, all pts had progressed (median PFS was 1.3 months, range 0.2-5.5). 15 pts were discontinued from study due to progression and 14 pts had died from melanoma. Median OS was 5 months (range 0.3-10.4 months) in pts who died.

Conclusions: In this treatment-refractory DMCM, high-dose ibrutinib did not induce any meaningful clinical benefit; therefore the study will not proceed to stage 2. Correlation between PFS and expression of ITK by melanoma cells and density of tumor-infiltrating T- and B-cells in pretreatment tumor specimens will be reported at the time of the meeting.

Clinical trial identification: NCT03427398.

Legal entity responsible for the study: NCI-CTEP.

Funding: NCI-CTEP, Pharmacyclics.

Disclosure: All authors have declared no conflicts of interest.

1269P Initial cohort expansion results of sustained arginine depletion with pegzilarginase in melanoma patients in a phase I advanced solid tumor trial

B. Chmielowski[1], M. Gordon[2], E.I. Buchbinder[3], R.J. Sullivan[4], J.V. Cohen[4], B.D. Curti[5], D. Davar[6], J. Homsi[7], K.M. Komatsubara[8], H. Lara-Guerra[9], S.E. Alters[10], S. Ferrati[10], S. Eckert[11], S.W. Rowlinson[10], J.E. Wooldridge[9], A. Ribas[1], R.D. Carvajal[8]

[1]Department of Medicine, Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA, USA, [2]Medical Oncology, HonorHealth Virginia G Piper Cancer Care Network, Scottsdale, AZ, USA, [3]Melanoma, Dana-Farber Cancer Institute, Boston, MA, USA, [4]Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA, [5]Oncology and Hematology, Providence Cancer Institute, Portland, OR, USA, [6]Medicine, University of Pittsburgh, Pittsburgh, PA, USA, [7]Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA, [8]Hematology/Oncology, Herbert Irving Comprehensive Cancer Center, New York, NY, USA, [9]Medical, Aeglea Biotherapeutics, Austin, TX, USA, [10]Translational Research, Aeglea Biotherapeutics, Austin, TX, USA, [11]Biometrics, Aeglea Biotherapeutics, Austin, TX, USA

Background: Tumors with low argininosuccinate synthetase 1 (ASS1) expression have impaired arginine synthesis and are dependent on extracellular arginine for survival. Pegzilarginase (AEB1102) is a pegylated, recombinant, cobalt-substituted human arginase I that depletes plasma arginine. MTD was previously reported as 0.33 mg/kg weekly (AACR 2018). Here we update the preliminary safety and activity of monotherapy pegzilarginase in uveal (UM) and cutaneous (CM) melanoma cohorts of an ongoing Phase 1 study (NCT02561234).

Methods: Adult patients (pts) with metastatic UM or CM were eligible after prior standard treatments. IV pegzilarginase was administered at the MTD. Primary objective was safety (CTCAE v4.03); additional endpoints included PK, PD, tumor ASS1 expression, and preliminary anti-tumor activity (RECIST 1.1).

Results: At analysis, 16 pts with melanoma (11 UM, 5 CM) received pegzilarginase in cohort expansions. 5 dose-escalation pts with UM (3) or CM (2) were also treated at MTD. For the 21 pts with UM or CM treated at MTD, treatment-related AEs (TRAE) in > 10% pts included fatigue, nausea, diarrhea, vomiting, decreased appetite, dizziness, gait disturbance, muscular weakness, and tremor. No Grade ≥4 TRAEs were observed, and Grade 3 TRAEs were reported by one pt each: asthenia, failure to thrive, and hypophosphatemia. Median weeks on pegzilarginase was 5.9 (range 0 [1 dose] to 17.1 weeks). Pegzilarginase depleted plasma arginine from a median of 58 μM at baseline to a median of 4 μM at 72 hours post-dose (n = 12). In 13 pts with week 8 response assessment, 6 had stable disease. 13 pts with UM or CM had prior IO therapy; 7 had PD as best response to last prior therapy. 10/16 tumors showed no or low ASS1 expression.

Conclusions: The safety, PD, and activity profile of pegzilarginase at the MTD continues to support weekly administration with a margin for dose adjustment. Given very poor outcomes in pts with advanced UM and CM, pre-clinical data showing enhanced effects of pegzilarginase when combined with PD-L1 inhibition, and the observation of stable disease this trial, further development of pegzilarginase in combination with anti-PD-L(1) therapy is warranted for these tumors.

Clinical trial identification: NCT02561234.

Editorial acknowledgement: Abstract was prepared by Aeglea Biotherapeutics.

Legal entity responsible for the study: Aeglea Biotherapeutics.

Funding: Aeglea Biotherapeutics.

Disclosure: R.J. Sullivan: Consultant: Novartis, Merck, Amgen, Syndax, Replimmune, Array Biopharma. D. Davar: Corporate-sponsored research (clinical trial support): Merck and Bristol-Myers Squibb. H. Lara-Guerra, S.E. Alters, S. Eckert, S.W. Rowlinson, J.E. Wooldridge: Full-time employee: Stock options: Aeglea Biotherapeutics. S. Ferrati: Full-time employee: Aeglea Biotherapeutics. R.D. Carvajal: Consulting: BMS, Castle Biosciences, Foundation Medicine, Immunocore, Incyte, Merck, Roche/Genentech advisory board: Aura Biosciences, Chimeron, Rgenix. All other authors have declared no conflicts of interest.

1270P Efficacy of immunotherapy in patients with metastatic mucosal or uveal melanoma

C. Mignard[1], A. Deschamps-Huvier[1], A-B. Duval-Modeste[1], C. Dutriaux[2], A. Khammari[3], M-F. Avril[4], L. Mortier[5], T. Lesimple[6], C. Gaudy-Marqueste[7], C. Lesage[8], L. Machet[9], F. Aubin[10], N. Meyer[11], N. Beneton Benhard[12], G. Jeudy[13], H. Montaudié[14], J-P. Arnault[15], M-T. Leccia[16], P. Joly[1], S.F.D. Oncology Research Group Of The French Society Of Dermatology[17]

[1]Dermatology Department, Institute for Research and Innovation in Biomedicine, INSERM 1234, Rouen University Hospital, University of Normandie, Rouen, France, [2]Department of Dermatology, Oncology Unit, Saint André Hospital, Bordeaux, France, [3]Onco-Dermatology Department, CHU Nantes, CRCINA, CIC1413, University Nantes, Nantes, France, [4]Department of Dermatology, APHP Cochin Hospital, Paris, France, [5]Department of Dermatology, Hôpital Huriez, Lille University Hospital, Lille, France, [6]Department of Medical Oncology, Eugene Marquis Center, Rennes, France, [7]Department of Dermatology and Skin Cancer, La Timone Hospital, Marseille, France, [8]Department of Dermatology, Montpellier University Hospital, Montpellier, France, [9]Department of Dermatology, CHRU de Tours et Université François Rabelais de Tours, Tours, France, [10]Department of Dermatology, EA3181, Besancon University Hospital, Besançon, France, [11]Department of Dermatology, Toulouse III University – Paul Sabatier, Institut Universitaire du Cancer and Toulouse University Hospital, Toulouse, France, [12]Department of Dermatology, Centre Hospitalier Du Mans, Le Mans, France, [13]Department of Dermatology, Dijon University Hospital, Dijon, France, [14]Department of Dermatology, Nice University Hospital, INSERM, U1065, Centre Méditerranéen de Médecine Moléculaire, Nice, France, [15]Department of Dermatology, Amiens-Picardie University Hospital, Amiens, France, [16]Dermatology and Photobiology, CHU Grenoble Alpes, Grenoble, France, [17]Oncology Research Group, French Society of Dermatology, Paris, France

Background: Only few studies on limited series of patients have evaluated the efficacy of immunotherapy in patients with metastatic mucosal melanoma (MM) or uveal melanoma (UM). The aim of the study was to assess the objective response rate and survival of patients with metastatic MM or UM treated with anti-CTLA-4 or anti-PD-1.

Methods: A multicenter retrospective study was performed in 25 Dermatology Departments in France. All patients with stage IIIC to IV MM or UM who were treated with anti-CTLA-4 or anti-PD-1 between 2008 and 2016 were included. Tumor response was evaluated according to RECISTv1.1 criteria at Week 12, and compared with a second cohort of patients treated with chemotherapy from 2000 to 2016. Overall survival (OS) was evaluated using Kaplan Meier method, and adjusted for main prognostic factors. UM or MM were analysed separately.

Results: A total of 439 patients were included, 229 with MM (151 treated with immunotherapy and 78 treated with chemotherapy) and 210 with UM (100 treated with immunotherapy and 110 treated with chemotherapy). Objective response rates of MM to anti-CTLA-4 and anti-PD-1 were 3/76 (3.9%, 95%CI=0.5%-8.3%) and 15/75 (20%, 95%CI=0.9%-29.1%) respectively, versus 11/78 (14.1%, 95%CI=6.4%-21.8%) in patients treated with chemotherapy ($p = 0.047$ and $p = 0.4$). No tumor response was observed in UM patients treated with immunotherapy, versus 4/110 responses (3.6%, 95%CI=0.2-7.4%) in patients treated with chemotherapy ($p = 0.12$). The OS of MM patients treated with immunotherapy was longer than that of patients treated with chemotherapy ($p = 0.002$), with a median OS of 15.97 [interquartile range (IQR)=6.89-27.12] and 8.82 months [IQR=5.2-14.9], respectively. After adjusting for main prognostic factors, the OS of MM patients treated with immunotherapy remained longer than that of patients treated with chemotherapy (HR = 0.61 [0.4; 0.95], $p = 0.028$). The adjusted and non-adjusted OS of UM patients treated with immunotherapy was not different from that of patients treated with chemotherapy (HR = 1.06 [0.70; 1.61], $p = 0.78$) with median of 13.38 months [IQR=6.03-29.57] and 11.02 months [IQR=5.8-23.9], respectively.

Conclusions: Anti-PD-1 should be considered for the treatment of patients with advanced MM. The prognosis of metastatic UM remains poor.

Legal entity responsible for the study: P. Joly.

Funding: Bristol-Myers Squibb.

Disclosure: N. Meyer: Consultant or investigator: BMS, MSD, Roche, GSK, Novartis, Amgen, Pierre Fabre. N. Beneton Benhard: Consultant: BMS, Novartis, Roche. J.-P. Arnault: Grant support for Congress: BMS, MSD; Investigator: Novartis. P. Joly: Consultant: BMS. All other authors have declared no conflicts of interest.

1271P Retrospective analysis of the treatment of metastatic uveal melanoma comparing systemic chemotherapy and transarterial chemoembolization

C.A. Peuker[1], L. Polzin[2], S. Ochsenreither[3], M. De Bucourt[4], S. Leyvraz[1], U. Keilholz[5], A. Joussen[6], J. Eucker[7]

[1]Medical Oncology, Haematology and Tumor Immunology, Charité Comprehensive Cancer Center, Berlin, Germany, [2]Department of Haematology and Medical Oncology, Campus Benjamin Franklin, Berlin, Germany, Charité - University Medicine Berlin, Berlin, Germany, [3]Charité Comprehensive Cancer Center, Charité University of Medicine, Berlin, Germany, [4]Department of Radiology, Campus Benjamin Franklin, Berlin, Germany, Charité - University Medicine Berlin, Berlin, Germany, [5]Oncology, Charite Comprehensive Cancer Center, Berlin, Germany, [6]Department of Ophthalmology, Campus Benjamin Franklin, Berlin, Germany, Charité - University Medicine Berlin, Berlin, Germany, [7]Medizinische Klinik M. S. Hämatologie und Onkologie, Charite, Campus Benjamin Franklin Medizinische Klinik III, Berlin, Germany

Background: Metastatic uveal melanoma (mUM) is a rare disease with poor prognosis, hardly responding to systemic treatment. As the liver is the most common and prognostic relevant metastatic site, liver-directed therapies have come into focus.

Methods: A retrospective analysis was carried out in patients who were treated at our center between 2008 and 2017 receiving chemotherapy (1000 mg/m^2 gemcitabine + 3500 mg/m^2 treosulfan (GeT) on days 1 + 8, 4-week cycles) or transarterial chemoembolization (TACE, EmboCept® S microspheres + 50 mg cisplatin, every 4-6 weeks) as 1st-line therapy for mUM.

Results: 287 patients were treated for mUM in the time period, 93 received TACE and 82 GeT as 1st-line therapy. Patient characteristics differed in the metastatic pattern: patients receiving GeT having a significant higher rate of non-liver dominant metastatic disease compared to the TACE group ($p < 0.001$), whereas there was no difference in age, sex, DFI, laboratory values and percentage of liver involvement. Median overall survival (OS) in the GeT group was 11.3 vs. 8.4 months in the TACE group ($p = 0.089$), with a median progression-free survival (PFS) of 2.7 and 2.8 months respectively (ns). Overall response rate for GeT was 6.8% and disease control rate was 41.1%, for TACE 10.2% and 47.7% respectively (both ns). Age, sex, baseline laboratory values, PFS and percentage of liver involvement were significantly associated with OS in univariate analysis. Multivariate Cox regression analysis identified male sex, elevated bilirubin, GGT, ALP, percentage of liver involvement >50% and PFS ≤2.7 months as significant independent prognostic factors for shorter survival. The metastatic pattern and the type of treatment did not show to be significant prognostic factors.

Conclusions: Liver-directed therapies can improve response rates compared to systemic therapies and should be preferred in patients with liver-dominant metastatic pattern. However, PFS and OS remain poor and not significantly different between intrahepatic and systemic therapies. Further research should focus on developing new therapies based on a better understanding of the biology of these tumors.

Legal entity responsible for the study: Charité Comprehensive Cancer Center, Charité - University Medicine Berlin.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1272P Outcome of an active surveillance programme for patients (pts) with uveal melanoma (UM) after primary curative therapy (PTx): Single institution 10-year experience

C.L. Lee[1], G. Gullo[1], N. Horgan[2], D. Smith[1], M. Moran[1], J.P. Crown[1]

[1]Medical Oncology, St Vincents University Hospital, Dublin, Ireland, [2]Surgery, Royal Victoria Eye & Ear Hospital, Dublin, Ireland

Background: About 30% of pts with UM develop metastatic disease (MUM) despite PTx. MUM has poor prognosis and no systemic treatment (STx) has been proven to improve overall survival (OS). The role of active surveillance after PTx is still controversial.

Methods: We performed an outcome analysis of all UM pts prospectively registered onto our active surveillance programme after PTx. All pts had systemic staging at diagnosis and then 6-monthly liver imaging (CT triple-phase, MRI, ultrasound) and clinical review for the first 5 years and 12-monthly afterwards. Progression-free survival (PFS) was calculated from time of first systemic relapse to first disease progression, OS from time of first systemic relapse to death or latest FU.

Results: Out of 169 pts registered between April 2008 and April 2018, 32 (19%) developed MUM during surveillance: 14 pts (44%) relapsed <2 yrs, 14 (44%) >2 and <5 yrs, 4 (12%) >5 yrs from PTx. Median FU is 46.8 mos. MUM pts characteristics: males 17 (53%); median age 59yrs (range 31-86); median tumour thickness at diagnosis 9mm (range 3-22); sites of metastases: liver only 10 (31%), liver + other sites 19 (60%), extrahepatic only 3 (9%). Relapses were asymptomatic and detected on surveillance imaging in 25 (78%) pts. Median duration to relapse after PTx is 27.4 mos. Eight pts (25%) were upfront resectable (PRx) and underwent radical hepatic metastasectomies, 24 pts (75%) were non-resectable (NRx) and underwent immunotherapy (n = 12), other systemic therapies (n = 5) [4 chemotherapy, 1 BRAF inhibitor], locoregional Tx (n = 3) [2 Delcath, 1 RFA], best supportive care (n = 4). At median FU of 46.8 mos (0-120 mos), 27 pts have died and the median OS is 13.5mos. PFS was longer in PRx pts compared to NRx pts (PFS: 9.8 vs 4.4 mos / OS: 20.7 vs 39.3 mos). All 8 resectable pts developed further disease relapse [median time to hepatic relapse 9.8 mons (range 5.2 -13.1)].

Conclusions: Our data indicate that active surveillance after PTx of UM can allow detection of asymptomatic potentially resectable liver metastases, especially in pts with high risk UM (i.e. thickness >5mm). Although durable remission after hepatic metastasectomy is rare, PFS and OS may be meaningfully prolonged.

Legal entity responsible for the study: St Vincents' Hospitals, Dublin, Ireland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1273P Activation of non-canonical NFκB (NC-NFκB) pathway in inflammatory environment of uveal melanoma

M.K. Singh[1], R. Meel[2], N. Pushker[2], S. Sen[1], K. Chodsol[3], S. Bakhshi[4], S. Kashyap[1]

[1]Ocular Pathology, All India Institute of Medical Sciences, New Delhi, India, [2]Ophthalmology, All India Institute of Medical Sciences, New Delhi, India, [3]Biochemistry, All India Institute of Medical Sciences, New Delhi, India, [4]Medical Oncology, All India Institute of Medical Sciences, New Delhi, India

Background: Uveal melanomas are considered as malignant phenotype having a high density of macrophages, blood vessels, and T-lymphocytes. Presence of epithelioid cells with high melanin pigmentation leads to worse patient's prognosis. Non-canonical NFκB (NC-NFκB) pathway plays an important role in inflammation which promotes cancer initiation and progression. p52 and RelB are the dimer proteins of the NC-NFκB pathway. The aim of the study is to detect the expression of p52/RelB protein dimer in the inflammatory microenvironment of uveal melanoma and its prognostic significance.

Methods: Evaluation of p52/RelB dimer was assessed by using immunohistochemistry and western blotting in 75 formalin fixed uveal melanoma tissues and transcriptional analysis was done on 58 fresh frozen tissues by real-time PCR. Immunopositive expression of both proteins was taken as a positive expression of the dimer ($p52^+/RelB^+$) and immunonegative of both proteins taken as ($p52^-/RelB^-$) negative expression of the dimer. Results were then correlated with clinicopathological parameters and disease-free survival.

Results: Immunoexpression of $p52^+/RelB^+$ protein showed both nuclear and cytoplasmic expression in 35 cases whereas 15 showed cytoplasmic only. qRT-PCR showed upregulation of $p52^+/RelB^+$ gene in 65.51% cases at the transcriptional level. Expression of both cytoplasmic and nuclear $p52^+/RelB^+$ dimers showed significant correlation with cases having high tumor infiltrated lymphocytes, macrophages (CD68+) and presence of blood vessels (CD34+). There was a statistically significant difference in the disease-free survival of patients with nuclear/cytoplasmic $p52^+/RelB^+$ immunopositivity ($p < 0.05$).

Conclusions: This preliminary data suggests that p52/RelB protein dimer plays an important role in the inflammatory microenvironment of uveal melanoma which might be responsible for the pathogenesis of this disease. Further translational studies are required to explore the nature of NC-NFκB pathway in the tumor microenvironment of uveal melanoma.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1274P The use of PD-1 inhibitors for the advanced melanoma of esophagus

L. Mao, X. Wang, L. Si, Y. Kong, Z. Chi, X. Sheng, C. Cui, B. Lian, B. Tang, X. Yan, J. Guo
Renal Cancer and Melanoma, Beijing Cancer Hospital, Beijing, China

Background: Melanoma of esophagus (ME) is a rare type of melanoma, accounting for <3% of cases. Patients with advanced melanoma of esophagus origin, tend to have lower response rates on traditional therapies. Thus, we report our experience with 11 patients with advanced esophageal melanoma who received PD-1 inhibitors.

Methods: A retrospective analysis of 77 patients with advanced ME were conducted from the database of Peking University Cancer Hospital between Jan 2008 and Sep 2017. We collected the clinical data and assessed objective response rates (ORR) and progression–free survival (PFS). The data cutoff date was Jan 1st 2018.

Results: We identified the 77 patients were unresectable or metastatic esophageal melanomas. The Median age was 57, with 67.5% being male. 78% patients had history of esophagectomy and 64 patients had received prior systemic therapy. There were 8 (10.4%) patients harbored C-KIT mutations and 5 (6.5%) harbored BRAF. We divided the patients into 3 cohorts according to different treatments: Chemotherapy (C: 8 DTIC/26 TMZ/ 23 PTX; 57 cases), Targeted therapy (T: 6 imatinib/3 vemurafenib; 9 cases) or PD-1 inhibitors (P, 11 cases). The PFS were 3.0 and 4.2 months with limited ORR of 5.7% and 25.0% respectively for C and T cohort. In the P cohort, 7/11 patients (63.6%) achieved PR and other 3 remained SD > 4+ months. The PFS for the P cohort was 13.0+ months. Toxicities were as expected and were usually grade 1or 2.

Conclusions: Although this cohort of patients was small, it was the largest report for now. To our knowledge this is also the first report of outcomes of PD-1 inhibitors in advanced esophageal melanomas. The dramatic response appears to be an available option for patients with advanced esophageal melanomas.

Legal entity responsible for the study: Beijing Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1275P Phase II trial on nivolumab in patients with unresectable or metastatic mucosal melanoma

M. Nomura[1], M. Andoh[2], T. Yokota[3], T. Miyazaki[4], H. Satake[5], S. Iwasawa[6], A. Sonoda[7], K. Kato[8], M. Muto[1]

[1]Medical Oncology, Kyoto University-Graduate School of Medicine, Kyoto, Japan, [2]Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [3]Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [4]Head and Neck Surgery, Kurashiki Central Hospital, Kurashiki, Japan, [5]Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [6]Respirology, Chiba University Graduate School of Medicine, Chiba, Japan, [7]Gastroenterology, Shiga University of Medical Science, Otsu, Japan, [8]Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Mucosal melanoma is rare and an aggressive malignancy with poor response compared with cutaneous melanoma. The prospective trial on immune-checkpoint inhibitors in unresectable or metastatic mucosal melanoma has not been reported except pooled analysis. The aim of this phase II trial was to assess the efficacy and safety of nivolumab monotherapy for unresectable or metastatic mucosal melanoma.

Methods: Eligibility criteria were as follows: histological diagnosis of unresectable or metastatic mucosal melanoma; age ≧ 20 years; ECOG performance status 0 or 1; and with measurable lesions. Patients received nivolumab 2 mg/kg every 3 weeks. The primary endpoint was response rate (RR) according to Response Evaluation Criteria in Solid Tumors version 1.1(≧ 20%). The secondary endpoints were overall survival, progression-free survival, disease control rate, and toxicity.

Results: A total of 20 patients were enrolled between December 2014 and July 2017. Two patients without measurable lesion were excluded from analysis of efficacy. The RR was 22%, suggesting that the primary endpoint was met. One patient achieved a complete response, three patients achieved partial response, and six patients achieved stable disease as their best response. The median progression-free survival was 1.4 months (95% CI, 1.15 to 5.47). The median overall survival was 12.03 months (95% CI, 3.50 to not reach). The 1-year overall survival data was 52.6% (95% CI, 28.5 to 72.0). Treatment-related adverse events of grade 3 or 4 occurred in 15% (3/20) of the patients. Grade 3 diarrhea was observed in two patients and grade 3 adrenal insufficiency was observed in one patient. They were resolved by corticosteroid.

Conclusions: Although this trial met the primary endpoint, the RR was still unsatisfactory. Therefore, the further treatment development is required.

Clinical trial identification: UMIN000015845.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1276P Outcomes of anti-PD1 antibodies for advanced melanoma in real-world population

M.C.T. van Zeijl[1], M.W.J.M. Wouters[2], A.J. van den Eertwegh[3], M.J. Aarts[4], A.C.J. van Akkooi[2], F.W.P.J. van den Berkmortel[5], M.G. Franken[6], J.W.B. de Groot[7], K.H. Herbschleb[8], J.J.M. van der Hoeven[8], G.A.P. Hospers[9], E. Kapiteijn[1], D. Piersma[10], R.S. van Rijn[11], K.P.M. Suijkerbuijk[12], A.J. Ten Tije[13], A.A.M. Van der Veldt[14], G. Vreugdenhil[15], J.B.A.G. Haanen[16]

[1]Medical Oncology, Leiden University Medical Centre, Leiden, Netherlands, [2]Surgical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [3]Medical Oncology, Vrije University Medical Centre, Amsterdam, Netherlands, [4]Medical Oncology, Maastricht University Medical Centre, Maastricht, Netherlands, [5]Medical Oncology, Zuyderland Medical Centre, Heerlen, Netherlands, [6]Institute for Medical Technology Assessment, Erasmus University, Rotterdam, Netherlands, [7]Medical Oncology, Isala Hospital, Zwolle, Netherlands, [8]Medical Oncology, Radboud University Medical Centre, Nijmegen, Netherlands, [9]Medical Oncology, University Medical Centre Groningen, Groningen, Netherlands, [10]Medical Oncology, Medisch Spectrum Twente, Enschede, Netherlands, [11]Medical Oncology, Medical Centre Leeuwarden, Leeuwarden, Netherlands, [12]Medical Oncology, University Medical Centre Utrecht, Utrecht, Netherlands, [13]Medical Oncology, Amphia Ziekenhuis, Breda, Netherlands, [14]Medical Oncology, Erasmus University Medical Center, Rotterdam, Netherlands, [15]Medical Oncology, Maxima Medisch Centrum, Veldhoven, Netherlands, [16]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: Anti-PD1 antibodies (aPD1s) for advanced melanoma have proven their superiority over chemotherapy and ipilimumab in phase III trials. However, in real-world many patients were not represented in these trials. We report real-world outcomes of aPD1 for advanced melanoma.

Methods: Pts with advanced (non-uveal) melanoma from 2014 to 2016 who received 1st line aPD1 were selected from the Dutch Melanoma Treatment Registry - a population based registry in the Netherlands. Outcomes of pts normally eligible (ELI) for trial participation (ECOG PS of 0-1, no brain metastasis, auto-immune disease, HIV, psychiatric disorder or corticosteroid use) were compared to pts normally non-eligible (N-ELI) for trial participation. Time to event was estimated with Kaplan-Meier method and overall survival (OS) with cox regression analysis.

Results: In total 552 patients with advanced melanoma received 1st line aPD1. Median age was 65yrs (range 21-94). At baseline 28% had elevated LDH, 90% ECOG PS of 0-1, 19% brain metastases, 65% stage IV-M1c disease and 41% had a BRAF mutation. Toxicity grade 3-4 occurred in 68 pts (12.3%). Median follow-up estimated with reverse Kaplan-Meier method was 18.8 mo (95%CI: 18-20). 1- and 2-yr OS (95%CI) was 72% (68-76%) and 59% (55-65%) and median OS was not reached. Median time to next treatment (TTNT) for ELI pts was not reached and TTNT for N-ELI pts was 10.6 mo (95%CI: 8.3-14.7). Median time of treatment duration was 8.8 mo (95%CI: 6.9-10.5) for ELI pts and 5.3 mo (95%CI: 4.1-7.1) for N-ELI pts. 1- and 2-yr OS were respectively 76% (72-81%) and 63% (57-70%) versus 65% (95%CI: 59-72%) and 53 (95%CI: 45-61% (log-rank test p-value: 0.003). Unadjusted hazard ratio (HR) for OS was 1.57 (95%CI: 1.17-2.09) for N-ELI compared to ELI pts and adjusted HR was 1.28 (95%CI: 0.94-1.73). HR for LDH >500 UI/L was 2.10 (95%CI: 1.23-3.58) and HR for BRAF neg. pts 1.74 (95%CI: 1.26-2.41).

Conclusions: Real-world outcomes of 1st line aPD1s in patients with advanced melanoma seem to be in accordance to results observed in phase III trials. These data support that N-ELI pts normally not represented in phase III trials may benefit from aPD1 treatment. LDH >500 UI/L and BRAF neg. status were associated with poorer survival.

Legal entity responsible for the study: Authors.

Funding: The Dutch Melanoma Treatment Registry is funded by Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis and Roche.

Disclosure: A.C.J. van Akkooi: Advisory boards, Consulting: Amgen, BMS, Novartis, MSD, Merck, Pfizer. J.W.B. de Groot: Advisory boards: BMS, Merck. G.A.P. Hospers, E. Kapiteijn: Advisory boards: BMS, Merck. K.P.M. Suijkerbuijk: Consulting/advisory relationship: Bristol-Myers Squibb, MSD; Honoraria: Novartis, Roche. A.A.M. Van der Veldt: Advisory boards: BMS, MSD, Roche, Novartis. All other authors have declared no conflicts of interest.

1277P Stereotactic radiation therapy in melanoma brain metastasis: A European, multicentric cohort

A. Paix[1], F. Thillays[2], F. Courtault-Deslandes[3], I. Popp[4], H. Herrscher[5], J. Biau[6], O. Briard[7], A-L. Grosu[8], G. Noël[9]

[1]Radiation Oncology, Centre Paul Strauss Centre de Lutte Contre le Cancer, Strasbourg, France, [2]Radiotherapy, Institut Cancérologique de l'Ouest, Saint Herblain, France, [3]Radiotherapy, Centre Georges-Francois Leclerc, Dijon, France, [4]Klinik für Strahlenheilkunde, Universitätsklinikum Freiburg, Freiburg, Germany, [5]Medical Oncology, University Hospital Strasbourg, Strasbourg, France, [6]Radiotherapy, Centre Jean Perrin, Clermont-Ferrand, France, [7]Radiotherapy, Centre Henry Kaplan – Centre Hospitalier Universitaire de Tours, Tours, France, [8]Radiation Oncology, Univeristy of Freiburg, Freiburg, Germany, [9]Radiotherapy, Centre Paul Strauss, Strasbourg, France

Background: Brain metastases are frequent in patients with melanoma and stereotactic radiotherapy is one of the main treatment options. We report the efficacy and safety of hypofractionated stereotactic radiation therapy (HFSRT) and stereotactic radiosurgery (SRS), and its role in melanoma brain metastasis management.

Methods: On behalf of the French-speaking neuro-oncologist association (ANOCEF), we retrospectively collected clinical data of 150 patients and 299 brain metastases from melanoma treated with SRS or HFRSRT in 6 radiation oncology departments in France and in Germany. The primary endpoint was the response to the treatment according to RANO criteria. Secondary endpoints were overall survival (OS).

Results: We conducted a Bayesian multivariate logistic regression for treatment response probability. Age, control of disease and stereotactic radiosurgery have an odds ratio (OR) of 1.02 [1.00 – 1.05], 4.61 [1.15 – 13.24] and 4.33 [0.94 – 13.38] respectively and a probability of being > 1 of 94%, 99% and 97% respectively. BRAF mutation, time between dosimetric MRI and treatment, Ipilimumab administration, multiple brain metastases and WHO performans status have an OR of 0.559 [0.21 – 1.33], [0.79 – 0.94], 0.57 [0.17 – 1.39], 0.41 [0.11 – 1.04] and 0.63 [0.25 – 1.28] respectively and a probability of being < 1 of 91%, 100%, 91%, 97% and 91% respectively. Median OS was 11 months [8 – 20] and the multivariate Cox analysis estimated a Hazard ratio of 0.37 ($p = 0.007$) and 0.8 ($p = 3.7E-6$) for the control of the disease and the brain progression-free survival respectively.

Conclusions: We report the results of one of the largest cohort of patients treated with SRS and HFSRT for melanoma brain metastases. Our analysis suggests that the age of the patient, the control of the disease and SRS are associated with higher response probability while BRAF mutation, the time between dosimetric MRI and treatment, Ipilimumab administration, multiple brain metastases and poor WHO PS are associated with lower response probability.

Legal entity responsible for the study: Association des neuro-oncologues de langue Française (ANOCEF).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1278P Health-related quality-of-life results for pembrolizumab versus placebo after complete resection of high-risk stage III melanoma from the EORTC 1325-MG/Keynote 054 trial: An international randomized double-blind phase III trial

C. Coens[1], A. Bottomley[2], C.U. Blank[3], M. Mandala[4], G.V. Long[5], V.G. Atkinson[6], S. Dalle[7], A. Haydon[8], M. Lichinitser[9], A. Khattak[10], M.S. Carlino[11], S.K. Sandhu[12], J. Larkin[13], S. Puig Sarda[14], P.A. Ascierto[15], D. Schadendorf[16], N. Ibrahim[17], S. Suciu[18], C. Robert[19], A.M.M. Eggermont[20]

[1]*Quality of Life Department, EORTC - European Organisation for Research and Treatment of Cancer, Brussels, Belgium,* [2]*Quality of Life Department, EORTC - European Organisation for Research and Treatment of Cancer, Brussels, Belgium,* [3]*Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands,* [4]*Oncology and Hematology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy,* [5]*Medical Oncology, Melanoma Institute Australia, University of Sydney, North Sydney, Australia,* [6]*Medical Oncology, Princess Alexandra Hospital, Woolloongabba, Australia,* [7]*Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France,* [8]*Medical Oncology, Cabrini Brighton, Brighton, Australia,* [9]*Chemotherapy and Combined Therapy, N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation,* [10]*Oncology, Fiona Stanley Hospital, Murdoch, Australia,* [11]*Medical Oncology, The Crown Princess Mary Cancer Centre, Westmead, Australia,* [12]*Division of Cancer Medicine, Peter MacCallum Cancer Center, Melbourne, Australia,* [13]*Department of Medical Oncology, Royal Marsden NHS Foundation Trust, London, UK,* [14]*Dermatology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain,* [15]*Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy,* [16]*Department of Dermatology, University Hospital Essen, Essen, Germany,* [17]*Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA,* [18]*Statistics, EORTC - European Organisation for Research and Treatment of Cancer, Brussels, Belgium,* [19]*Department of Dermatology, Institut Gustave Roussy, Villejuif, France,* [20]*Institut Gustave Roussy, Villejuif, France*

Background: The EORTC 1325-MG/Keynote 054 trial demonstrated prolonged recurrence-free survival with adjuvant pembrolizumab compared to placebo (hazard ratio = 0.57; $P < 0.001$. Eggermont et al, NEJM, 2018). Incidence of adverse events grades 3 or higher related to treatment were higher in the pembrolizumab arm (14.7%) than the placebo arm (3.4%). Here we report results from the health-related quality of life (HRQoL) exploratory endpoint.

Methods: A total of 1019 patients with histologically confirmed, cutaneous melanoma metastatic to a lymph node, classified as stage IIIA, IIIB or IIIC were randomized after complete resection to receive 200 mg pembrolizumab (514 patients) or placebo (505 patients). Treatment was administered every 3 weeks for 1 year, or until disease recurrence or unacceptable toxicity. All enrolled patients were required to complete a HRQoL questionnaire at baseline and every 12 weeks (during 2 years after randomization). The primary HRQoL outcome was global health/QoL (GHQ) as measured by the EORTC QLQ-C30. All other scales from this questionnaire were secondary. Scores were compared according to the average score per patient overall, during treatment and after treatment.

Results: HRQoL compliance was >90% at baseline, >70% during the first year and >60% thereafter for both arms. Data attrition limited the analyses to week 84 (19 months). Baseline GHQ scores were similar between arms at 77 points and remained stable over time. The average GHQ score was 2.2 points (95% CI: 4.3-0.2), 1.1 points (95% CI: 3.2 - -0.9) and 2.2 points (95% CI: 4.8 - -0.4) lower in the pembrolizumab arm compared to placebo for the average overall, during and after treatment respectively. These differences are within 5 point clinical relevance threshold for the QLQ-C30. Results from the secondary scales revealed a similar pattern with scores stable over time and treatment differences never reaching the 5 point threshold.

Conclusions: Pembrolizumab maintains health-related quality of life compared to placebo, when given as adjuvant therapy for patients with resected high-risk stage III melanoma.

Clinical trial identification: EudraCT: 2014-004944-37; NCT02362594.

Legal entity responsible for the study: Merck.

Funding: Merck.

Disclosure: All authors have declared no conflicts of interest.

1279P The real-world impact of modern treatments on the survival of patients with metastatic melanoma

M. Donia[1], E. Ellebaek[2], T.H. Øllegaard[3], L. Duval[3], J.B. Aaby[4], L. Højberg[4], U.H. Køhler[5], H. Schmidt[3], L. Bastholt[4], I-M. Svane[1]

[1]*Center for Cancer Immune Therapy and Department of Oncology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark,* [2]*Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark,* [3]*Department of Oncology, Aarhus University Hospital, Aarhus, Denmark,* [4]*Medical Oncology, Odense University Hospital, Odense, Denmark,* [5]*Braintrust Consult, Braintrust Consult, Odense, Denmark*

Background: Phase III trials with strict enrolment criteria led to the approval of several new treatments for unresectable or metastatic melanoma (MM) between 2010 and 2015. The impact of modern treatments on the overall survival of the whole "real world" population of MM is unknown.

Methods: The Danish MM database contains data on the entire, unselected population diagnosed with MM within a nationwide area. To evaluate the impact of novel treatments, all MM cases diagnosed in three non-consecutive years marked by major changes in the availability of 1st line treatments (2012: i.v. IL-2 and BRAFi; 2014: anti-CTLA-4; 2016: anti-PD-1 and MEKi) were retrieved. Patients were grouped into "trial-like" and "trial-excluded" based on seven predefined eligibility criteria used in all MM registration immunotherapy clinical trials, including CNS metastases and PS ≥ 2. The database was locked on February 1st 2018.

Results: We retrieved the data of all 838 patients diagnosed with MM (excluding ocular melanoma) in Denmark during 2012, 2014 and 2016. The baseline characteristics of patients diagnosed in 2012, 2014 and 2016 were similar. In the "trial-like" population (39% of all MM), which met all seven eligibility criteria for trial participation, the median overall survival (OS) was not yet reached in the 2016 group versus 20.1 months in 2014 (hazard ratio [HR] for death 0.57, 95% CI 0.38-0.84; $p = 0.0049$) and 16.5 months in 2012 (HR 0.47, 95% CI 0.30-0.73; $p = 0.0008$). No major survival differences were observed in 2014 versus 2012 (HR 0.77, 95% CI 0.55-1.08; $p = 0.1354$). In the "trial-excluded" population (61% of all MM), 75% of patients had known CNS metastases and/or PS ≥ 2. Here, the median OS was improved to 6.8 months in the 2016 group versus 5.2 months in 2014 (HR 0.67, 95% CI 0.52-0.86; $p = 0.0013$) and 4.3 months in 2012 (HR 0.67, 95% CI 0.53-0.86; $p = 0.0016$), with no difference between 2012 and 2014 ($p = 0.65$).

Conclusions: "Trial-like" patients represent only 39% of the total MM population in the real world. Our data show that the introduction of modern treatments led to an improved survival of real world patients with MM, regardless of their clinical trial eligibility.

Legal entity responsible for the study: Danish Melanoma Oncology Group.

Funding: Herlev and Gentofte Research Council.

Disclosure: M. Donia: Honoraria for lectures: Bristol-Myers Squibb, Sanofi-Genzyme, MSD, AstraZeneca. H. Schmidt: Advisory board: MSD, Incyte, BMS; Limited grants for research: MSD. L. Bastholt: Advisory board: MSD, Incyte, BMS, Roche, Eisai, Novartis. I-M. Svane: Advisory board, Lectured: Roche, Novartis, MSD, Celgene, Incyte, TILT Bio, Pfizer, BMS, AstraZeneca, IO Biotech; Limited grants for translational research: BMS, Roche, Novartis, Incyte; Stock owner: IO biotech. All other authors have declared no conflicts of interest.

1280P Treatment patterns of melanoma by BRAF mutation status in the US in 2011-2017: A retrospective cohort study

L. Raskin[1], S. Shah[2], M. Braunlin[1], J. Buchanan[2], D. Cohan[3]

[1]*Global Center for Observational Research, AMGEN (Headquarters), Thousand Oaks, CA, USA,* [2]*Global Health Economics, AMGEN (Headquarters), Thousand Oaks, CA, USA,* [3]*Medical Affairs, AMGEN (Headquarters), Thousand Oaks, CA, USA*

Background: New therapies have changed melanoma treatment after 2011; however, these changes have not been studied well, especially in $BRAF^{Mut}$ melanomas.

Methods: We studied 4197 melanoma patients who received systemic therapy in 2011-17 in the US electronic medical record database OSCER. Among these, 1687 (40%) were studied for treatments by line of therapy (LOT) and biomarkers from 2011-16.

Results: Therapies included: 64% checkpoint inhibitors (CPI), 19% BRAF/MEK inhibitors (BRAF/MEKi), 17% chemotherapy, 16% cytokines, and 1% oncolytic viral therapy. In 2011-17, overall CPI use increased from 23% to 81% (pembrolizumab 32%,

nivolumab 23%, ipilimumab/nivolumab 21%) but ipilimumab use decreased to 13%. BRAF/MEKi use did not change (20-21%) but vemurafenib (2% in 2017) was replaced by dabrafenib/trametinib and cobimetinib/vemurafenib (14% and 4%). Cytokine and chemotherapy use declined (43% to 3% and 35% to 7%, respectively). During 2011-17, CPI and BRAF/MEKi were used more in LOT 1-4 (60% and 25%) than as adjuvant (30% and 2%), whereas cytokines were used as adjuvant only (64%). CPI were used most in $NRAS^{Mut}$ (85%) and less in $BRAF^{Mut}$, $BRAF^{wt}$, or $NRAS^{wt}$ (57-66%). In $BRAF^{Mut}$, CPI use was higher in stage III (62%) than IV (52%) unlike in $BRAF^{wt}$ (52% stage III vs. 90% stage IV). BRAFi were used in 65% of $BRAF^{Mut}$, more in stage IV than III (79% vs. 34%). $BRAF^{Mut}$ and $NRAS^{Mut}$ received less adjuvant therapy than wild-type (20-22% vs. 28-31%) but more LOT ($BRAF^{Mut}$ had 89% LOT 1, 37% LOT 2, 13% LOT 3, 5% LOT 4+). The table compares treatment changes in $BRAF^{Mut}$ melanoma between 2011-14 and 2015-16.

Table: 1280P Treatment changes in $BRAF^{mut}$ melanoma between 2011-14 and 2015-16

Therapy	2011-14			2015-16		
	Adjuvant	LOT 1	LOT 2	Adjuvant	LOT 1	LOT 2
BRAF/MEKi						
Vemurafenib	12%	28%	12%	0	5%	5%
Dabrafenib/Trametinib	4%	21%	26%	9%	43%	38%
Cobimetinib/Vemurafenib	0	<1%	2%	0	4%	10%
Dabrafenib	0	4%	8%	0	4%	2%
Trametinib	0	2%	4%	0	1%	2%
CPI						
Ipilimumab	14%	23%	20%	35%	8%	5%
Pembrolizumab	1%	7%	11%	7%	13%	21%
Nivolumab	0	7%	12%	9%	10%	21%
Ipilimumab/Nivolumab	1%	6%	7%	7%	15%	12%
Cytokines	60%	7%	1%	33%	3%	0
Chemotherapy	2%	4%	7%	0	3%	0

Conclusions: Checkpoint inhibitors have replaced other advanced melanoma therapies, providing more treatment options to patients with $BRAF^{Mut}$ melanoma.

Legal entity responsible for the study: Amgen Inc.

Funding: Amgen Inc.

Disclosure: L. Raskin: Employee, Stock ownership: Amgen Inc. S. Shah, J. Buchanan, D. Cohan: Employee, Stockholder: Amgen Inc. All other authors have declared no conflicts of interest.

1281P Assessment of real-world effectiveness of first-line (1L) nivolumab (NIVO) plus ipilimumab (IPI) or NIVO monotherapy for advanced melanoma: A retrospective cohort study

M. Freeman[1], K. Gupte-Singh[2], M. You[3], T.K. Le[3], C. Ritchings[4], S. Rao[2], S. Jang[5]

[1]Department of Medical Oncology & Therapeutics Research, City of Hope, Duarte, CA, USA, [2]Health Economics Outcomes Research, Bristol-Myers Squibb, Princeton, NJ, USA, [3]Center for Observational Research & Data Sciences, Bristol-Myers Squibb, Princeton, NJ, USA, [4]Melanoma, Bristol-Myers Squibb, Princeton, NJ, USA, [5]Hematology Oncology, Inova Melanoma and Skin Cancer Center, Fairfax, VI, USA

Background: NIVO+IPI and NIVO are approved for 1L treatment of patients with unresectable or metastatic (advanced) melanoma. This study assessed real-world outcomes (objective response rate [ORR], progression-free survival [PFS], and overall survival [OS]) with NIVO+IPI or NIVO alone in patients with advanced melanoma using the US Flatiron Health electronic health record database from January 2011 to June 2017.

Methods: Eligible patients were aged ≥18 years, diagnosed with advanced melanoma, and treated with 1L NIVO+IPI or NIVO (index date). Outcomes were assessed based on an in-depth review of patient charts. Patients were followed until death, database discontinuation, or end of the study period. Factors associated with ORR, PFS, and OS were evaluated using logistic and Cox proportional hazards regression models. An evaluation of safety outcomes is ongoing.

Results: 463 patients were eligible (NIVO+IPI, n = 254; NIVO, n = 209), with a mean follow-up of 9.2 months (range 1.0-31.6). Of those with data available, 39% of patients had elevated LDH, 35% had ECOG PS 1, and 33% were BRAF mutant. Compared with NIVO patients, NIVO+IPI patients were younger (71 vs 61 years) and a higher proportion were treated in academic centers (7.7% vs 18.9%). For NIVO+IPI and NIVO, ORR was 51% and 41%, median PFS was 12.2 and 5.4 months (1-year PFS rate 51% and 37%), and median OS was not reached and 20.1 months (1-year OS rate 71% and 60%), respectively. After adjusting for patient characteristics, NIVO+IPI patients were twice as likely to respond within 3 months, had a 35% lower likelihood of progression, and had a 35% lower likelihood of death compared with NIVO (Table).

Table: 1281P

Factor	Model value vs reference value	Hazard/odds ratio (95% CI)	P value
PFS			
Treatment	NIVO+IPI vs NIVO	0.65 (0.50, 0.83)	0.0006
LDH	≤ULN vs >ULN	0.56 (0.41, 0.77)	0.0003
OS			
Treatment	NIVO+IPI vs NIVO	0.65 (0.47, 0.90)	0.0354
LDH	≤ULN vs >ULN	0.44 (0.29, 0.67)	<0.0001
ECOG PS	0–1 vs 2–5	0.48 (0.31, 0.75)	0.0016
Response			
Treatment	NIVO+IPI vs NIVO	2.13 (1.27, 3.56)	0.0039

Conclusions: In this real-world clinical practice database, 1L NIVO+IPI was associated with improved efficacy outcomes compared with NIVO alone in patients with advanced melanoma.

Editorial acknowledgement: Editorial assistance was provided by StemScientific, funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: M. Freeman: Consulting role: Merck, Merck Serono, Novartis, Amgen; Speakers' bureau: Bristol-Myers Squibb. K. Gupte-Singh, M. You, T.K. Le, C. Ritchings, S. Rao: Employee: Bristol-Myers Squibb. S. Jang: Personal fees: Bristol-Myers Squibb.

1282P Responder analysis based on patient-reported outcomes (PROs) and clinical endpoints (CEPs) in patients (pts) with metastatic Merkel cell carcinoma (mMCC) treated with avelumab

S.P. D'Angelo[1], F. Fofana[2], M. Schlichting[3], M. Henry-Szatkowski[4], M. Hennessy[5], M. Bharmal[6]

[1]Medical Oncology, Memorial Sloan Kettering Cancer Center & Weill Cornell Medical College, New York, NY, USA, [2]Patient-Centered Outcomes, Mapi Group, Leiden, Netherlands, [3]BioStatistics, Merck KGaA, Darmstadt, Germany, [4]Patient-Centered Outcomes, Mapi Group, Lyon, France, [5]Medical Oncology, EMD Serono, Billerica, MA, USA, [6]Global Evidence & Value Development, Merck KGaA, Darmstadt, Germany

Background: To better understand the impact of the anti–PD-L1 antibody avelumab, clinical outcomes and PROs in chemotherapy-refractory pts with mMCC enrolled in a single-arm, international phase 2 trial (NCT02155647) were analysed. Here we explore the proportion of pts categorised as responders based on these outcome measures.

Methods: PROs were assessed at baseline (BL), at week 7, thereafter Q6W until disease progression, and at end of treatment using EQ-5D, a generic health-related quality of life (HRQoL) tool, and FACT-M, a cancer-specific HRQoL tool. Pts were categorised as meaningfully improved/stable or as meaningfully worsened. HRQoL deterioration-free survival (QFS) was defined as the time from BL to either a meaningful worsening from BL with no further improvement in HRQoL or death. QFS rates of PRO endpoints were computed at specific time points. Responders based on PRO meaningfully improved/stable and QFS analyses were described along with the best overall response (BOR) and progression-free survival (PFS) analyses assessed by IERC per RECIST v1.1.

Results: As of Sept 26, 2017, 88 pts had been followed for a minimum of 24 months (mo; median, 29.2 [range, 24.8-38.1]). The table presents responders based on PROs and CEPs at 6, 12, 18, and 24 mo. In addition, PRO-based, 2-year rates of improved/stable endpoints tended to be higher than the BOR rate of 33%, ranging from 41% for FACT-M physical well-being to 58% for FACT-M melanoma surgery scale.

Table: 1282P

		6 mo	12 mo	18 mo	24 mo
CEPs					
PFS rate, %		40	29	29	26
PRO endpoints					
QFS rate, %	EQ-5D VAS	52	52	49	38
	FACT-M total	45	40	36	32
	FACT-M physical well-being	44	37	33	33
	FACT-M social/family well-being	40	40	31	26
	FACT-M emotional well-being	45	40	33	33
	FACT-M functional well-being	41	34	31	27
	FACT-M melanoma subscale	53	42	39	39
	FACT-M melanoma surgery scale	46	43	38	38
	FACT-G total	41	39	35	31

Conclusions: The findings show similarity in the proportion of responders based on clinical and PRO endpoints, reiterating the potential association of both outcome measures in this mMCC population. This confirms the interest in using PROs in trials to contribute to the interpretation of objective CEPs.

Clinical trial identification: NCT02155647.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking Inc., Hamilton, NJ, USA.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: This trial was sponsored by Merck KGaA, Darmstadt, Germany and is part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.

Disclosure: S.P. D'Angelo: Financial interest from EMD Serono, Pfizer, and Nektar. F. Fofana: Employee: Mapi Group. M. Schlichting, M. Bharmal: Employee: Merck KGaA. M. Henry-Szatkowski: Employee: Mapi Group; Paid consultant: Merck KGaA. M. Hennessy: Employee, Financial interest: EMD Serono.

1283P Treatment pattern and clinical outcomes of patients with locally advanced and metastatic melanoma in a real-world setting in China

C. Cui[1], X. Yan[1], S. Liu[2], A. Deitz[3], L. Si[4], Z. Chi[1], X. Sheng[1], B. Lian[1], J. Li[2], J. Ge[2], X. Wang[1], L. Mao[1], B. Tang[1], L. Zhou[1], X. Bai[1], S. Li[1], B. Li[2], H. Wu[2], J. Guo[1]

[1]Urology and Melanoma, Beijing Cancer Hospital, Beijing, China, [2]Medical Oncology, MSD China, Beijing, China, [3]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA, [4]Department of Renal Cancer and Melanoma, Peking University Cancer Hospital-Beijing Cancer Hospital, Beijing, China

Background: In China, treatment options for late-stage melanoma, particularly for second-line (2L) therapy, are limited. This retrospective, observational study used electronic medical records (EMRs) of patients (pts) with melanoma treated at Beijing Cancer Hospital (BCH) to describe the treatment pattern and real-world clinical outcomes in locally advanced, metastatic melanoma in China.

Methods: All adult pts with unresectable stage III or IV melanoma who initiated treatment between Jan 1, 2014, and Dec 31, 2015, were eligible. Pts were treated and followed up with regular imaging (every 3 mo). Trained researchers performed additional medical chart reviews to supplement data captured in the EMR database. Complete or partial responses, per RECIST v1.1 were adjudicated case by case. Survival analysis involved the Kaplan-Meier method, pts were censored at last known date alive before Dec 31, 2017.

Results: Of 248 pts included in the study, 40.7% and 30.6% had acral and mucosal histology, respectively; almost all (~95%) had stage IV melanoma; 221 received first-line (1L) therapy and 116 received 2L therapy (89 received both at BCH within the treatment period). The most common 1L regimens were dacarbazine + cisplatin + recombinant human endostatin (RHE) (36.7%) and paclitaxel + carboplatin + bevacizumab (22.2%). The most common 2L regimens were paclitaxel albumin + carboplatin + bevacizumab (22.4%), paclitaxel + carboplatin + RHE (15.5%) and paclitaxel albumin + cisplatin + RHE (12.1%). Clinical outcomes in pts with advanced melanoma are summarized in the table and are generally unfavorable: ORR <10%; median PFS <4 months; median OS < 1 year. Median DOR was 9.1 mo for 1L and 7.5 mo for 2L therapy.

Table: 1283P

	1L Therapy (N = 221)	2L Therapy (N = 116)
Response		
CR, n	2	0
PR, n	12	4
ORR, % (95% CI)	6.3% (3.5-10.4)	3.4% (0.9-8.6)
Median DOR (range), months	9.1 (1.7-28.4+)	7.5 (4.6-24.2+)
Median PFS (95% CI), months	3.5 (2.9-4.2)	2.3 (2.0-3.0)
12-month PFS rate	10.6%	5.2%
Deaths, n (%)	171 (77.4)	101 (87.1)
Median OS (95% CI), months	10.5 (9.2-12.1)	7.5 (6.5-8.7)
12-month OS rate	43.5%	30.5%

CI, confidence interval; CR, complete response; DOR, duration of response; 1L, first-line therapy; 2L, second-line therapy; ORR, objective response rate; OS, overall survival; PR, partial response; PFS, progression-free survival.

Conclusions: The poor outcomes observed in this study suggest a high degree of unmet medical need for advanced melanoma in China in both the 1L and 2L settings.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Doyel Mitra, PhD, of the ApotheCom pembrolizumab team, Yardley, PA, USA. This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: C. Cui, X. Yan, L. Si, Z. Chi, X. Sheng, X. Wang, L. Mao, B. Tang, L. Zhou, X. Bai, S. Li: Research funding: Merck & Co., Inc. S. Liu, J. Li, J. Ge, H. Wu: Employee, Stockholder: MSD China. A. Deitz: Employee, Stockholder: Merck & Co., Inc. B. Lian: Research funding: Merck. B. Li: Employee: MSD China. J. Guo: Research funding, Advisory board: Merck & Co., Inc.

1284P Real life costs associated with the management of unresectable metastatic melanoma (uMM)

D. Strens[1], M. Peeters[2], P.M.C. Specenier[3]

[1]Realidad, Grimbergen, Belgium, [2]Oncology, U.Z.A. University Hospital Antwerp, Edegem, Belgium, [3]Oncology, Antwerp University Hospital, Grimbergen, Belgium

Background: Cancer care costs are a major concern for patients and society. We aimed to assess real life costs for the medical management of uMM.

Methods: We performed a retrospective patient chart review collecting data on demographics, disease characteristics and management. A complete registry of patients diagnosed with melanoma at the Antwerp University Hospital between 2007 and 12/2017 was compiled. Eligible for this chart review were all patients with uMM with sufficient data available and who either had an observation period of > 1 year at the time of this review or who deceased before December 31, 2017. Direct costs were calculated by multiplying each item of resource use, obtained from each individual patient chart, with its unit cost (2018, €) using the Belgian public health care payer's perspective (PHCP) and patient's perspective. A Kaplan–Meier sample average (KMSA) estimator was used to weight expected costs by the probability of survival and to adjust for censored data.

Results: 89 patients fulfilled all eligibility criteria for this chart review. Ten of the patients (11%) are still alive. 9 patients (10%) received best supportive care (BSC) only. 40 patients (45%) received > 1 immunotherapy or targeted agent. Mean overall monthly cost/patient for the entire cohort was € 7,244, of which € 7,153 was covered by the public health care payer. The cost was driven by systemic treatment costs (69% of cost). Median overall survival (OS) was 8.18 months (95 % CI: 6.0-10.3). Mean monthly overall cost was € 9,269 for patients (n = 40) with potential access to anti-PD1, anti-CTLA-4, BRAFi, and MEKi; median OS in this cohort was 13.83 months (95 % CI: 8.6-19.0). Mean monthly overall cost was € 3,258 for patients (n = 33) treated with chemotherapy/BSC only. Median OS in this cohort was 3.91 months (95 % CI: 2.2-5.6). Mean monthly overall cost was € 5,398 for patients (n = 16) who had access to anti-CTLA-4 and/or BRAFi but not to MEKi and anti-PD1. Median OS in these patients was 11.0 months (95 % CI 7.5-14.6).

Conclusions: Management of uMM results in considerable costs for the PHCP, mainly driven by systemic treatment costs. Also in a real-life setting, the introduction of immunotherapy and targeted agents substantially improved survival. However, mean monthly cost has nearly tripled.

Legal entity responsible for the study: Antwerp University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1285P Drug treatment in melanoma: A real-world analysis across Europe and Japan

A. Martinez de Pinillos, P. Nasuti, C. Anger

Real World & Analytics Solutions, IQVIA, London, UK

Background: Incidence/prevalence of melanoma in Asia are both 3% of that in Europe. However, westernization of the Asian population (increase in UV exposure and sun-seeking), is impacting these traditionally low figures. Local drug regulatory agencies have anticipated a shift in treatment from standard to novel molecular targeted and immunotherapeutic products. This study examines treatment differences in melanoma patients in EU5 and Japan, considering dissimilarities between populations.

Methods: A large sample of 4,209 drug treated melanoma cases were collected January 2017-March 2018 through a cross sectional survey in EU5 (France, Germany, Spain, Italy, UK), and Japan. Testing for genetic mutations and drug use were analysed for 3,997 advanced/metastatic (adv/met) patients.

Results: When specified, Acral Lentiginous Melanoma (ALM) and Nodular Melanoma were the most common histology in Japan (25%) during the investigated period, while being only 4% in EU5, where nodular melanoma (23%) and superficial spreading melanoma (21%) were the most frequent. Anti PD1/CTLA4 lead the adv/met melanoma setting in EU5 (58%), followed by BRAF (35%) and MEK inhibitors (19%). In Japan, although anti PD1/CTLA4 play an important role in adv/met melanoma (57%), BRAF and MEK inhibitors are uncommon (up to 2% use) and other standard drugs (Interferons, Anthracyclines, Platinum-based, other chemotherapy) which are uncommon in EU5 (4% use at most), are used in up to 21% of Japanese patients. BRAF mutations were tested in 96% in EU5 vs. 52% in Japan for adv/met patients, with 48% and 26% positive cases respectively. PD1 testing was higher in Japan (40%), also presenting a larger PD1 positive population (17%) than the European counterpart.

Conclusions: We have demonstrated penetration of novel immuno-oncology drugs both in Europe and Japan. Existing differences in melanoma treatment between both regions provide insights on Asian populations, which are not as well documented. Although these might be influenced by ethnic and genetic factors, maturity of the region should be considered and further analyses would provide an interesting observation on the trend of both regions.

Legal entity responsible for the study: IQVIA.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1286P EUMelaReg: A European platform for outcome research on real world treatment data of patients with advanced melanoma

M. Weichenthal[1], A.C.J. van Akkooi[2], P. Mohr[3], E. Ellebaek[4], I-M. Svane[4], S. Ugurel-Becker[5], U. Leiter[6], L. Hoejberg[7], J.B.A.G. Haanen[8], H. Schmidt[9], T.H. Oellegaard[10], M.W.J.M. Wouters[2], D. Schadendorf[11], L. Bastholt[12]

[1]Dermatology, University of Kiel, Kiel, Germany, [2]Surgical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [3]Skin Cancer Center, Dermatologic Center Buxtehude, Buxtehude, Germany, [4]Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [5]Dermatology, University Hospital Essen, Essen, Germany, [6]Dermatooncology, Department of Dermatology, University Hospital Tuebingen, Tuebingen, Germany, [7]Oncology, Odense University Hospital, Odense, Denmark, [8]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [9]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [10]Oncology, Aarhus University Hospital, Aarhus, Denmark, [11]Department of Dermatology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany, [12]Medical Oncology, Odense University Hospital, Odense, Denmark

Background: During the past ten years several fundamental breakthroughs have radically changed the treatment options in metastatic melanoma. Both targeted therapies (TT) and immunotherapies (IT) randomized clinical trials have shown significant benefit in relapse free and overall survival. Since the underlying clinical trials represent selected patient populations who had to meet several inclusion and exclusion criteria, the EuMelaReg consortium sought to evaluate "real world" melanoma cases presenting for initial treatment decision with stage IV or unresectable stage III disease.

Methods: Data sources from Denmark (Danish metastatic melanoma database), Germany (ADOReg Registry) or The Netherlands (Dutch Melanoma Treatment Registry) were merged in a stepwise procedure into a standardized data representation format. The harmonized database for the current analysis included subgroups of patients presenting in 2014 for treatment of non-resectable stage III or metastatic stage IV disease on a regular basis. Criteria used to validate the process of data harmonization contained primary demographic data as well as data concerning the advanced disease status (ECOG status, serum LDH, and baseline tumor burden including the presence of brain metastasis), and the different treatment strategies and regimens.

Results: It could be shown that more than 30 percent of the cases included would not have qualified for common inclusion and/or exclusion criteria of clinical phase III trials in advanced melanoma. Moreover, the distribution of prognostic and predicive factors varied substancially between the real-world populations and published study populations.

Conclusions: Final endpoints of the ongoing data collection and analysis will contain among other parameters progression free survival, overall survival, and tolerability of treatment. Collaboration is sought to a range of other European registries and countries.

Legal entity responsible for the study: The EUMelaReg Consortium (European Melanoma Registries Network).

Funding: BMS, MSD, Roche, Novartis.

Disclosure: M. Weichenthal: Grants, honoraria, fees: BMS, MSD, Roche, Novartis, Millennium, Medac, Takeda, Amgen, Pierre-Fabre. A.C.J. van Akkooi, P. Mohr, E. Ellebaek, I-M. Svane, S. Ugurel-Becker, U. Leiter, L. Hoejberg, J.B.A.G. Haanen, H. Schmidt, T.H. Oellegaard, M.W.J.M. Wouters, D. Schadendorf, L. Bastholt: BMS, MSD, Roche, Novartis.

1287P Advanced melanoma treatment patterns in the modern era: United Kingdom (UK) real world retrospective chart review study

J.J. Sacco[1], P.G. Corrie[2], O. Oladipo[3], M. Payne[4], J. Larkin[5], T. Talbot[6], J. Wagstaff[7], S. Cheetham[2], D. Stein[8], M. Soni[8], C. Coombs[9], A. Amadi[10], M. Wang[11], J. Ellis[11]

[1]Medical Oncology, Clatterbridge Cancer Center, Bebington, UK, [2]Medical Oncology, Addenbrooke's Hospital, Cambridge, UK, [3]Medical Oncology, Belfast City Hospital, Belfast, UK, [4]Medical Oncology, Churchill Hospital, Oxford, UK, [5]Medical Oncology, Royal Marsden Hospital, London, UK, [6]Medical Oncology, Royal Cornwall Hospital, Cornwall, UK, [7]Medical Oncology, Singleton Hospital, Swansea, UK, [8]Real-World Evidence, Evidera, London, UK, [9]Real-World Evidence, Evidera, Bethesda, MD, USA, [10]Outcomes Research, Bristol-Myers Squibb, London, UK, [11]Medical Affairs, Bristol-Myers Squibb, London, UK

Background: In 2016, all licensed single agent and combination BRAF-targeted therapies (BT) and checkpoint inhibitors (CI) were approved for advanced melanoma in the UK. An evaluation of treatment choices in routine clinical practice was undertaken.

Methods: A retrospective chart review was conducted in 7 UK cancer centres, which included patients ≥18 years old with advanced melanoma who started 1st-line (1L) therapy and received at least 1 dose between July 2016 and June 2017. Patients taking part in clinical trials were not eligible. Patient demographics, disease characteristics, and 1L and subsequent therapy lines were recorded. Interim analyses were descriptive.

Results: 280 patients were followed for median 9 (range: <1-19) months; 80%, 19%, and 1% patients received 1, 2, or 3 therapy lines. 92% of patients had BRAF testing, 26% had NRAS testing, and <1% of tumours were tested for PDL1. BRAF and NRAS mutation rates were 41% and 7%, respectively. 73% of patients received CIs 1L: 46% pembrolizumab (Pem), 26% nivolumab+ipilimumab (N+I), 1% ipilimumab (Ipi), <1% nivolumab (N); 27% patients received BT 1L: 20% dabrafenib+trametinib (D+T), 7% dabrafenib (D). 38% of BRAF mutant patients received 1L CI. Most common reasons for therapy selection were biomarker status (42%) and perceived benefit (27%). Two-thirds of patients discontinued 1L therapy (BT: 76%, CI: 62%), 79% within 6 months of starting. Most common reasons for stopping were adverse events for N+I (59%) and progressive disease for BT and Pem (54% each). 40% of patients who discontinued BT received 2nd-line (2L) therapy 71% N+I, 29% Pem, <1% vemurafenib. 17% of patients who discontinued Pem received 2L therapy: 57% Ipi, 21% BT (7% D+T, 14% D), 14% other, and 7% trial agents. 41% of patients who discontinued N+I received 2L therapy: 63% BT (58% D+T, 5% D), 21% Pem, 8% other, and 8% trial agents.

Conclusions: The most common 1L therapy was CI. BRAF mutation status, however, influenced treatment choice, with two-thirds of BRAF mutant melanoma patients receiving BT 1L. More than double the number of patients receiving BT and N+I 1L received 2L therapy compared with patients receiving Pem 1L. Further exploration of these data will be presented.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: J.J. Sacco: Lead investigator: Clatterbridge hospital which is a site participating in this chart review study which received funding from BMS. P.G. Corrie: Lead investigator from Addenbrooke's hospital which is a site participating in this chart review study which received funding from BMS. O. Oladipo: Lead investigator from Belfast City hospital which is a site participating in this chart review study which received funding from BMS. M. Payne: Lead investigator from Churchill hospital which is a site participating in this chart review study which received funding from BMS. J. Larkin, T. Talbot: Lead investigator from Royal Marsden hospital which is a site participating in this chart review study which received funding from BMS. J. Wagstaff: Lead investigator from Singleton hospital which is a site participating in this chart review study which received funding from BMS. S. Cheetham: Data manager from Addenbrooke's hospital which is a site participating in this chart review study which received funding from BMS. D. Stein, M. Soni, C. Coombs: Employee of Evidera. Evidera received funding from BMS for development of this abstract. A. Amadi, M. Wang, J. Ellis: Employee of BMS.

1288P The national melanoma research registry: A fundamental for disease characterization and epidemiology

F. Gwadry-Sridhar[1], H. McConkey[2], X. Teng[3], D.S. Ernst[4]

[1]Informatics, Pulse infoframe Inc., London, ON, Canada, [2]Research Coordinator, Global Melanoma Research Network, London, ON, Canada, [3]Data Science, Pulse Infoframe Inc., London, ON, Canada, [4]Dept of Oncology, London Regional Cancer Program, London, ON, Canada

Background: Approximately 7200 Canadians are diagnosed with primary melanoma each year resulting in 1240 deaths. While the advent of new treatment provides hope, the emergence of precision medicine requires genomic data and clinical trials benefit from real-world data. To avail of these advances, a better understanding of both disease characterization and the impact of treatment on both clinical endpoints and patient reported outcomes is necessary to assess morbidity and mortality. We initiated a Pan-Canadian Melanoma Research Network (CMRN) in 2010 to collect both clinical and patient reported data.

Methods: The CMRN collects data retrospectively and prospectively from ten cancer centers in Ontario, Alberta and Quebec. The data dictionary includes 250 disease specific variables collected to produce structured data, including stage, pathology, tumour mutation types, time from primary diagnosis to recurrence, sites of metastases, and lines of treatment. Outcomes such as metastasis free interval, quality of life and survival and performance status are collected.

Results: 3016 patients (pts) have consented to this registry. 11% pts are $<$ 50 years; 42% pts are 41-70 years; whereas 47% pts are $>$ 71 years. 58% are male and 42% are female. 67% of pts presented with Stage I or II melanoma, and 33% presented with Stage III or IV. Of pts with known primary histology, 73% were classified as superficial spreading or nodular (36.5% each). Of the 589 pts who received mutation testing, 51% were found to have a BRAF mutation. Interferon treatment accounted for 80% of adjuvant therapies, whereas $<$ 3% were checkpoint inhibitors or targeted therapies. 931 pts received metastatic systemic treatment. 14% of 1st line treatments were targeted therapies, whereas 18% were checkpoint inhibitors. 49% of metastatic patients received a 2nd line treatment, with checkpoint inhibitors and targeted therapies accounting for 65% and 10%, respectively.

Conclusions: This CMRN allows for detailed analysis of both patient and disease characteristics, providing a key tool for future research. This network is still expanding to include additional provinces and continues to conduct real-world research to advance care and improve outcomes.

Legal entity responsible for the study: Global Melanoma Research Network.

Funding: Global Melanoma Research Network.

Disclosure: All authors have declared no conflicts of interest.

1289P Assessment of quality of life in patients with metastatic melanoma in real clinical practice in France

M. Kandel[1], C. Allayous[2], S. Dalle[3], L. Mortier[4], S. Dalac Rat[5], C. Dutriaux[6], M-T. Leccia[7], B. Guillot[8], P. Saiag[9], J-P. Lacour[10], D. Legoupil[11], F. Brunet-Possenti[12], B. Dreno[13], A. Ballon[14], A. Bardet[15], S. Michiels[1], C. Lebbe[2], I. Borget[1]

[1]Team Oncostat, CESP, Gustave Roussy, Villejuif, France, [2]Dermatology, Hôpital St. Louis, Paris, France, [3]Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [4]Dermatology, Hopital Claude Huriez, Lille, France, [5]Dermatology, CHU Dijon, Dijon, France, [6]Department of Dermatology, Oncology Unit, Saint André Hospital, Bordeaux, France, [7]Dermatology, CHU Grenoble - Hopital Michallon, La Tronche, France, [8]Dermatology, CHU de Montpellier, Montpellier, France, [9]Dermatology, Hopital Ambroise Pare, Boulogne-Billancourt, France, [10]Dermatology, Archet Hospital, CHU Nice, Nice, France, [11]Dermatology, Brest Hospital, Brest, France, [12]Dermatology, AP-HP Bichat Hospital, Paris, France, [13]Dermatology, Polyclinic Saint Jean, Cagnes-sur-Mer, France, [14]Dermatology, AP-HP, Saint-Louis Hospital, Paris, France, [15]SBE, Gustave Roussy, Villejuif, France

Background: Significant advances were recently observed in the treatment of metastatic melanoma (MM). With 60% of patients now reaching a second line of treatment (trt) and a significant improvement in survival, the assessment of quality of life (QoL) during whole disease is necessary. The objective of this work is to describe the evolution of QoL of patients (pts) over trt lines until death.

Methods: QoL is collected through MelBase, a prospective French multicentric cohort dedicated to the follow-up of adults with MM. It is assessed using the EQ-5D (called utility, with range 0-1) and the FACT-M (score range 0-172) questionnaires, at inclusion (i.e. at MM diagnosis) and then every 3 months or at each trt change, until death. Evolution of QoL as compared to the beginning of the 1st line is described at the beginning of the 2nd line, at progression and one month before death.

Results: QoL is assessed on 1183 pts included between 2013 and 2017. Median follow-up is 12 months and 605 patients died during follow-up. At inclusion, the mean score is 0.831 [CI$_{95\%}$: 0.817; 0.843] for utility and 128.487 [CI$_{95\%}$: 127.047; 129.924] for FACT-M scores. Between baseline and 6 months of 1st trt line, QoL decreased of 0.008 [CI$_{95\%}$: -0.010; 0.030] (-0.8%) for utility score and of 1.62 [CI$_{95\%}$: -0.770; 4.010] (-0.9%) for the FACT-M scores compared to baseline, whereas it evolves of -0.003 [CI$_{95\%}$: -0.030; 0.010] (-0.3%) for utility score and of 0.256 [CI$_{95\%}$: -2.550; 3.060] (0.2%) for the FACT-M at the beginning of 2nd line. At progression, QoL evolves of -0.015 [CI$_{95\%}$: -0.03; 0.01] (-1.5%) for utility score and of -2.640 [CI$_{95\%}$: -1.420; 3.450] (1.5%) for the FACT-M. The greatest QoL deterioration was observed one month before death by -0.129 [CI$_{95\%}$: -0.170; -0.090] (-13%) for utility score and by 18.961 [CI$_{95\%}$: -22.880; -15.040] (11%) for the FACT-M score.

Conclusions: In Melbase cohort, patient's QoL with MM seems to be fairly stable through trt lines and disease progression. The QoL of pts appears to be mainly degraded during the "pre-death" period. Complementary analyses are ongoing to evaluate the impact on prognostic factors, treatments and time on the evolution of QoL.

Legal entity responsible for the study: DRCI AP-HP.

Funding: National Cancer Institute (INCa).

Disclosure: C. Allayous: Travel, accomodations, expenses: BMS, Amgen. S. Dalle: Research funding (institution): Roche, BMS; Travel, accomodations, expenses: BMS, MSD. L. Mortier: Travel, accomodations, expenses: BMS, Novartis, Roche. S. Dalac Rat: Honoraria: BMS; Consulting or advisory role: Roche, BMS; Speakers' bureau: BMS; Travel, accomodations, expenses: BMS, Roche. C. Dutriaux: Consulting or advisory role: Roche, BMS, Novartis, MSD. P. Saiag: Honoraria: BMS, Roche, MSD, Novartis, Array, Pierre-Fabre; Consulting or advisory role: BMS, Roche, MSD, Novartis, Array, Pierre-Fabre; Research funding: Roche; Travel, accomodations, expenses: BMS, Roche, MSD, Novartis. J.-P. Lacour: Honoraria: BMS; Research funding (institution): Roche, BMS,Novartis, GSK. D. Legoupil: Honoraria: BMS Consulting or advisory role: BMS; Travel, accomodations, expenses: BMS. A. Bardet: Employee, Shareholder: Roche. C. Lebbe: Honoraria: BMS, Roche, MSD, Novartis, Amgen; Consulting or advisory role: BMS, Roche, MSD, Novartis, Amgen; Speakers' bureau: Roche, MSD, Novartis, Amgen; Research funding: Roche, BMS; Travel, accomodations, expenses: BMS, Roche, Amgen. I. Borget: Honoraria: BMS, Roche, Janssen Consulting or advisory role: BMS, Roche, Novartis, Janssen, Merck; Travel, accomodations, expenses: Janssen, Merck, Novartis, Roche. All other authors have declared no conflicts of interest.

1290P Avelumab in European patients (pts) with metastatic Merkel cell carcinoma (mMCC): Experience from an ad-hoc expanded access program (EAP)

P. Nathan[1], V. Kasturi[2], L. Dirix[3], E. Fenig[4], P.A. Ascierto[5], M. Hennessy[6], J. Reed[6], A. Engelsberg[7], S. Hariharan[8], C. Lebbé[9]

[1]Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, Middlesex, UK, [2]Medical Affairs, EMD Serono USA, Rockland, MA, USA, [3]Medical Oncology, GZA Ziekenhuizen Campus Sint-Augustinus University of Antwerp, Antwerp, Belgium, [4]Medical Oncology, University of Tel Aviv, Tel Aviv, Israel, [5]Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [6]Medical Oncology, EMD Serono, Billerica, MA, USA, [7]Medical Oncology, Pfizer Pharma GmbH, Berlin, Germany, [8]Medical Oncology, Pfizer, New York, NY, USA, [9]CIC and Dermatology, Saint-Louis Hospital, Paris, France

Background: Avelumab—a human anti–PD-L1 IgG1 monoclonal antibody—showed favorable efficacy and safety in pts with mMCC in the phase 2 JAVELIN Merkel 200 trial (NCT02155647), leading to its approval in multiple countries. Here, we describe real-world experience with avelumab in European pts with mMCC.

Methods: European pts participating in the EAP (NCT03089658) had stage IV mMCC and progressive disease (PD) on/after chemotherapy or were ineligible for either chemotherapy or participation in clinical trials. In contrast to JAVELIN Merkel 200, pts could have ECOG PS $\geq$ 2, treated brain metastases, or immunosuppressive conditions. Pts received a 3-mo supply of avelumab (administered 10 mg/kg IV Q2W until PD or unacceptable toxicity); resupply was allowed for pts with complete response (CR), partial response (PR), stable disease, or clinical benefit per physician assessment. No central imaging was obtained.

Results: As of April 30, 2018, of 521 requests for avelumab across 37 countries, 343 were received in Europe: 305 were approved (including 20 for immunocompromised [IC] pts), 29 were medically rejected, and 9 were withdrawn. Most requests were from France (n = 96) and Italy (n = 87). 275 European pts received avelumab. Median age was 73 y (range, 28-95 y), and 69% of pts were male. Of 250 pts on treatment $>$3 mo, 145 (58%) had either unevaluable tumors or no data reported (including 11 IC pts). Of 105 evaluable pts, physician-assessed objective responses were observed in 54.3% (57 pts; including 3 IC pts [2 CR and 1 PR]) with 25.7% CR (27 pts) and 28.6% PR (30 pts). Median duration of treatment in pts with response was 195 d (range, 30-570 d). The disease control rate in evaluable pts was 75%. No new safety signals were reported. The EAP is ongoing but closing in 2018 as required postapproval.

Conclusions: The avelumab EAP provides an alternative treatment option for pts with mMCC with PD on/after chemotherapy or who are ineligible for either chemotherapy or clinical trials. In a real-world setting, avelumab showed efficacy and safety consistent with JAVELIN Merkel 200.

Clinical trial identification: Trial Protocol Number: NCT03089658.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking Inc., Hamilton, NJ, USA.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Funding was provided by Merck, KGaA, Darmstadt, Germany in alliance with Pfizer, Inc.

Disclosure: P. Nathan: Honoraria: AstraZeneca, Bristol-Myers Squibb, Novartis, Immunocure, Roche, Pfizer; Membership on any entity's Board of Directors or

advisory committees: AstraZeneca, Bristol-Myers Squibb, Novartis, Immunocure, Roche, Pfizer. V. Kasturi, M. Hennessy, J. Reed: Employee: EMD Serono. P.A. Ascierto: Consultancy (Includes expert testimony): Bristol-Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Array, Novartis, Amgen, Merck-Serono, Pierre-Fabre, Incyte, Genmab, Newlink Genetics, Medimmune, Syndax, AstraZeneca; Research Funding: Bristol-Myers Squibb, Roche-Genentech, Array; Membership on any entity's Board of Directors or advisory committees: Bristol-Myers Squibb, Roche-Genentech, Array, Novartis. A. Engelsberg: Employee: Pfizer Pharma GmbH. S. Hariharan: Employee, Equity ownership: Pfizer. C. Lebbé: Financial interest: Roche, BMS, Novartis, Amgen, MSD. All other authors have declared no conflicts of interest.

1291P Cost-effectiveness (CE) of avelumab vs standard care (SC) for the treatment of patients (pts) with metastatic Merkel cell carcinoma (mMCC)

M. Bharmal[1], A. Amin[2], C. Stapelkamp[2], C. Pescott[1], A. Hatswell[3], C. Lilley[4], A. Bullement[4], A. Willis[4]

[1]Global Evidence & Value Development, Merck KGaA, Darmstadt, Germany, [2]Global Evidence & Value Development, Merck Serono Ltd, Feltham, UK, [3]Department of Statistical Science, University College London and Delta Hat Limited, London, UK, [4]Health Economics, BresMed Health Solutions, Sheffield, UK

Background: mMCC is a rare, aggressive skin cancer with limited response to chemotherapy and a poor prognosis. Avelumab, an anti–PD-L1 IgG1 monoclonal antibody, provides a new treatment option with demonstrated durable responses and promising survival outcomes in the only registrational, prospective study of mMCC, JAVELIN Merkel 200 (JM 200; NCT02155647). This analysis assesses the CE of avelumab vs SC in pts with mMCC.

Methods: A 3-state partitioned-survival model was generated to assess the lifetime costs and effects of avelumab and SC from a UK National Health Service (NHS) perspective. Survival and health-related quality-of-life data were taken from JM 200 and observational studies to inform estimates of life-years (LYs) and quality-adjusted LYs (QALYs). Published literature and NHS reference costs were sought to quantify costs within the model, with other parameters sourced from JM 200, literature, or clinical opinion. Overall costs and QALYs were used to calculate the incremental CE ratio (ICER [cost per QALY gained]). Treatment-experienced (TE) pts had a minimum follow-up of 24 months, while data were extrapolated using hazard ratios for treatment-naive (TN) pts due to data immaturity.

Results: When costs and QALYs were discounted at 3.5% per annum, avelumab was associated with ICERs of £32,612 (TE) and £36,635 (TN) per QALY gained. Probabilistic sensitivity analysis demonstrated that avelumab was associated with a 93.3% (TE) and 76.4% (TN) probability of being CE at a willingness-to-pay threshold of £50,000 per QALY gained.

Table: 1291P

Population	Incremental		ICER
	Costs	QALYs	
TE	£78,558	2.41	£32,612
TN	£77,434	2.11	£36,635

Conclusions: This CE analysis from JM 200 demonstrates that avelumab is a CE treatment option for pts with mMCC vs SC. The UK National Institute for Health and Care Excellence recommended avelumab for TE and TN pts; hence, an effective treatment is now available to all UK pts with mMCC. A confirmatory analysis will be conducted with more-mature TN data.

Clinical trial identification: Clinical Trial Number: NCT02155647.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking Inc., Hamilton, NJ, USA.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: This trial was sponsored by Merck KGaA, Darmstadt, Germany, and is part of an alliance between Pfizer, Inc. and Merck KGaA, Darmstadt, Germany.

Disclosure: M. Bharmal, C. Pescott: Employee: Merck KGaA, Darmstadt, Germany. A. Amin, C. Stapelkamp: Employee: Merck Serono Ltd. A. Hatswell: Employee: BresMed Health Solutions. C. Lilley, A. Willis, A. Bullement: Employee: BresMed Health Solutions.

1292P Phase I study of cemiplimab, a human monoclonal anti-PD-1, in patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC): Longer follow-up efficacy and safety data

T.K. Owonikoko[1], K.P. Papadopoulos[2], M. Gil-Martin[3], V. Moreno[4], A.K. Salama[5], E. Calvo[6], H. Safran[7], A. González-Martín[8], R. Aljumaily[9], D. Mahadevan[10], J. Niu[11], K. Kal Mohan[12], J. Li[13], E. Stankevich[14], M. Mathias[12], I. Lowy[12], M.G. Fury[12], H.M. Babiker[15]

[1]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA, [2]Clinical Research, South Texas Accelerated Research Therapeutics (START), San Antonio, TX, USA, [3]L'Hospitalet de Llobregat, Institut Català d'Oncologia, Barcelona, Spain, [4]Clinical Research Phase 1 Trials Unit, START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain, [5]Division of Medical Oncology, Duke University, Durham, NC, USA, [6]Clinical Research, START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain, [7]Department of Medicine, Brown University, Providence, RI, USA, [8]Clinica Universidad de Navarra, Formerly of MD Anderson International España, Madrid, Spain, [9]Department of Hematology/Oncology, Oklahoma University Medical Center, Oklahoma City, OK, USA, [10]Department of Medicine, The University of Arizona Cancer Center, Tucson, AZ, USA. Formerly of The University of Tennessee Health Science Center and West Cancer Center, Memphis, TN, USA, [11]Department of Medical Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ, USA, [12]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [13]Biostatistics & Data Management, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA, [14]Clinical Sciences, Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA, [15]Department of Medicine, University of Arizona Cancer Center, Tucson, AZ, USA

Background: Cemiplimab (REGN2810) demonstrated a positive risk/benefit profile and produced antitumour activity in patients (pts) with advanced CSCC in the primary analysis, by independent central review, of a phase 1 CSCC expansion cohorts (ECs). We now report longer follow-up data from the CSCC ECs of the phase 1 study (NCT02383212).

Methods: Pts with distantly metastatic or unresectable locally/regionally advanced CSCC were enrolled in ECs 7 and 8, respectively. All pts received cemiplimab 3 mg/kg every 2 weeks over 30 minutes by intravenous infusion for up to 48 weeks. Tumour measurements were performed by RECIST 1.1 every 8 weeks to determine overall response rate (ORR; complete response [CR] + partial response [PR]) according to intention to treat. The data cut-off date was 20 Jan, 2018. Tumour response in this report was by investigator assessment.

Results: A total of 26 pts were enrolled (21 M/ 5 F; 10 in EC 7, 16 in EC 8; median age: 72.5 years [range: 55–88]; ECOG performance status was 1 in 16 pts and 0 in 10 pts). Median duration of follow-up was 11.9 months (range: 1.1–18.2). Median duration of cemiplimab exposure was 36.0 weeks. The most common treatment-emergent adverse event (TEAE) of any grade was fatigue (26.9%). The only TEAEs of grade $\geq$3 that occurred in more than one pt were hypercalcaemia and skin infection (each 7.7%). ORR was 50.0% (95% CI: 29.9–70.1), with 2 CRs and 11 PRs; 5 patients had stable disease (SD), 6 had progressive disease, and 2 were not evaluable for response. Durable disease control rate (SD or response for $\geq$105 days) was 57.7% (95% CI: 36.9–76.6). Median time to response was 1.9 months (range: 1.7–7.5). The median duration of response has not been reached, and as of the data cut-off date, for pts with CR or PR, the observed duration of response exceeded 6 months in 9 pts and 12 months in 5 pts.

Conclusions: The increasing duration of response in this analysis provides further evidence of a positive risk/benefit profile for cemiplimab in pts with advanced CSCC.

Clinical trial identification: NCT02383212.

Editorial acknowledgement: Medical writing support under the direction of the authors was provided by Emmanuel Ogunnowo, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc. and Sanofi according to Good Publication Practice guidelines (http://annals.org/aim/fullarticle/2424869/good-publication-practice-communicating-company-sponsored-medical-research-gpp3).

Legal entity responsible for the study: Regeneron Pharmaceutical, Inc. and Sanofi.

Funding: The study was sponsored by Regeneron Pharmaceutical, Inc. and Sanofi.

Disclosure: T.K. Owonikoko: Fees for consulting or advisory: Novartis, Celgene, Lilly, Sandoz, Abbvie, Eisai, G1 Therapeutics, Takeda, Seattle Genetics, Bristol-Myers Squibb, MedImmune. A.K. Salama: Fees for consulting or advisory, Speakers' bureau: Bristol-Myers. E. Calvo: Research funding: Boehringer Ingelheim, Roche/Genentech, BMS, Novartis, PsiOxus, Nanobiotix, Janssen, Abbvie, PharmaMar, PUMA, Sanofi, Lilly, Pfizer, Merck, Nektar, Amcure, Amgen, AstraZeneca, Principia, Bayer, CytomX, H3, Incyte, Kura, LOXO, Macrogenics, Menarini, Merck, Serono, Merus, Millenium, Rigontec, Tahio, TesaroReceipt; Honoraria, Consultation fees: Novartis, Nanobiotix, Janssen-Cilag, PsiOxus Therapeutics, Seattle Genetics, Pierre Fabre, Boehringer Ingelheim, Cerulean Pharma, EUSA, Abbvie, Celgene; Speaker's bureau fees: Novartis. A. González-Martín: Consulting, advisory, speakers' bureau, Travel accommodation expenses: AstraZeneca, Tesaro, Roche, Pharmamar. D. Mahadevan: Speakers' bureau, Travel, accommodation expenses: Abbvie. J. Niu: Consulting, Advisory role: Genentech, Biodesix, Paradigm, Ignyta, AstraZeneca, Teueda. K. Kal Mohan: Employee, Shareholder: Regeneron Pharmaceuticals, Inc. J. Li: Jingjin Employee, Shareholder: Regeneron Pharmaceuticals, Inc., Novartis. E. Stankevich: Employee: Regeneron Pharmaceuticals, Inc.; Shareholder: Regeneron Pharmaceuticals, Inc., Celgene, Bristol-Myers Squibb, Merck. M. Mathias: Employee, Shareholder: Regeneron Pharmaceuticals, Inc. I. Lowy: Employee, Shareholder, Fees Travel and

accommodation expenses, Leadership: Regeneron Pharmaceuticals, Inc. M.G. Fury: Employee, Shareholder, Patents, Royalties, Other intellectual property: Regeneron Pharmaceuticals, Inc. H.M. Babiker: Honoraria: Bayer, Sirtex; Consulting, Advisory role fees: Celgene, Endocyte. All other authors have declared no conflicts of interest.

1293P Cetuximab in patients with unresectable cutaneous squamous cell carcinoma is safe and effective: A real-life analysis

F. Peyrade[1], M. Kogay[1], J. Viotti[2], P. Combemale[3], C. Dutriaux[4], N. Dupin[5], C. Robert[6], L. Mortier[7], A-B. Duval-Modeste[8], S. Dalle[9], J. De Quatrebarbes[10], A. Stefan[11], F. Brunet-Possenti[12], A. Picard[13], G. Poissonnet[14], H. Montaudié[15]

[1]Medical Oncology, Centre Anticancer Antoine Lacassagne, Nice, France, [2]Unit of Epidemiology and Biostatistics (UEB), Centre Antoine Lacassagne, Nice, France, [3]Dermatology, Venereology, Centre Léon Bérard, Lyon, France, [4]Dermatology Department, CHU Bordeaux Hopital St. André, Bordeaux, France, [5]Dermatology Department, APHP, Hôpital Cochin, Paris, France, [6]Department of Dermatology, Institut Gustave Roussy, Villejuif, France, [7]Onco Dermatology, Hopital Claude Huriez, Lille, France, [8]Dermatology Department, Institute for Research and Innovation in Biomedicine, INSERM 1234, Rouen University Hospital, University of Normandie, Rouen, France, [9]Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [10]Dermatology, CH Annecy Genevois, Annecy, France, [11]Dermatology, CHU de Caen, Caen, France, [12]Dermatology Venerology, AP-HP BICHAT, Paris, France, [13]Dermatology, Centre Hospitalier Universitaire, Hôpital Archet, Nice, France, [14]Head and Neck, Centre Antoine Lacassagne, Nice, France, [15]Department of Dermatology, Centre Hospitalier Universitaire de Nice, Nice, France

Background: Approximately 20-30% of non-melanoma skin cancers are squamous cell carcinomas of the skin (SCCS). SCCS incidence is increasing and they often occur in elderly or immunosuppressed patients (pts). SCCS can progress to stages impossible to treat by surgical excision or radiotherapy. Cisplatin-based combinations show efficacy but are too toxic for elderly pts. Cetuximab (Ce) demonstrates 69% disease control rate (DCR) at 6 weeks but in few, highly selected pts. This study aims to evaluate the efficacy of Ce in non-selected pts with SCCS.

Methods: This retrospective study included pts with relapsing unresectable or metastatic SCCS treated with Ce monotherapy (weekly loading dose 400 and 250 mg/m^2). The primary objective was DCR at 6 weeks. 60 pts (38 male) with local relapses of metastatic CSCC (100%), were treated between 30/05/2007 and 07/04/2017 in 13 centers. Median age was 83.1 yrs (min 47.4, max 96.1 yrs). Two-thirds of pts had one or two comorbidities, including 13% (n = 8) with immune disorder. 54% had local relapse. Main metastatic locations were nodes (n = 15), lung (n = 8) and skin (n = 5). 90% were chemotherapy-naïve, 57% had previous radiotherapy, and all were primarily resected. Mean time between previous treatment and Ce was 20.1 months (min 0, max 300). Mean Ce injection number was 24.8 (min 4, max 60).

Results: Complete response, partial response, stabilization (S) and progression were 7%, 48%, 32% and 13%, respectively, at 6 weeks and 2%, 42%, 29% and 27% at 3 months. 90% of pts experienced at least a disease S as best overall response. Ce was discontinued in 1 patient after first injection due to grade III infusion-related toxicity. All other grade III toxicities were cutaneous (n = 8) with 5 discontinuations. No toxic deaths were reported. Median follow-up, progression-free survival and overall survival were 11.7 months [95% CI: 9.6-30.1], 9.7 months [95% CI: 4.8-43.4] and 17.5 months [95% CI: 9.4-43.1] respectively.

Conclusions: Cetuximab is a safe and efficient treatment for patients, even very old, with SCCS. The toxicity profile of Ce compares very favorably with cisplatine-based protocols. These results indicate that Ce is a promising platform to test new combinations.

Legal entity responsible for the study: Centre Antoine Lacassagne.

Funding: Merck KGaA.

Disclosure: F. Peyrade: Board member: Merck KGaA. All other authors have declared no conflicts of interest.

1294P Sonidegib preplanned subgroups analyses of objective response rates: Final 42-month results from the BOLT study

R. Dummer

Dermatology, University Hospital Zürich-Dermatology, Zurich, Switzerland

Background: Based on results of the phase 2 BOLT study (NCT01327053), sonidegib 200 mg once daily (QD) was approved in the US for patients with locally advanced basal cell carcinoma (laBCC) not amenable to curative surgery or radiotherapy and in Switzerland and Australia also for metastatic BCC (mBCC). Here we report the final 42-month results—the longest follow-up data available from a hedgehog inhibitor (HHI) clinical trial—for a preplanned prespecified subgroup analysis for the primary endpoint, the objective response rate (ORR), in patients receiving 200 mg.

Methods: BOLT was a double-blind phase 2 study where HHI treatment–naïve patients with laBCC not amenable to curative surgery/radiotherapy, or with metastatic BCC (mBCC) were randomized 1:2 to sonidegib 200 or 800 mg QD, respectively. The primary endpoint was ORR. Analyses were performed at 12, 30, and 42 months after the last patient was randomized.

Results: For prespecified groups at 42 months, the ORRs for 200 mg QD were consistent for laBCC aggressive (59.5%; n = 37) and laBCC nonaggressive (51.7%; n = 29) histologies; male (43.8%; n = 48) and female (54.8%; n = 31); patients aged <65 years (59.4%; n = 32) and those aged ≥65 years (40.4%; n = 47); white (49.3%; n = 71) and nonwhite patients (37.5%; n = 8); and for patients not receiving (51.8%; n = 56) and those receiving (39.1%; n = 23) gastric pH agents. Subgroup analyses by disease strata (laBCC [56.1%; n = 66] vs mBCC [7.7%; n = 13]) and Eastern Cooperative Oncology Group performance status (0 [60%; n = 50] vs ≥ 1 [29.6%; n = 27;]) for the primary ORR endpoint showed heterogeneous results like those reported at 30 months. The safety/tolerability profile was consistent across 42 months with no new AEs emerging.

Conclusions: These results confirmed the consistency of treatment effect for sonidegib 200 mg QD at 42 months across several preplanned subgroups, including age, disease histology, gender, race, and use of gastric pH agents.

Clinical trial identification: NCT01327053.

Editorial acknowledgement: Leonard Lionnet, PhD, CMPP of Lev Medical Communications provided medical writing support for this abstract.

Legal entity responsible for the study: Sun Pharmaceuticals Ltd.

Funding: Sun Pharmaceuticals Ltd.

Disclosure: R. Dummer: Consultant: Novartis Pharmaceuticals, Sun Pharma.

1295P Treatment of advanced basal cell carcinoma with sonidegib: Duration of response and quality of life evaluation from BOLT

M.R. Migden

Dermatology and Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Background: For patients with advanced basal cell carcinoma (BCC), including those with locally advanced BCC (laBCC) and metastatic BCC (mBCC), hedgehog pathway inhibitors (HPIs) are a treatment option. Sonidegib is an HPI approved for use in patients with advanced BCC (Switzerland and Australia) and laBCC (USA and EU), based on data from the BOLT study (NCT01327053). Here we report the duration of response (DOR) at 42 months and quality of life (QoL) results at the 12- and 30-month analyses from BOLT.

Methods: BOLT was a multicenter, randomized, double-blind, phase 2 trial that evaluated sonidegib in treatment-naïve patients with mBCC (n = 36) or laBCC (n = 194) who were not amenable to curative surgery or radiation therapy. Patients were randomized 1:2 to either 200 mg or 800 mg PO QD, and data analyses were performed at 6, 12, 18, 30, and 42 months. The primary endpoint was objective response rate (ORR) and a key secondary endpoint included DOR as assessed by central review. QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the associated Head and Neck Cancer Module 35 (EORTC H&N35).

Results: At the 42-month analysis, the median DOR was 26.1 months in laBCC patients treated with sonidegib 200 mg vs 23.3 months in patients treated with 800 mg. The ORR was higher in the 200 mg group vs the 800 mg group (Table). In mBCC patients, the median DOR was 24 months for sonidegib 200 mg and not estimable for the 800 mg group. The ORR was lower in the 200 mg group vs the 800 mg group (Table). During the course of treatment, the QoL for these patients was analyzed, and the majority of patients in both dosage groups had maintenance of or improvement in QoL relative to baseline.

Table: 1295P ORR in sonidegib-treated patients with advanced BCC

	laBCC		mBCC	
	200 mg n = 66	800 mg n = 128	200 mg n = 13	800 mg n = 23
ORR %	56	46	8	17
Complete Response, n (%)	3 (4.5)	2 (1.6)	0	0
Partial Response, n (%)	34 (51.5)	57 (44.5)	1 (7.7)	4 (17.4)

Conclusions: Data from the 42-months analysis demonstrated that patients receiving sonidegib had a long duration of response. Results from the 12- and 30-month analyses show maintenance and improvement in QoL consistent with that of the primary data observed in BOLT.

Clinical trial identification: NCT01327053 CLDE225A2201.

Editorial acknowledgement: Medical writing support provided by Adriana Vela, PhD, Medical Exchange International, LLC, New York, NY.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: M.R. Migden: Honorarium for advisory boards and consulting: Regeneron, Sun Pharmaceuticals, Novartis.

1296P Discovery of novel germline genetic biomarkers of melanoma recurrence impacting exonic and long non-coding RNA (lncRNA) transcripts

T. Kirchhoff[1], D. Simpson[2], T. Hekal[2], R. Ferguson[2], E. Kazlow[2], U. Moran[2], Y. Lee[3], A. Izsak[3], M.A. Wilson[4], R. Shapiro[4], A. Pavlick[4], I. Osman[3]

[1]Perlmutter Cancer Center, New York University, New York, NY, USA, [2]Perlmutter Cancer Center, New York University Medical Center, New York, NY, USA, [3]Dermatology, New York University Medical Center, New York, NY, USA, [4]Department of Medicine, New York University - Perlmutter Cancer Center - Langone Medical Center, New York, NY, USA

Background: One challenge in clinical management of cutaneous melanoma (CM) is the limited predictability of recurrence and hence the progression to advanced stages that associate with less favorable outcomes. Aggressive follow-up care and novel adjuvant therapy strategies in early-stage patients with high-risk of recurrence would likely improve CM-specific survival and reduce mortality. We developed a genome-wide approach to identify germline genetic determinants of melanoma prognosis as putative personalized biomarkers for patients at risk of CM recurrence.

Methods: Exploring both the coding and non-coding transcribed genome we performed germline whole genome sequencing (WGS) and tumor RNA-seq on 96 CM patients with tumor/blood matched specimens. All patients were of primary stages I-IIB and of Ashkenazi Jewish ancestry to reduce genetic heterogeneity. We compared 48 patients that recurred in < 4 years versus 48 patients with recurrence in > 6 years. Univariate and multivariate logistic regression, gene-burden analysis (SKAT), and differential expression analyses of both mRNA and lncRNAs were used to identify germline regions associated with melanoma recurrence.

Results: Several gene regions were associated with melanoma recurrence, with NEGR1 and MGST3 both passing SKAT levels of significance ($p < 1e-05$), and logistic regression analysis on common WGS variants found over 100 variants with significance $p < 1e-03$. In addition, we found 200 differentially expressed putative lncRNAs ($p < 0.05$). The analysis of germline WGS found rs199818927, a 1bp insertion previously associated with both NEGR1 and lncRNA LINC01360, among our top 5 most significant regression results ($OR = 9.107$ $p = 2.31e-05$).

Conclusions: This initial phase of our large scale whole genome scan has uncovered germline variants in several coding loci and putative lncRNAs that associate with melanoma recurrence. Most notably, we identified germline variation in a lncRNA near NEGR1, a putative tumor suppressor that has been shown to be under-expressed in advanced cancers, indicating its putative role in cancer progression to metastatic stages. We are currently expanding the patient cohorts and validating these results.

Legal entity responsible for the study: Tomas Kirchhoff.

Funding: NIH.

Disclosure: All authors have declared no conflicts of interest.

1297P Pilot study: Localizing target lymph node using a magnetic marker allows reliable and representative judgement of pathological responses after neo-adjuvant ipilimumab (IPI) + nivolumab (NIVO) in macroscopic stage III melanoma

A.C.J. van Akkooi[1], B. Schermers[2], V. Franke[1], M. Wouters[1], C.L. Zuur[3], W.M.C. Klop[3], E.A. Rozeman[4], B.A. van de Wiel[5], T.J.M. Ruers[1], C.U. Blank[6]

[1]Surgical Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital (NKI-AVL), Amsterdam, Netherlands, [2]Surgical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [3]Head and Neck Surgery and Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital (NKI-AVL), Amsterdam, Netherlands, [4]Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [5]Pathology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands, [6]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: The outcome of high risk stage III melanoma patients (pts) is poor, with a 5-year overall survival (OS) rate of $< 50\%$. Adjuvant (adj) high dose IPI , adj NIVO and pembrolizumab improved RFS. Neo-adjuvant (neoadj) treatment may be an even more favorable approach as immune checkpoint inhibition is of greatest value at the moment of TCR triggering and therefore dependent on the amount of antigen present. In our previous phase Ib OpACIN study the pathological RR (pRR) was 78% in the neoadj arm, and to date after 25 months of median follow-up none of the responders has relapsed. This raises the question whether such pts need to undergo complete lymph node dissection (CLND). A prerequisite for such an approach would be an analysis method that reliably indicates pathological response within the whole lymph node bed, without the need for CLND.

Methods: To address this question an in-house developed magnetic marker was placed ultrasound-guided at baseline into the largest regional lymph node metastasis of pts participating in OpACIN-neo, (NCT02977052), a phase 2 trial aiming at identification of the optimal neoadj combination scheme of IPI and NIVO in stage IIIB/C melanoma pts followed by CLND.

Results: So far, 11 pts participated in this side trial of OpACIN-neo. No complications from marker placing were observed, and all magnetic markers were retrieved during the CLND after 6 weeks of neoadj IPI+NIVO. 10/11 marked lymph-nodes (LN were representative in their response for the whole CLND specimen, i.e. index node showed a complete or partial response (PR), all others on CLND showed the same or better responses. Only 1 case was incongruent, as the index LN had 60% vital tumor (no response) compared to another LN (40% vital tumor, PR).

Conclusions: Our early exploratory data from this pilot study indicate that marked LN in stage III melanoma could serve as response indicators for the outcome of the whole CLND after neoadj IPI+NIVO. If confirmed, our data can open the path towards response-driven extent of lymph-node dissection in macroscopic stage III melanoma.

Clinical trial identification: NCT02977052.

Legal entity responsible for the study: Alexander C.J. van Akkooi.

Funding: Has not received any funding.

Disclosure: A.C.J. van Akkooi: Consulting or advisory: Amgen, Novartis, MSD Oncology, Merck; Travel, accommodations, expenses: Amgen, Roche, Novartis; Research funding: Amgen, Novartis. C.U. Blank: Personal fees, Advisory role: MSD, BMS, Roche, GSK, Novartis, Pfizer, Lilly; Grants: BMS, Novartis, outside the submitted work. All other authors have declared no conflicts of interest.

1298P Discovery of KIRREL as a biomarker for prognostic stratification of patients with thin melanoma

S. Lundgren, H. Fagerström-Vahman, L. Ben-Dror, B. Nodin, K. Jirstrom

Department of Clinical Sciences, Oncology and Pathology, Lund University, Faculty of Medicine, Lund, Sweden

Background: There is a great unmet clinical need to identify patients with thin primary cutaneous melanomas (T1, Breslow thickness ≤ 1 mm) who have a high risk for tumor recurrence and death from melanoma. Kin of IRRE-like protein 1 (KIRREL/NEPH1) is expressed in podocytes and involved in glomerular filtration, but its expression in human cancer has not yet been reported. Screening in the Human Protein Atlas portal revealed a particularly high expression of KIRREL in melanoma, both at the mRNA and protein levels. In this study, we followed up on these findings and examined the prognostic value of KIRREL in a population-based cohort of melanoma.

Methods: Immunohistochemical analysis of KIRREL was performed on tissue microarrays with a subset of primary tumors and paired lymph node metastases from an original cohort of 268 incident cases of melanoma in the Malmö Diet and Cancer study. Kaplan Meier analysis and Cox proportional hazards modelling were used to assess the relationship between KIRREL expression and time to recurrence (TTR) and melanoma-specific survival (MSS). The prognostic value of KIRREL mRNA expression was examined in 102 melanoma cases in The Cancer Genome Atlas (TCGA).

Results: Membranous/cytoplasmic expression of KIRREL was detected in 158/185 (85.4%) primary tumours and 18/19 (94.7%) metastases, in various fractions and intensities. High expression of KIRREL was significantly associated with several unfavourable clinicopathological factors. KIRREL expression was not prognostic in tumours >1 mm thickness, but in T1 tumours ($n = 106$, median thickness 0.58, range 0.08-1.00), high expression of KIRREL was significantly associated with a reduced TTR, independent of and outperforming absolute thickness in mm and ulceration ($HR = 4.54$, 95% CI 1.01-20.45), and borderline significantly associated with MSS. High mRNA levels of KIRREL were associated with a significantly reduced overall survival in the TCGA ($p = 0.028$).

Conclusions: KIRREL is not only a novel potential diagnostic marker for melanoma, but may also be a useful prognostic biomarker for improved stratification of patients with thin melanoma. These findings may be of high clinical relevance and therefore merit further validation.

Legal entity responsible for the study: Lund University.

Funding: Swedish Cancer Society, the Swedish Research Council; the Swedish Government Grant for Clinical Research, the Mrs Berta Kamprad Foundation, Lund University Faculty of Medicine and University Hospital Research Grants.

Disclosure: All authors have declared no conflicts of interest.

1299P BRAF V600E mutation in melanoma sustains IFN-gamma inducible PD-L1 expression by coactivating STAT1 and increasing protein translation

M.M. Wasylecka-Juszczyńska, P. Górniak, M. Szydłowski, A. Polak, P. Juszczyński

Department of Experimental Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

Background: Approximately 40-60% of melanoma patients have activating BRAF mutations. Targeting BRAF inhibits proliferation of melanoma cells and increases their immunogenicity. PD-1 immune checkpoint blockade is another breakthrough in melanoma therapy, shown to effectively restore T cell function. These observations indicate that combinatorial use of BRAF inhibitors and immunotherapy might be a rational therapeutic strategy. Herein, we studied the role of BRAF V600E in regulating the expression of PD-L1 in melanoma cells.

Methods: CD274 gene transcript abundance and PD-L1 protein level was measured with qPCR, Western-blot and FACS. Identification of signaling pathways responsible for regulation of PD-L1 expression was performed using western blot, FACS and

reporter assays. Azide-alkyne cycloaddition ("Click-it" chemistry) was used to analyze de novo protein synthesis.

Results: BRAF-mutant melanoma cell lines exhibited low basal expression of PD-L1 that was markedly induced by IFN-γ, pointing to an adaptive mechanism of PD-L1 expression. BRAF inhibitor significantly reduced IFN-γ-induced PD-L1 levels. In cell lines treated with IFN-γ, vemurafenib decreased STAT1 S727 phosphorylation and expression of PD-L1, suggesting direct regulation of STAT1 by ERK. In A375 cells with constitutively active MEK kinase, vemurafenib had no effect on STAT1 phosphorylation and CD274 transcript level. These results indicate that RAS/RAF/MEK/ERK axis is crucial for maintaining IFN-γ-induced CD274 gene transcription. In addition, vemurafenib decreased activity of proteins responsible for translation regulation (pS6, p4E-BP1), suggesting that inhibition of protein synthesis could be another mechanisms leading to PD-L1 decrease. To test this hypothesis, we measured de novo PD-L1 synthesis following BRAF inhibition, and found markedly reduced PD-L1 translation. Importantly, we also noted decreased translation of other immunoregulatory proteins, such as galectin-1.

Conclusions: BRAF mutations influence PD-L1 expression by modulating its transcription and translation. BRAF inhibition has a potential immunomodulatory effect, at least in part by decreasing IFN-γ induced PD-L1 expression.

Legal entity responsible for the study: Institute of Hematology and Transfusion Medicine.

Funding: Polish National Science Center.

Disclosure: All authors have declared no conflicts of interest.

1300TiP A randomised phase II feasibility study of intermittent versus continuous dosing of targeted therapy in patients with BRAFV600 mutant advanced melanoma (INTERIM)

P.G. Corrie[1], R.N. Matin[2], A. Gupta[3], W. Qian[4], S. Wordsworth[5], E. Gibbons[6], A. Chhabra[7], C. Harman[8], C. Mather[8], M.R. Middleton[9]

[1]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust - Addenbrooke's Hospital, Cambridge, UK, [2]Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, UK, [3]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [4]Cambridge Clinical Trials Unit - Cancer Theme, Cambridge University Hospitals NHS Foundation Trust - Addenbrooke's Hospital, Cambridge, Cambridgeshire, UK, [5]Health Economics Research Centre, Nuffield Department of population Health, University of Oxford, Oxford, UK, [6]Health Services Research Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK, [7]Cambridge Cancer Trials Centre, Cambridge University Hospitals NHS Foundation Trust - Addenbrookes Hospital, Oxford, UK, [8]Cambridge Clinical Trials Unit - Cancer Theme, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK, [9]Oxford NIHR Biomedical Research Centre, Churchill Hospital University of Oxford, Oxford, Oxfordshire, UK

Background: BRAF and MEK inhibitor (BRAF+MEKi) combination therapy has helped extend median life expectancy of BRAF mutant advanced melanoma patients to over 2 years. Acquired resistance limits duration of benefit and treatment-related toxicity can be a problem. Clinical reports suggest that intermittent dosing to manage side-effects does not compromise efficacy and can help patients to remain on treatment longer. In a mouse model, tumour cells resistant to the BRAF inhibitor vemurafenib appear to suffer a fitness deficit in the absence of drug, so that intermittent dosing could delay or prevent the emergence of resistant tumours. We hypothesise that intermittent dosing with BRAF+MEKi will sustain patients on treatment for longer, delay disease progression and improve quality of life (QoL). However, patient and investigator acceptance of randomisation and compliance with less treatment is uncertain.

Trial design: INTERIM is a UK national portfolio multi-centre feasibility trial developed by the NCRI Skin Cancer Clinical Studies Group. Patients with $BRAF^{V600}$ mutant stage 3 unresectable or metastatic melanoma with ECOG performance status (PS) 0-2 due to start BRAF+MEKi are randomised to receive dabrafenib (150mg bid) and trametinib (2mg od) either continuously or intermittently (dabrafenib days 1-21 and trametinib days 1 – 14) on a 28 day cycle. Concomitant immunotherapy is not allowed. Randomisation is stratified for brain metastases, PS, stage and lactate dehydrogenase level. We will recruit 150 patients (75 patients per arm) in 18 months at 20 UK sites to provide reliable information on recruitment, treatment compliance, progression-free survival and overall QoL (composite primary endpoint). Secondary endpoints include safety, health-economic evaluation, patient reported outcomes focusing on skin toxicity and patient experience. In addition we will explore ctDNA as a predictive biomarker and in tracking evolution of patients' tumours. Pharmacokinetic sampling will be performed in a subset of patients to help refine the intermittent schedule. From November 2017 until April 2018, 11 patients have been randomised at 9 sites.

Clinical trial identification: EudraCT: 2016-005228-27.

Legal entity responsible for the study: Cambridge University Hospital NHS Foundation Trust.

Funding: National Institute for Health Research (NIHR) Research for Patient Benefit Grant.

Disclosure: P.G. Corrie: Honoraria: Merck Sharp & Dohme (MSD), Novartis, Bristol Myers Squibb (BMS); Consultancy/ advisory role: Celgene, Incyte, BMS, Novartis, MSD, Pierre Fabre; Speakers' bureau: Novartis, MSD; Travel, accommodation, expenses: MSD, BMS; Research funding (institution): Celgene. R.N. Matin: Consultancy/advisory role: Simon-Kucher and Partners, Healthcare Partners Institution; Research funding: Barco NV, Skin MD Now, Inc. A. Gupta: Travel, accommodation, expenses: Bristol-Myers Squibb. C. Mather: Immediate family member employed: Aegerion and Cardiome in last 2 years; Immediate family member holds stock: Aegerion and Cardiome. M.R. Middleton: Honoraria: Amgen, Roche; Consultancy: Merck, CytomX, Therapeutics, RigonTEC, BMS, Newlink Genetics, Novartis; Expenses: Merck; Institution funding: Immunocore, Novartis, AstraZeneca, Roche, Amgen, Millennium, BMS, Vertex, Merck, Pfizer, RogonTEC, Replimune, Array BioPharma, TC Biopharma, Regneron. All other authors have declared no conflicts of interest.

1301TiP A phase I/Ib study of concurrent intravenous (IV) and intrathecal (IT) nivolumab (Nivo) for melanoma patients (pts) with leptomeningeal disease (LMD)

I.C. Glitza, M.L. Rohlfs, M. Iqbal, J. Richard, E. Burton, S. Duncan, C. Brown, J. Anderson, P. Hwu, W-J. Hwu, M. Wong, C. Yee, S. Patel, S. Woodman, R. Amaria, A. Diab, H. Tawbi, M. Davies

Melanoma Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

Background: Although advances in treatment with immune checkpoint inhibitors (CPI) have greatly improved the survival for pts with metastatic melanoma (MM), many still progress and ultimately die from this disease. Metastases to the Central Nervous System (CNS) are one of the most common and devastating complications of MM, occurring in up to 60% of pts and those with LMD have the worst prognosis (overall survival only weeks) and limited treatment options. Our program has demonstrated that IT administration of interleukin-2 (IL2) induces durable disease control and prolonged survival in pts with LMD, with 1, 2, 5- year survival rates of 36%, 26%, and 13% respectively. Given the favorable clinical activity and safety compared to systemic IL2 and supported by pre-clinical data, we hypothesize that IT administration of nivo is safe and will induce CNS immune responses in pts with LMD.

Trial design: This single center Phase I/Ib trial (NCT03025256) will treat MM LMD pts with concurrent IT (via Ommaya) and IV nivo. The initial dose escalation phase (up to 18pts) will determine the safety and recommended dose (primary objective) followed by an expansion cohort (12 pts) at the recommended dose to assess overall survival (secondary objective). Cycle 1 will consist of IT nivo only at a starting flat dose of 5mg. In subsequent cycles, IT nivo will be followed the next day by IV nivo 240mg Q2W. Pts will be hospitalized overnight for the IT dosing and monitored for neurotoxicity, including signs of elevated intracranial pressure. We will use the Bayesian mTPI method to determine the recommended dose. Pts must have radiographic and/or CSF cytopathologic (CSF) confirmed LMD. Prior therapy with systemic CPI and steroid use ($\leq$ 4 mg / 24 hrs of dexamethasone or equivalent) to control CNS symptoms is allowed. Exploratory objectives include the evaluation of immunological effects of this treatment on immune cells in the CSF versus peripheral blood and non-LMD tumors. This is the first in human study for LMD pts to receive CPI via IT and systemic administration concurrently. This approach has great potential to be a safe and more efficacious therapy in MM patients with LMD for which there is an urgent unmet need.

Clinical trial identification: NCT03025256.

Legal entity responsible for the study: University of Texas MD Anderson Cancer Center.

Funding: Bristol-Myers Squibb.

Disclosure: I.C. Glitza: Research trial funding: BMS. W-J. Hwu: Research grant: BMS. M. Wong: Advisory board: EMD-Serono, Pfizer, Merck. R. Amaria: Research trial funding: BMS. H. Tawbi: Consulting/participated advisory boards: Merck, BMS, Genentech, Novartis; Research funding (institution): Merck, GSK, BMS, Genentech, Celgene. M. Davies: Advisory board, BMS. All other authors have declared no conflicts of interest.

1302TiP CA224-047: A randomized, double-blind, phase II/III study of relatlimab (anti–LAG-3) in combination with nivolumab (anti–PD-1) versus nivolumab alone in previously untreated metastatic or unresectable melanoma

E.J. Lipson[1], G.V. Long[2], H. Tawbi[3], D. Schadendorf[4], V.G. Atkinson[5], M. Maurer[6], K.L. Simonsen[7], C. Harbison[8], F.S. Hodi[9]

[1]Medical Oncology, Johns Hopkins University, Baltimore, MD, USA, [2]Melanoma Institute Australia, The University of Sydney Northern Clinical School and Royal North Shore Hospital, Sydney, Australia, [3]Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]Department of Dermatology, University Hospital Essen, Essen, Germany, [5]Gallipoli Medical Research Foundation, Greenslopes Private Hospital and University of Queensland, Brisbane, Australia, [6]Oncology Development, Bristol-Myers Squibb, Princeton, NJ, USA, [7]Global Biometric Sciences, Bristol-Myers Squibb, Princeton, NJ, USA, [8]Translational Medicine, Bristol-Myers Squibb, Princeton, NJ, USA, [9]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Immune checkpoint inhibitors targeting the programmed death receptor1 (PD1) and cytotoxic Tlymphocyte antigen 4 (CTLA4) pathways have provided significant clinical benefit for patients with unresectable or metastatic melanoma. However, a proportion of patients may not respond or may progress with current

therapies. Lymphocyteactivation gene 3 (LAG3) is an additional immune checkpoint pathway that negatively regulates effector Tcell function and is a marker of Tcell exhaustion. Dual checkpoint inhibition of the LAG3 and PD1 pathways, by relatlimab and nivolumab, respectively, showed clinical activity in patients with previously treated metastatic or unresectable melanoma whose disease progressed during prior anti–PD(L)1 therapy, with a safety profile similar to nivolumab monotherapy (Ascierto P, et al. Presented at the ESMO 2017 Congress; September 8–12, 2017; Madrid, Spain. Oral LBA18). CA224047 will assess the clinical efficacy and safety of relatlimab in combination with nivolumab versus nivolumab alone in previously untreated metastatic or unresectable melanoma.

Trial design: This is a randomized, multicenter, doubleblind, phase 2/3 study of relatlimab in combination with nivolumab versus nivolumab alone, in previously untreated metastatic or unresectable melanoma. Approximately 700 patients aged ≥12 years, with no prior systemic anticancer therapy for histologically confirmed stage III (unresectable) or stage IV (metastatic) melanoma and biopsy tissue available for biomarker analyses, are being randomized. Patients with active brain metastases or leptomeningeal metastases, or ocular melanoma are excluded. The primary endpoint for the phase 2 component is objective response rate, and for phase 3 is progressionfree survival. Other endpoints include overall survival, duration of response, disease control rate, and safety and tolerability. This study has started to enroll patients.

Clinical trial identification: NCT03470922.

Editorial acknowledgement: Medical writing assistance was provided by Katerina Pipili, PhD, of Spark Medica Inc. (US), funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: E.J. Lipson: Research support: Bristol-Myers Squibb and Merck. Advisory board: Array BioPharma. G.V. Long: Consultancy services: Amgen, BMS, Merck MSD, Novartis, Roche, Pierre Fabre, Array. Honoraria: BMS, MSD, Roche, Novartis, Incyte. H. Tawbi: Research funding (institution): Merck, GlaxoSmithKline, Celgene; Research funding institution, Consulting fees: Bristol-Myers Squibb, Roche/Genentech. D. Schadendorf: Advisory board: BMS, Novartis, MSD, Sanofi, Regeneron, Incyte, Merck-Serono, Pfizer, Immunocore; Pierre Fabre, Roche; Corporate-sponsored research: BMS, Novartis. V.G. Atkinson: Advisory board: BMS, MSD, Novartis, Merck Serono, Pierre Fabre; Speakers fee: BMS, MSD, Roche, Novartis; Travel support: BMS, MSD. M. Maurer, K.L Simonsen, C. Harbison: Employee, Stock ownership: BMS. F.S. Hodi: Research support (institution): BMS; Consultant: BMS, Merck, Novartis, EMD Serono, Sanofi.

1303TiP Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukine-2 to standard ipilimumab treatment in metastatic melanoma

M.W. Rohaan[1], T.H. Borch[2], J.H. van den Berg[3], M.H. Geukes Foppen[1], M. Donia[2], Ö. Met[4], B. Nuijen[5], M. van Zon[3], E.A.M. Bakker[3], R. de Boer[3], L.M. Pronk[6], S. Wilgenhof[1], C.U. Blank[7], J.V. van Thienen[8], A.C.J. van Akkooi[9], I-M. Svane[2], J.B.A.G. Haanen[10]

[1]Medical Oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, [2]Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [3]Biotherapeutics Unit, Netherlands Cancer Institute, Amsterdam, Netherlands, [4]Center for Cancer Immunotherapy and Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [5]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute and MC Slotervaart, Amsterdam, Netherlands, [6]Biometrics, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, [7]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [8]Medical Oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, [9]Surgical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [10]Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: Less than a decade ago, the prognosis of advanced melanoma was extremely poor, with a 5-year overall survival (OS) of only 9-28%. Introduction of targeted therapies and immunotherapies have significantly improved the outcome of these patients. Ipilimumab, an anti-CTLA-4 antibody, was the first to show clinical benefit in advanced melanoma patients and 20% achieved long-term survival. The PD-1-blocking agents pembrolizumab and nivolumab further increased objective response rates (ORR) up to 40% and are now often used as first-line therapy. However, a large group of patients still does not benefit from this treatment. Adoptive cell therapy with tumor infiltrating lymphocytes (TIL) has shown promising clinical ORR of 40-70% in patients with advanced melanoma in several phase I/II trials, with durable responses in a substantial group of patients. TIL treatment consists of infusion of ex vivo expanded tumor resident T cells following non-myeloablative (NMA) chemotherapy and subsequent high-dose interleukine-2 (HD IL-2).

Trial design: In this international, multicenter, open-label phase III trial, 168 patients with irresectable stage IIIc or IV melanoma, between 18 and 75 years of age, with resectable metastatic lesion(s) of at least 2-3 cm diameter and sufficient organ function, will be randomized 1:1 to either ipilimumab or TIL treatment. Patients will be stratified for $BRAF^{V600}$ mutation status, treatment line (1^{st} or 2^{nd}) and treatment center. Patients randomized to ipilimumab (3 mg/kg i.v.) receive this once every 3 weeks, maximum of 4 doses. Patients randomized to TIL will undergo resection of a metastatic lesion for the outgrowth of TIL. Subsequently, NMA chemotherapy with cyclophosphamide (60 mg/kg/day for 2 days i.v.) and fludarabine (25 mg/m^2/day for 5 days i.v.) is administered prior to infusion of $> 5x10^9$ TIL followed by HD IL-2 (600.000 IU/kg/dose every 8 hours, maximum of 15 doses). The primary endpoint is progression free survival at 6 months. Secondary endpoints are ORR, complete response rate, OS and safety. Enrollment started in September 2014.

Clinical trial identification: NCT02278887.

Legal entity responsible for the study: Netherlands Cancer Institute, Amsterdam, The Netherlands.

Funding: The Dutch Cancer Association, the Netherlands Organisation for Health Research and Development, the Dutch Ministry of Health, the Danish Cancer Society and Capital Region of Denmark Research Foundation.

Disclosure: T.H. Borch: Travel support: Roche; Travel support, Speaker's fee: Bristol-Myers Squibb. J.H. van den Berg: Grants: Neon therapeutics, BMS, Medimmune. E.A.M. Bakker: Research funding: Neon therapeutics. C.U. Blank: Personal fees, Advisory role: MSD, BMS, Roche, GSK, Novartis, Pfizer, Lilly; Grants: BMS, Novartis. J.V. van Thienen: Travel support: Roche. A.C.J. van Akkooi: Grants and personal fees: Amgen, Novartis, Personal fees: MSD-Merck, Bristol-Myers Squibb. J.B.A.G. Haanen: Compensation to NKI for Advisory roles: BMS, Merck, Roche, Neon Therapeutics, Pfizer, Ipsen; Grants to NKI: BMS, Merck, Novartis, Neon Therapeutics. All other authors have declared no conflicts of interest.

1304TiP A randomized, open-label, phase II open platform study evaluating the efficacy and safety of novel spartalizumab (PDR001) combinations in previously treated unresectable or metastatic melanoma (PLATForM)

J. Weber[1], G.V. Long[2], J.B. Haanen[3], A. Arance[4], R. Dummer[5], P. Nathan[6], A. Ribas[7], P.A. Ascierto[8], C. Robert[9], E. Gasal[10], A. D'Amelio Jr[11], S. Bettinger[12], A.D. Boran[13], D. Schadendorf[14]

[1]Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA, [2]Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia, [3]Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands, [4]Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain, [5]Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zurich, Switzerland, [6]Mount Vernon Cancer Centre, East and North NHS Trust, Northwood, UK, [7]David Geffen School of Medicine, the Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA, [8]Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori-IRCCS Fondazione "G. Pascale", Naples, Italy, [9]Department of Medicine, Institute Gustave Roussy, Paris, France, [10]Global Clinical Program, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [11]Biostatistics, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [12]Global Clinical Program, Novartis Pharma AG, Basel, Switzerland, [13]Oncology Precision Medicine, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [14]Department of Dermatology, University Hospital Essen, Essen, Germany

Background: Significant advancements, including development of immune checkpoint inhibitors and targeted therapies, have transformed outcomes for patients (pts) with unresectable or metastatic melanoma. However, pts who do not respond or who progress while receiving these regimens have limited options. Spartalizumab (PDR001) is a high-affinity, humanized monoclonal antibody blocking the programmed cell death 1 (PD-1) receptor. This study is evaluating combinations of spartalizumab with novel compounds to restore antitumor T-cell activity in pts with melanoma progressing after prior PD-1 blockade therapy.

Trial design: This randomized, open-label, 2-part, multicenter, open platform, phase II study (NCT03484923; PLATforM) will evaluate safety and efficacy of spartalizumab combination treatment in pts with unresectable or metastatic melanoma progressing after prior anti–PD-1/L1 therapy and a BRAF inhibitor if the tumor harbors a BRAF V600 mutation. The primary endpoint will be objective response rate per RECIST v1.1, with duration of response and assessment of paired tumor biopsies for biomarkers of antitumor T-cell activity as part of the secondary endpoints. The first "selection" part of the study will begin with 3 combination arms: (1) spartalizumab + LAG525 (LAG-3 antibody), (2) spartalizumab + capmatinib (c-MET inhibitor), and (3) spartalizumab + canakinumab (IL-1β antagonist). For the selection part, the PLATforM study uses an adaptive design that, during the selection phase, allows dropping arms for futility, adding new arms, and selecting 1 or multiple arms for further expansion. Bayesian methodology is used with specific probability criteria for futility and efficacy assessments at each interim analysis. Pts (≈ 60-85) will be stratified by baseline lactate dehydrogenase level and randomized equally to all open arms during the selection part. In the second "expansion" part, efficacy and safety of treatment combination(s) selected during part one will be further investigated. Sample size for part two will be adaptive and based on predictive power calculations considering the results from the selection part.

Clinical trial identification: NCT03484923.

Editorial acknowledgement: Medical writing assistance was provided by William Fazzone, PhD (ArticulateScience LLC), funded by Novartis Pharmaceuticals Corporation.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: J. Weber: Honoraria: Novartis; Research funding paid to institution: Novartis. G.V. Long: Consultancy: Amgen, Bristol-Myers Squibb, Merck MSD, Novartis, Roche, Pierre Fabre, Array; Honoraria: Bristol-Myers Squibb, MSD, Roche, Novartis, Incyte. A. Arance: Honoraria and Speakers' bureau: Novartis, Roche, Bristol-Myers Squibb, MSD. R. Dummer: Intermittent, project focused consulting and/or advisory relationships: Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma outside the submitted work. P. Nathan: Advisory board, Speakers' bureau, Honoraria: Novartis. A. Ribas: Stock ownership: Lutris, PACT, Tango; Advisory board member: Advaxis, Arcus, BioncoTech, Compugen, CytomX, Five Prime, FLX-Bio, ImaginAb, Isoplexis, Kite-Gilead, Rgenix; Honoraria: Amgen, Bristol-Myers Squibb, Chugai, Genentech, Merck, Novartis, Roche. P.A. Ascierto: Consultancy: Bristol-Myers Squibb, Roche-Genentech, MSD, Array, Novartis, Amgen, Merck-Serono, Pierre Fabre, Incyte, Genmab, Newlink Genetics, Medimmune, Syndax, AstraZeneca; Research funding: Bristol-Myers Squibb, Roche-Genetech, Array; Membership on Board of directors or Advisory committees: Bristol-Myers Squibb, Roche-Genentech, Array, Novartis. C. Robert: Advisory board participation: Merck, MSD, Novartis, Roche. E. Gasal: Employment and stock or other ownership: Novartis. A. D'Amelio Jr: Employment and stock ownership: Novartis. S. Bettinger, A.D. Boran: Employment: Novartis. D. Schadendorf: Personal fees: Amgen, Boehringer Ingelheim, Leo Pharma, Roche, Novartis, Incyte, Regeneron, 4SC, AstraZeneca, Bristol-Myers Squibb, MS, Pierre Fabre, Merck-EMD, Pfizer, Philiogen, Array; Patients' fees to institution: MSD, Roche, Novartis, Regeneron, Brisol-Myers Squibb, Merck-EMD, Philiogen. All other authors have declared no conflicts of interest.

1305TiP Phase I dose-escalation and expansion study of intratumoral CV8102, a RNA-based TLR- and RIG-1 agonist in patients with advanced solid tumors

P. Terheyden[1], C. Weishaupt[2], L. Heinzerling[3], U. Klinkhardt[4], J. Krauss[5], P. Mohr[6], F. Kiecker[7], J.C. Becker[8], A.) Dähling (Submitter[4], F. Döner[9], R. Heidenreich[9], B. Scheel[4], O. Schönborn-Kellenberger[10], T. Seibel[4], U. Gnad-Vogt[4]

[1]Klinik für Dermatologie, Allergologie zund Venerologie, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany, [2]Haut- und Geschlechtskrankheiten, Universitätsklinikum Münster (UKM), Münster, Germany, [3]Dermatologie, Universitätsklinikum Erlangen, Erlangen, Germany, [4]Clinical Development, CureVac AG, Frankfurt am Main, Germany, [5]Onkologie, Universitätsklinikum Heidelberg (NCT), Heidelberg, Germany, [6]Dermatologie, Elbe Klinikum Buxtehude, Buxtehude, Germany, [7]Dermatologie, Charité Universitätsmedizin Berlin, Berlin, Germany, [8]Dermatologie, Universitätsklinikum Essen, Essen, Germany, [9]Research, CureVac AG, Tübingen, Germany, [10]Statistical Consulting, Cogitars GmbH, Heidelberg, Germany

Background: Local activation of innate immune signaling pathways, such as Toll-like Receptors (TLRs) or RIG-I-like Receptors (RLRs), is a promising cancer immunotherapeutic approach to overcome the tumor immunosuppressive microenvironment and to induce/restore anti-tumor immunity. CV8102 consists of a single-stranded, non-coding RNA complexed with a cationic peptide and acts as an agonist to human TLR-7, -8 and RLRs. Local administration of CV8102 was shown to induce upregulation of inflammatory cytokines, chemokines and IFN-γ related genes at the injection site followed by activation of T, NK, NKT cells and migratory dendritic cells in the draining lymph node (Heidenreich 2015; Ziegler 2017). In a syngeneic murine model, intratumoral (IT) delivery of CV8102 induced dose-dependent anti-tumor activity and synergized with systemic anti-PD1 antibody treatment.

Trial design: This phase I study is evaluating IT injection of CV8102 alone or in combination with a systemic anti-PD-1 antibody in patients with advanced solid tumors. Patients with advanced inoperable melanoma, cutaneous/head and neck squamous cell or adenoid cystic carcinoma and at least one lesion accessible for IT injection are eligible. After determination of the maximum tolerated/ recommended dose of CV8102 alone and in combination with an anti-PD1 antibody, expansion cohorts are planned in different indications. A Bayesian logistic regression model with overdose control will be used to guide the dose escalation. Patients in each cohort will receive up to 8 injections into a single tumor lesion over a 12 weeks period. The primary objective is to determine safety and tolerability, secondary/explorative objectives are to evaluate tumor response and changes in tumor tissue and blood-based biomarkers. The study has been initiated and enrollment is ongoing.

Clinical trial identification: NCT03291002.

Legal entity responsible for the study: CureVac AG, Paul-Ehrlich-Str. 15, 72076 Tübingen, Germany.

Funding: Has not received any funding.

Disclosure: P. Terheyden: Honoraria, Travel expenses: Novartis, Merck, Roche, BMS, Biofrontera; Advisory board: Roche, BMS, Sanofi Novartis, Merck. L. Heinzerling: Consultant: CureVac AG PI in clinical study at site Erlangen. P. Mohr: Consultant or advisory role: Merck, Roche, GSK, BMS, Novartis, SciBase, LEO; Honoraria: GSK, Roche, Merck, BMS, Novartis, LEO, SciBase; Research funding: Merck. F. Kiecker: Payments, Travel grants for symposia, Advisory boards, Meetings: Amgen, BMS, Merck-Serono, MSD, Novartis, Pierre-Fabre, Regeneron, Roche. J.C. Becker: Speaker honoraria: Amgen, MerckSerono and Pfizer; Advisory board honoraria: Amgen, CureVac, eTheRNA, Lytix, MerckSerono, Novartis, Rigontec, Takeda; Research funding: Boehringer Ingelheim, BMS, MerckSerono. U. Gnad-Vogt: Stock, Other ownership interests: Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1306TiP ILLUMINATE 301: A randomized phase III comparison of IMO-2125 with ipilimumab (ipi) versus ipi alone in subjects with anti PD 1 refractory melanoma

P.A. Ascierto[1], P. Arenberger[2], V.G. Atkinson[3], J. Hansson[4], E. Kapiteijn[5], C. Loquai[6], S. Negrier[7], H.M. Shaw[8], A. Tarhini[9], J. Walker[10], J. Geib[11], S. Rahimian[12], S. Swann[13], A. Diab[14]

[1]Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [2]Dermatovenerologika Klinika, Fakultni nemocnice Kralovske Vinohrady, Prague, Czech Republic, [3]Gallipoli Medical Research Foundation, Greenslopes Private Hospital and University of Queensland, Brisbane, Australia, [4]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, [5]Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [6]Department of Dermatology, Universitätsmedizin Mainz, Mainz, Germany, [7]Medical Oncology, Centre Léon Bérard, Lyon, France, [8]Medical Oncology, University College London Hospital UCLH NHS Foundation Trust, London, UK, [9]Melanoma and Skin Cancer Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA, [10]Department of Oncology, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, [11]Oncology Clinical Development, Idera Pharmaceuticals, Exton, PA, USA, [12]Oncology Clinical Development, Idera Pharmaceuticals, Exton, PA, USA, [13]Biometrics, Idera Pharmaceuticals, Exton, PA, USA, [14]Melanoma Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

Background: IMO-2125 (tilsotolimod) is a TLR9 agonist with potent immunostimulating activity. An ongoing Phase 1/2 clinical study of intratumoral tilsotolimod + ipi (NCT02644967) shows the combination to be well-tolerated over the range of tilsotolimod doses tested, with evidence of dendritic cell activation and infiltration of tumor-specific immune cells in subject samples. Clinical responses (including durable CR > 21 months) have been seen in anti-PD-1-refractory subjects. Because no therapy has been shown to prolong survival after failure of first-line anti-PD-1 immunotherapy, this study is designed to show superiority of tilsotolimod + ipi over ipi alone.

Trial design: This is a randomized phase 3 global, multi-center, open-label comparison of ipi (3 mg/kg) +/- intratumoral tilsotolimod (8mg) in subjects with advanced cutaneous or mucosal melanoma with disease progression while on anti-PD-1 therapy. Eligible subjects are age ≥18 years with histologically confirmed Stage III or IV melanoma, ≥1 measurable lesion accessible for injection, ECOG ≤1, adequate organ function, and excluding those with previous TLR agonist treatment, prior ipi (except adjuvant), or CNS disease other than stable (≥4 wks) brain mets. Subjects will be randomized 1:1 to either ipi alone (Arm A) or tilsotolimod + ipi (Arm B) and stratified on the duration of prior antiPD-1 therapy (≥12 weeks/<12 weeks), stage (M1c/other), BRAF status and prior targeted therapy (TT) (BRAF wt/BRAF mut+ with TT/BRAF mut+ no TT). Primary endpoints comprise RECIST v1.1 ORR by independent central review and OS. Secondary endpoints include DRR, TTR, PFS, PRO, and safety. Treatment duration is 10 weeks (4 ipi doses) for subjects in Arm A and 24 weeks (9 tilsotolimod + 4 ipi doses) in Arm B. Final analysis (ORR and OS) will occur when 219 death events have occurred, estimated at 36 months after the first randomization. After 110 deaths, an interim analysis will be done for OS. Enrollment is planned as 308 subjects at around 80 centers in 10 countries. It is currently recruiting in the US and Australia with study initiation ongoing in EU and Canada.

Clinical trial identification: NCT03445533.

Legal entity responsible for the study: Idera Pharmaceuticals, Inc.

Funding: Idera Pharmaceuticals, Inc.

Disclosure: J. Geib, S. Rahimian, S. Swann: Employee: Idera Pharmaceuticals. A. Diab: Advisory board: Idera Pharmaceuticals. All other authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii467–viii478, 2018
doi:10.1093/annonc/mdy293

NEUROENDOCRINE TUMOURS

1307O Efficacy of lenvatinib in patients with advanced pancreatic (panNETs) and gastrointestinal (giNETs) grade 1/2 (G1/G2) neuroendocrine tumors: Results of the international phase II TALENT trial (GETNE 1509)

J. Capdevila[1], N. Fazio[2], C. Lopez[3], A. Teule[4], J.W. Valle[5], S. Tafuto[6], A. Custodio[7], N. Reed[8], M. Raderer[9], E. Grande[10], R. Garcia-Carbonero[11], P. Jimenez Fonseca[12], V. Alonso[13], L. Antonuzzo[14], A. Spallanzani[15], A. Berruti[16], I. Sevilla Garcia[17], A. La Casta[18], J. Hernando[1], T. Ibrahim[19]

[1]Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain, [2]Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, Istituto Europeo di Oncologia, Milan, Italy, [3]Medical Oncology, Marques de Valdecilla University Hospital, Santander, Spain, [4]Medical Oncology, Catalan Institute of Oncology (ICO), Bellvitge, Spain, [5]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [6]Medical Oncology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [7]Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain, [8]Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK, [9]Medical Oncology, Vienna General Hospital (AKH) - Medizinische Universität Wien, Vienna, Austria, [10]Head of Medical Oncology Department, MD Anderson Cancer Center Center Espana, Madrid, Spain, [11]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [12]Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain, [13]Medical Oncology Service, Hospital Miguel Servet, Zaragoza, Spain, [14]Medical Oncology Service, Azienda Ospedaliera Careggi, Florence, Italy, [15]Medical Oncology, University Hospital of Modena, Modena, Italy, [16]Department of Medical and Surgical Specialties, Radiological Sciences, and Publi, Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy, [17]Medical Oncology Service, Hospital Regional Universitario Carlos Haya, Malaga, Spain, [18]Medical Oncology, Donosti University Hospital, Donosti, Spain, [19]Medical Oncology, Istituto Tumori della Romagna I.R.S.T., Meldola, Italy

1308O Activity & safety of spartalizumab (PDR001) in patients (pts) with advanced neuroendocrine tumors (NET) of pancreatic (Pan), gastrointestinal (GI), or thoracic (T) origin, & gastroenteropancreatic neuroendocrine carcinoma (GEP NEC) who have progressed on prior treatment (Tx)

J.C. Yao[1], J. Strosberg[2], N. Fazio[3], M.E. Pavel[4], P. Ruszniewski[5], E. Bergsland[6], D. Li[7], S. Tafuto[8], N. Raj[9], D. Campana[10], S. Hijioka[11], M. Raderer[12], R. Guimbaud[13], P. Gajate[14], S. Pusceddu[15], A. Reising[16], E. Degtyarev[17], B. Mookerjee[18], P. Aimone[19], S. Singh[20]

[1]Department of Gastrointestinal Medical Oncology, University of Texas/MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Medicine, Moffitt Cancer Center, Tampa, FL, USA, [3]Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Milan, Italy, [4]Department of Endocrinology, University of Erlangen-Nuremberg, Erlangen, Germany, [5]Gastroenterology and Pancreatology Department, Beaujon Hospital, Clichy, France, [6]Division of Hematology/Oncology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [7]Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA, [8]Dipartimento di Oncologia Addominale, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, ENETS Center of Excellence, Naples, Italy, [9]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, New York, NY, USA, [10]Department of Medical and Surgical Sciences, Policlinico Sant'Orsola-Malpighi, Bologna, Italy, [11]Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan, [12]Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria, [13]Department of Digestive Medical Oncology, CHU de Toulouse, Toulouse, France, [14]Clinical Oncology Department, Hospital Universitário Ramón y Cajal, Madrid, Spain, [15]Department of Medical Oncology, Fondazione IRCCS Istituto Naz, Milan, Italy, [16]OPM Translational Precision Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [17]Oncology Biostatistics, Novartis Pharma AG, Basel, Switzerland, [18]Global Drug Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [19]Global Drug Development, Novartis Pharma AG, Basel, Switzerland, [20]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

1309O **Efficacy and safety of PD-1 blockade with JS001 in patients with advanced neuroendocrine neoplasms: A non-randomized, open-label, phase Ib trial**

P. Zhang[1], M. Lu[1], J. Li[1], L. Shen[2]

[1]*GI department, Beijing Cancer Hospital, Beijing, China,* [2]*Beijing Cancer Hospital, Beijing, China*

1310PD **Prospective genome and transcriptome sequencing in advanced-stage neuroendocrine neoplasms**

L. Apostolidis[1], S. Kreutzfeldt[2], M. Oles[2], L. Gieldon[3], C. Heining[4], P. Horak[2], B. Hutter[5], M. Fröhlich[5], B. Klink[3], M. Lamping[6], S. Uhrig[5], A. Stenzinger[7], E.C. Winkler[1], B. Wiedenmann[8], D. Jäger[1], E. Schröck[3], U. Keilholz[6], M.E. Pavel[9], H. Glimm[4], S. Fröhling[2]

[1]*Department of Medical Oncology, National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany,* [2]*Department of Translational Oncology, National Center for Tumor Diseases (NCT) Heidelberg and German Cancer Research Center (DKFZ), Heidelberg, Germany,* [3]*Institute for Clinical Genetics, Faculty of Medicine Carl Gustav Carus, Dresden, Germany,* [4]*National Center for Tumor Diseases (NCT) Dresden, University Hospital Carl Gustav Carus, Dresden, Germany,* [5]*Division Applied Bioinformatics, DKFZ and NCT, German Cancer Consortium (DKTK), Heidelberg, Germany,* [6]*Charité Comprehensive Cancer Center, Charité University Medicine, Berlin, Germany,* [7]*Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany,* [8]*Department of Gastroenterology and Hepatology, Charité University Medicine, Berlin, Germany,* [9]*Department of Medicine, Division of Endocrinology, Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany*

1311PD Health-related quality of life (HRQoL) for octreotide long-acting (oct l-a) vs. placebo (PBO) in patients (pts) with metastatic midgut neuroendocrine tumors (mmNETs) in the phase IIIb PROMID trial

A. Rinke[1], M.P. Neary[2], J. Eriksson[3], M. Hunger[4], T. Doan[5], D. Karli[5], R. Arnold[1]

[1]Department of Gastroenterology and Endocrinology, Philipps-University of Marburg, Marburg, Germany, [2]Global Value and Access, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [3]RWES&A, Mapi (ICON plc), Stockholm, Sweden, [4]RWES&A, Mapi (ICON plc), Munich, Germany, [5]Product Lifecycle Services, Novartis Ireland Ltd., Dublin, Ireland

1312PD Everolimus after transarterial liver therapy of metastases from gastrointestinal neuroendocrine tumors: The FFCD 1104-EVACEL-GTE phase II study

T. Walter[1], C. Lepage[2], R. Coriat[3], E. Barbier[4], G. Cadiot[5], F.X. Caroli Bosc[6], T. Aparicio[7], K. Bouhier Leporrier[8], O. Hentic Dhome[9], A-C. Dupont-Gossart[10], M. Duluc[11], C. Lepere[12], T. Lecomte[13], D. Smith[14], C. Petorin[15], I. Iwanicki Caron[16], M.P. Ducreux[17], C. Lombard Bohas[18], T. de Baere[19]

[1]Gastroenterology and Medical oncology Department, CHU Edouard Herriot, Lyon, France, [2]HepatoGastroenterology and Digestive Oncology Department, University Hospital Dijon, University of Burgundy and Franche Comté, FFCD, EPICAD INSERM LNC-UMR 1231, Dijon, France, [3]Gastroenterology Department, Cochin Hospital, Paris, France, [4]Biostatistics, FFCD, EPICAD INSERM LNC-UMR 1231, University of Burgundy and Franche Comté, Dijon, France, [5]Gastroenterology Department, CHU Robert Debré, Reims, France, [6]Gastroenterology Department, CHU Angers, Angers, France, [7]Gastroenterology Department, Saint Louis Hospital AP-HP, Paris, France, [8]Gastroenterology Department, CHU Côte de Nacre, Caen, France, [9]Gastroenterology Department, Beaujon Hospital, Clichy, France, [10]Gastroenterology Department, Jean Minjoz Hospital, Besançon, France, [11]Gastroenterology Department, CHU La Timone, Marseille, France, [12]Gastroenterology Department, European Georges Pompidou Hospital, Paris, France, [13]Gastroenterology Department, CHU Tours, Tours, France, [14]Digestive Oncology Department, CHU Haut Lévêque, Bordeaux, France, [15]Digestive Oncology Department, CHU Estaing, Clermont-Ferrand, France, [16]Gastroenterology Department, CHU Charles Nicolle, Rouen, France, [17]Medical Oncology Department, Gustave Roussy, Paris Saclay University, Villejuif, France, [18]Oncology Department, Edouard Herriot Hospital, Cancer Institute Hospices Civils de Lyon, Lyon, France, [19]Interventional Radiology Department, Gustave Roussy Villejuif & UFR Medecine Kremlin Biceter Paris Sud University, Villejuif, France

1313PD A phase II study of everolimus in patients with unresectable pancreatic neuroendocrine carcinoma refractory or intolerant to platinum-containing chemotherapy

H. Okuyama[1], M. Ikeda[2], T. Okusaka[3], J. Furuse[4], M. Furukawa[5], S. Ohkawa[6], A. Hosokawa[7], Y. Kojima[8], K. Yamaguchi[9], G. Murohisa[10], K. Shioji[11], H. Ishii[12], N. Mizuno[13], M. Kojima[14], T. Yamanaka[15]

[1]Department of Clinical Oncology, Kagawa University, Kagawa, Japan, [2]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [3]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Medical Oncology, Kyorin University, Tokyo, Japan, [5]Department of Hepato-Biliary-Pancreatology, National Kyushu Cancer Center, Fukuoka, Japan, [6]Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan, [7]Department of Gastroenterology and Hematology, University of Toyoma, Toyama, Japan, [8]Department of Gastroenterology, National Center for Global Health and Medicine, Tokyo, Japan, [9]Division of Gastroenterology, Saitama Cancer Center, Saitama, Japan, [10]Department of Gastroenterology, Seirei Hamamatsu General Hospital, Hamamatsu, Japan, [11]Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan, [12]Clinical Research Center, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [13]Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan, [14]Division of Pathology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Kashiwa, Japan, [15]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan

1314P Efficacy and safety of telotristat ethyl (TE) in combination with lanreotide (LAN) in patients with a neuroendocrine tumour and carcinoid syndrome (CS) diarrhoea (CSD): Meta-analysis of phase III double-blind placebo (PBO)-controlled TELESTAR and TELECAST studies

D. Hörsch[1], R. Garcia-Carbonero[2], J.W. Valle[3], P. Perros[4], S. Welin[5], L. Keeber[6], A. Houchard[7], P. Lapuerta[8]

[1]Department of Gastroenterology/Endocrinology, ENETS Center of Excellence, Zentralklinik Bad Berka, Bad Berka, Germany, [2]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [3]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [4]Department of Endocrinology, Royal Victoria Infirmary, Newcastle Upon Tyne, UK, [5]Department of Endocrine Oncology, Uppsala University Hospital, Uppsala, Sweden, [6]Rare Diseases, Ipsen Ltd, Slough, UK, [7]Clinical Statistics, Ipsen Pharma France, Boulogne-Billancourt, France, [8]Clinical Development, Lexicon Pharmaceuticals, Princeton, NJ, USA

Background: LAN 120 mg, a somatostatin analogue (SSA), is approved in the EU and recently in the USA for CS. In two phase 3 trials in CS, TE 250 mg or 500 mg three-times daily (tid) combined with SSA therapy (LAN or octreotide) demonstrated reduced bowel movement (BM) frequency and urinary 5-hydroxyindole acetic acid (u5-HIAA) levels vs. PBO. TE 250 mg is approved by the FDA and EMA for CSD inadequately controlled by SSAs. This post hoc meta-analysis used patient-level data from the two phase 3 studies to further examine the efficacy and safety of TE + LAN.

Methods: In the TELESTAR (NCT01677910) and TELECAST (NCT02063659) studies, patients using and continuing stable-dose SSAs were randomly assigned 1:1:1 to PBO, TE 250 mg or TE 500 mg tid for a 12-week double-blind (DB) period. Here, only data for patients using LAN during the run-in periods were included. Endpoints included descriptive changes from baseline in 24-hour u5-HIAA, BMs/day, flushing episodes and incidence of adverse events (AEs).

Results: Of 211 patients in the studies, 54 receiving LAN were included in the analysis (44% women, mean [SD] age 61.8 [10.5] years, mean [SD] BMI 25.7 [5.0] kg/m^2; 34 [63%] used LAN 4-weekly, 20 [37%] used LAN 3-weekly). One patient received octreotide instead of LAN during the DB period. Randomization of this cohort is shown with efficacy and safety data in the table.

Table: 1314P

	PBO tid	TE 250 mg tid	TE 500 mg tid
Number of LAN patients randomly allocated	n = 29	n = 10	n = 15
u5-HIAA (mg/24 hour)			
Patients with levels > upper limit of normal (at randomization): n (%)	15 (51.7)	6 (60.0)	9 (60.0)
Baseline: median [95% CI]	24.9 [12.2; 80.9]	57.6 [12.9; 159.8]	31.0 [19.0; 259.2]
Week-12 change from baseline: median [95% CI]	1.6 [–6.7; 5.0]	–12.4 [–86.4; 77.2]	–24.6 [–134.6; –10.0]
BMs/day: median [95% CI]			
Baseline	3.5 [2.4; 4.4]	3.1 [1.3; 5.6]	5.3 [3.6; 6.1]
Week-12 change from baseline	–0.2 [–1.1; 0.2]	–0.9 [–2.6; –0.0]	–1.29 [–3.3; –0.0]
Flushing (counts/day): median [95% CI]			
Baseline	3.5 [1.5; 5.1]	2.8 [0.5; 4.9]	2.9 [0.8; 4.3]
Week-12 change from baseline	0.00 [–1.1; 0.4]	–0.5 [–1.2; 0.7]	–0.5 [–2.0; 0.4]
Safety: n (%) patients			
Any AE	26 (90)	9 (90)	14 (93)
Treatment-related AEs	8 (28)	6 (60)	12 (80)
Serious AEs	3 (10)	1 (10)	4 (27)
Treatment-related serious AEs	1 (3)	0	0
Deaths	1 (3)	0	0

Conclusions: Changes from baseline in u5-HIAA, BMs and flushing suggest a trend towards meaningful efficacy of TE + LAN in CSD, in a population with moderately elevated baseline BM frequency. The combination TE + LAN was generally well tolerated. No power calculation was performed for this exploratory post hoc analysis; imbalanced groups and low patient numbers preclude any formal comparison with PBO. Evaluation of this TE + LAN regimen as first-line therapy in patients with CSD may be warranted.

Clinical trial identification: TELESTAR: NCT01677910 TELECAST: NCT02063659.

Editorial acknowledgement: Writing and editorial/submission support provided by Emma Leah, PhD (Ipsen); Tom Vizard, PhD, and Richard McDonald (Watermeadow Medical), funded by Ipsen.

Legal entity responsible for the study: Lexicon Pharmaceuticals

Funding: The TELESTAR and TELECAST studies were sponsored by Lexicon Pharmaceuticals. This analysis was sponsored by Ipsen.

Disclosure: D. Hörsch: Consultant: Ipsen, Lexicon, Novartis, Pfizer; Research investigator: Ipsen, Lexicon, Novartis, Pfizer; Speaker's bureau: Ipsen, Lexicon, Novartis, Pfizer. R. Garcia-Carbonero: Honoraria: AAA, Ipsen, Novartis, Pfizer; Consultant: AAA, Ipsen, Novartis, Pfizer; Grant recipient: Pfizer; Research investigator: Ipsen, Novartis, Pfizer. J.W. Valle: Honoraria: Ipsen. Consultant: Ipsen; Grant recipient: Ipsen; Research investigator: Ipsen. Speaker's bureau: Ipsen. S. Welin: Honoraria: Ipsen, Novartis. L. Keeber: Employee: Ipsen. A. Houchard: Grant recipient, Employee, Stock owner: Ipsen. P. Lapuerta: Employee, Stock owner: Lexicon Pharmaceuticals. All other authors have declared no conflicts of interest.

1315P Development and internal validation of a predictive nomogram of progression-free survival in well-differentiated stage IV gastroenteropancreatic neuroendocrine tumours treated with somatostatin analogues: GETNE-TRASGU study

R. Garcia-Carbonero[1], V. Alonso[2], J. Capdevila[3], M. Sanchez Canovas[4], T. Alonso[5], M. Benavent[6], A. Custodio[7], G. Crespo Herrero[8], C. Lopez[9], J. Hernando[10], M.C. Riesco Martinez[11], P. Escudero[12], J. Gallego Plazas[13], M. Marazuela[14], J.A. Diaz[15], M. Llanos-Munoz[16], A. La Casta[17], J.C. Percovich[18], P. Jimenez-Fonseca[19], A. Carmona-Bayonas[20]

[1]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [2]Medical Oncology Service, Hospital Miguel Servet, Zaragoza, Spain, [3]Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Medical Oncology Service, Hospital Universitario Morales Meseguer, Murcia, Spain, [5]Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain, [6]Medical Oncology Service, Hospital Universitario Virgen del Rocío, Seville, Spain, [7]Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain, [8]Medical Oncology Service, Hospital Universitario de Burgos, Burgos, Spain, [9]Medical Oncology, Marques de Valdecilla University Hospital, Santander, Spain, [10]Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron University Hospital. Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain, [11]Medical Oncology, University Hospital 12 de Octubre, Madrid, Ontario, Spain, [12]Medical Oncology Service, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain, [13]Medical Oncology Service, Hospital General Universitario de Elche, Elche, Spain, [14]Endocrinology, Hospital Universitario La Princesa, Madrid, Spain, [15]Endocrinology, Hospital Universitario Clínico San Carlos, Madrid, Spain, [16]Medical Oncology Service, Hospital Universitario de Canarias, San Cristobal De La Laguna, Santa Cruz de Tenerife, Canary Islands, Spain, [17]Medical Oncology, Donosti University Hospital, Donosti, Spain, [18]Endocrinology, Hospital Universitario Gregorio Marañon, Madrid, Spain, [19]Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain, [20]Medical Oncology, Hospital Universitario Morales Meseguer, Murcia, Spain

Background: Treatment with somatostatin analogs (SSA) in monotherapy is the most attractive first-line option for most patients with well-differentiated stage IV unresectable gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The objective is to develop and internally validate tool for predicting progression-free survival (PFS) during treatment with SSA.

Methods: The GETNE-TRASGU study is a subanalysis of the Spanish Group of NETs registry (R-GETNE). The cohort contains 309 patients treated between 2000-2017 with SSA in the first-line of advanced disease. PFS data were evaluated using Cox proportional risk regression and graphically represented as a nomogram. Missing data were controlled by multiple imputation. Bootstrap Harrell's c-index with 150 replications was used to assess discrimination.

Results: The median PFS was 25.5 months (95% CI, 20.8-30.8). The nomogram contains 5 covariates significantly associated with PFS: Ki67% index, neutrophil-lymphocyte ratio (NLR), extrahepatic metastases, liver tumor burden and primary tumor location. The median PFS was 3.7 (95% CI, 2.5-not computable) in poor prognosis group, 8.3 (95% CI, 6.0-30.0) in intermediate-bad, 18.4 (95% CI, 14.3-23.6) in intermediate-good, and 37.1 months (95% CI, 30.8-53.5) in good prognosis group. Ki67% (continuous variable) predicted PFS with HR 1.03 (95% CI, 1.01-1.06), RNL (continuous variable) with HR 1.08 (95%CI, 1.01-1.16), extrahepatic metastases with HR 1.70 (I95% CI 1.23-2.32), liver tumor burden >50% with HR 2.07 (95% CI, 1.28-3.34); compared with intestinal (reference), pancreatic with HR 2.18 (95%CI, 1.56-3.04), rectal with HR 1.99 (95% CI, 1.11-3.58), unknown origin with HR 1.71 (95% CI, 1.02-2.85), and other tumors with HR 2.58 (95% CI, 1.22-5.43). This model shows adequate calibration, with acceptable discrimination capability [c-index of 0.641 (95% CI, 0.60-0.68)].

Conclusions: The GETNE-TRASGU nomogram allows stratification of patients with advanced and well-differentiated GEP-NETs into four prognostic groups, with potential implications for treatment selection.

Legal entity responsible for the study: Grupo Español de Tumores Endocrinos y Neuroendocrinos (GETNE).

Funding: Grupo Español de Tumores Endocrinos y Neuroendocrinos (GETNE).

Disclosure: All authors have declared no conflicts of interest.

1316P Impact of liver tumor burden on therapeutic effect of 177Lu-dotatate treatment in NETTER-1 study

J. Strosberg[1], A. Hendifar[2], J.C. Yao[3], M. Kulke[4], T. O'Dorisio[5], M. Caplin[6], R.P. Baum[7], P. Kunz[8], T. Hobday[9], E. Wolin[10], E.S. Mittra[11], K. Oberg[12], P. Ruszniewski[13], B. Polack[14], B. He[15], D. Barton[14], P. Santaro[14], E. Krenning[16]

[1]GI Oncology, H. Lee Moffitt Cancer Center University of South Florida, Tampa, FL, USA, [2]IM/Hematology/Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [3]Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [5]Gastrointestinal Neurocrine MOG, University of Iowa, Iowa City, IA, USA, [6]Neuroendocrine Tumour Unit, Royal Free Hospital School of Medicine, London, UK, [7]Nuclear Medicine, Zentralklinik, Bad Berska, Germany, [8]School of Medicine, Stanford University, California, CA, USA, [9]Oncology, Mayo Clinic College of Medicine, Rochester, NY, USA, [10]Oncology, Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA, [11]Diagnostic Radiology, Oregon Health and Science University, Portland, OR, USA, [12]University Hospital, Uppsala University, Uppsala, Sweden, [13]Gastroenterology, Hôpital Beaujon, Clichy, France, [14]Medical Affairs, Advanced Accelerator Applications, New York, NY, USA, [15]Biometrics and Biostatistics, Advanced Accelerator Applications, Geneva, Switzerland, [16]Erasmus Medical Center, Rotterdam, Netherlands

Background: The aim of this study was to assess Progression Free Survival (PFS), Safety and Quality of Life (QoL) in subgroups of varying hepatic burden in the NETTER-1 study population.

Methods: Patients (pts) were randomized to receive either ^{177}Lu-DOTATATE (Lu)(n = 117) or high-dose octreotide (Oct) (n = 114). The liver tumor burden (LTB) was defined as tumor volume/total liver volume by CT, and categorized as low (<25%), moderate (25-50%), and high (>50%). PFS, QoL and hepatotoxicity were assessed based on baseline LTB. QoL was analysed using EQRTC QLQC 30 and G.I. NET 21 questionnaires completed at baseline and every 12 weeks thereafter for low and moderate/high LTB subgroups. Deterioriation was defined if the score decreased by $\geq$ 10 points at any time point after baseline. Time to deterioration (TTD) was defined as the time from randomization to the first QoL deterioration.

Results: Median PFS (months) in Lu vs Oct was 28.35 vs 11.04 in low (HR = 0.218, 95% CI 0.120 to 0.394); Not Reached (NR) vs 8.67 in moderate (HR = 0.202, 95% CI 0.077 to 0.525); 19.38 vs 5.52 in high LTB (HR = 0.193, 95% CI 0.079 to 0.474), respectively. Median TTD (months) for Global Health Status was 28.81 vs 6.11 in low (HR = 0.376, 95% CI 0.196 to 0.720); NR vs 5.98 in moderate/high LTB (HR = 0.453, 95% CI 0.178 to 1.152). In Lu arm, Grade 3/4 (CTCAE v 4.03) AST and ALT toxicities occurred in the low LTB in 2 and 3 patients, and in the high LTB group in 3 and 1 patients, respectively. Grade 3/4 hyperbilirubinemia occurred in one patient from the low LTB and one from the moderate LTB group. All liver function tests abnormalities were resolved without sequela. There were no high grade ALT, AST and Biliriubin toxicities in Oct arm.

Conclusions: ^{177}Lu-DOTATATE treatment demonstrated significant PFS improvement regardless of the extent of baseline liver tumor burden in patients with well-differentiated, metastatic midgut NET. Clinically significant liver function test abnormalities were rare, were not associated with high liver tumor burden, and resolved without sequela. The analysis shows that ^{177}Lu-DOTATATE treatment also provides quality of life benefit regardless of baseline liver tumor burden.

Clinical trial identification: NCT01578239.

Legal entity responsible for the study: Advanced Accelerator Applications, a Novartis company.

Funding: Advanced Accelerator Applications, a Novartis company.

Disclosure: B. Polack, B. He, D. Barton, P. Santaro: Employment: Advanced Accelerator Applications. All other authors have declared no conflicts of interest.

1317P Treatment outcomes for well differentiated grade 3 neuroendocrine tumors (NET G3)

L. Apostolidis, D. Jäger, E.C. Winkler

Department of Medical Oncology, National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany

Background: In the most current WHO classification for tumors of the endocrine organs, well differentiated grade 3 neuroendocrine tumors (NET G3) have been distinguished from poorly differentiated grade 3 neuroendocrine carcinomas (NEC G3).

Retrospective data suggest that commonly applied first-line chemotherapy protocols with cisplatin or carboplatin in combination with etoposide (PE) are less effective in NET G3 than NEC G3. Therefore current treatment guidelines suggest alternative first-line treatment with protocols like temozolomide-based (TEM) which have only been evaluated in second-line so far. The aim of this study was to evaluate treatment outcomes for NET G3 with a focus on efficacy of different first-line regimens.

Methods: Retrospective analysis of all patients with NET G3 in the NEN database of our center. All histopathological findings were reviewed by the investigators in order to comply with the most current WHO classification.

Results: A total of 89 patients could be identified. Primary tumors were mainly located in the pancreas. Median overall survival (OS) was not reach during a median follow-up of 18.4 months. 79 patients received palliative first-line therapy: PE 34, FOLFOX 17, TEM 12, other (including streptozotocin-based regimens, targeted agents, peptide receptor radionuclide therapy, somatostatin analogues) 16. Overall response (ORR) and disease control rate (DCR) was 38.2 % and 70.6 % for PE, 64.7 % and 82.4 % for FOLFOX, 12 % and 58.3 % for TEM, 25 % and 62.5 % for other respectively. Median progression-free survial for PE was 6.7 months. Compared to PE, the other treatment groups showed a trend towards a prolonged PFS (FOLFOX 8.6 months, $p = 0.151$; TEM 10.8 months; $p = 0.333$, other 12.0 months, $p = 0.085$). All non-PE patients combined showed a significantly prolonged PFS vs. PE (10.8 months; $p = 0.039$).

Conclusions: In this first comparative analysis of first-line treatments for NET G3, patients treated with non-PE regimens show a significantly prolonged PFS. Regarding ORR, FOLFOX seems to be the most active therapeutic regimen. Further prospective evaluation of the optimal therapeutic strategy for this newly defined tumor entity is needed.

Clinical trial identification: The trial was approved by the institutional research ethics committee (approval S-428/2014).

Legal entity responsible for the study: National Center for Tumor Diseases (NCT) Heidelberg.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1318P Carboplatin (CB) combined with oral or intravenous (IV) etoposide (ET) for advanced extra-pulmonary (EP) poorly differentiated (PD) neuroendocrine carcinoma (NEC): Real-world findings from two European neuroendocrine tumour society centres of excellence

M. Frizziero[1], F. Spada[2], A. Lamarca[3], Z. Kordatou[3], J. Barriuso[4], C. Nuttall[3], M.G. McNamara[4], R. Hubner[3], W. Mansoor[3], P. Manoharan[5], N. Fazio[2], J.W. Valle[4]

[1]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [2]Gastrointestinal and Neuroendocrine Tumors Unit, Medical Oncology, Istituto Europeo di Oncologia, Milan, Italy, [3]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [4]Medical Oncology/Division of Cancer Sciences, The Christie NHS Foundation Trust/Univeristy of Manchester, Manchester, UK, [5]Radiology and Nuclear Medicine, The Christie NHS Foundation Trust, Manchester, UK

Background: Carboplatin-Etoposide is a 1st-line (1L) option for patients (pts) with advanced EP-PD-NEC. Schedules with oral or IV ET are used in clinical practice. Data from randomised trials are lacking.

Methods: Records of pts diagnosed with advanced EP-PD-NEC and treated with CB/oral-ET and CB/IV-ET were reviewed retrospectively (09/96-02/17). First-line survival/activity/toxicity data are reported.

Results: One-hundred-thirteen pts were identified: median (med) follow-up was 11.5 months (m); med age was 65.8 years (range 24-88); male=64%; ECOG performance status 0-1=81%; no/mild comorbidities=81%; gastro-entero-pancreatic origin=54%; stage IV = 90% (53% liver metastases). Median Ki-67=70% (95%CI 60-80%), Ki-67>55%=59%. A total of 123 courses of CB-ET were administered: 106 (86%) 1L, 16 (13%) 2nd-line (2L) and 1 (1%) 3rd-line; med cycles/line=4; oral-ET 45%, IV-ET 55%. Median CB-ET dose-intensity (available for 82 courses): 96% (1L), 90% (2L). Median 1L-progression free survival (PFS) was 5.9m (95%CI 5.0-7.1): oral-ET 5.6m, IV-ET 6.2m, hazard ratio (HR)=0.76 (95%CI 0.51-1.14). Median 1L-overall survival (OS) was 11.5m (95%CI 8.9-13.6): oral-ET 8.9m, IV-ET 12.1m, HR = 0.68 (95%CI 0.45-1.03), $p = 0.07$. Radiological response (assessed for 95 pts), 1L-disease control rate was 75.8% (95%CI 67.1-84.6): oral-ET 69.8% (95%CI 55.5-84.1), IV-ET 80.8% (95%CI 69.7-91.8). Liver metastases were the only independent factor related to worse 1L-PFS on multivariable analysis, HR = 1.71 (95%CI 1.11-2.63). Commonest 1L-grade 3-4 adverse event (AE) was myelosuppression (47.2%); no significant differences between oral-ET and IV-ET AEs, except for venous thromboembolism; oral-ET 12.5%, IV-ET 1.7% ($p = 0.04$).

Conclusions: This is one of the largest series of pts with advanced EP-PD-NEC treated with CB-ET in the current literature. Oral-ET and IV-ET schedules are associated with comparable 1L-PFS/activity/toxicity data. There is a trend towards better 1L-OS for IV-ET schedules; this, however, may be driven by differences in patient selection between the two subgroups.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1319P Post-hoc analysis of CLARINET phase III study to investigate the influence of diabetic status on progression-free survival (PFS) of patients with neuroendocrine tumours (NETs) treated with lanreotide (LAN) or placebo (PBO)

S. Pusceddu[1], C. Vernieri[1], M. Di Maio[2], N. Prinzi[3], M. Torchio[1], R. Buzzoni[1], X-M. Truong-Thanh[4], V. Mazzaferro[5], F.G.M. de Braud[6]

[1]Medical Oncology, ENETS Center of Excellence, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Division of Medical Oncology, "Ordine Mauriziano" Hospital, Turin, Italy, [3]Medical Oncology ENETS Center of Excellence, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [4]Global Medical Affairs, Ipsen Pharma France, Boulogne-Billancourt, France, [5]Gastrointestinal Surgery and Liver Transplantation Department, ENETS Center of Excellence, University of Milan, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [6]Medical Oncology, ENETS Center of Excellence, University of Milan, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

Background: Diabetes mellitus (DM) is a risk factor for pancreatic NETs, but its prognostic role in stage IV NETs is less defined. We evaluated the impact of diabetes on PFS in patients with advanced, non-functioning GEP-NETs.

Methods: Post hoc analysis of data from the phase III double-blind, placebo-controlled CLARINET study (NCT00353496) to investigate association between DM (any of: medical history of type 1 or 2; use of antihyperglycemic medication; HbA1c ≥6.5%, fasting plasma glucose ≥7mmol/L; non-fasting plasma glucose ≥11.11mmol/L [at baseline or during study]) and PFS (Kaplan-Meier). Multivariate Cox analysis including treatment (LAN vs PBO), DM at baseline, previous therapy and progression at baseline was used to test interaction between DM and LAN efficacy.

Results: The overall population (total, n = 204; LAN, n = 101; PBO, n = 103) had well-differentiated (Ki-67 <10%) foregut (45%), midgut (36%), or hindgut (7%) and unknown (13%) NET. 79 patients had DM, 125 did not (N-DM); 24 received metformin in combination with LAN (n = 14) or PBO (n = 10). Median PFS (mPFS) was 96.0 months (mo) [95% CI: 70.4; not reached (NR)] for DM vs 98.0 mo [72.1;NR] for N-DM (HR 1.20 [0.79;1.82], $p = 0.38$). For DM, mPFS with LAN (n = 42) was NR [95.9;NR] vs 60.0 mo [48.0;74.4] with PBO (n = 37) (HR 0.27, [0.13-0.57], $p = 0.0002$). For N-DM, mPFS with LAN (n = 59) was NR [96.0;NR] vs 72.1 mo [52.0;NA] with PBO (n = 66) (HR 0.64 [0.35-1.15], $p = 0.04$). In multivariate analysis, DM at baseline was not significantly associated with PFS (HR 1.64 [0.95;2.84], $p = 0.08$). Significant impact of LAN on PFS was confirmed (HR 0.53 [0.31;0.89], $p = 0.02$), without significant interaction between LAN efficacy and DM ($p = 0.62$).

Conclusions: DM did not emerge as a negative prognostic factor in advanced stage IV NETs. Efficacy of LAN in DM and N-DM was confirmed. Although LAN–DM interaction was not significant, LAN efficacy seemed particularly favorable in DM compared to N-DM patients, in terms of HR. These findings, along with a potential favorable association with hypoglycemic drugs such as metformin, should be evaluated and validated in prospective biomarker studies.

Clinical trial identification: Post hoc analisys of phase III double-blind, placebo-controlled CLARINET study (NCT00353496).

Editorial acknowledgement: Editorial assistance for the preparation of this abstract was provided by Emma Leah, Global Publications Manager, Rare Diseases, Ipsen.

Legal entity responsible for the study: Ipsen.

Funding: Ipsen.

Disclosure: S. Pusceddu: Honoraria, advisory boards: Novartis; Research funding, honoraria, advisory boards, consulting role, grants: Ipsen; Advisory boards: Italfarmaco; Research funding, advisory boards, grants: Pfizer; Advisory boards: Advanced Accelerate Application (AAA). R. Buzzoni: Research funding, advisory boards: Ipsen. F.G.M. de Braud: Research funding, honoraria, advisory boards, consulting role, grants: Ipsen. N. Prinzi: Honoraria: Ipsen. X-M. Truong-Thanh: Employment: Ipsen. V. Mazzaferro: Honoraria: Ipsen. All other authors have declared no conflicts of interest.

1320P The prognostic role of morphology and Ki67 in grade 3 gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN)

A.R. Hayes[1], M. Furnace[1], C. Rundell[2], R. Shah[2], G. Muller[2], C. Thirlwell[1], T.V. Luong[1], C. Toumpanakis[1], M. Caplin[1], D. Mandair[1]

[1]Neuroendocrine Tumour Unit, Royal Free Hospital, London, UK, [2]School of Medicine, University College of London, London, UK

Background: GEP NEN are classified according to morphology and proliferation index. According to the WHO 2010 classification, grade 3 (G3) GEP NEN are defined as having a Ki67 >20%. However, G3 well-differentiated NETs (WD-NETs) and poorly-differentiated neuroendocrine carcinomas (PD-NECs) may overlap in their proliferation index leading to prognostic and therapeutic uncertainties. Recently, WHO 2017, defined a new subgroup of G3 pancreatic NETs (PNET); G3a for WD-NETs and G3b for PD-NECs.

Methods: We retrospectively identified patients with G3 GEP NEN and divided them into WD-NETs and PD-NECs according to histological reports. The relationship between baseline characteristics and OS was analysed using the Kaplan Meier logrank

test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. Optimal Ki67 cut-points were explored using R version 2.15.0.

Results: 145 patients with G3 GEP NENs had median follow-up 17 mo (59% male, 50% PD-NEC, 37% PNEN). There was a trend in improved survival in the WD-NET cohort (median Ki67 30%) compared to PD-NECs (median Ki67 60%); 29 vs 22 months ($p = 0.1$) more marked in the non-PNET cohort (median OS WD-NET 44 mo vs PD-NEC 20 mo; $p = 0.1$). Of the entire cohort, an independent effect of Ki67 was demonstrated on risk of mortality ($p = 0.02$). A Ki67 cutoff of 50% was found to have the highest logrank statistic. Ki67 $\geq$50% was associated with poorer OS compared to lower Ki67 index (median OS 38 mo vs 20 mo; $p = 0.005$). Somatostatin receptor imaging (SRI) was positive in 81% of WD-NETs compared to 45% of PD-NECs.

Conclusions: Our findings suggest that morphology and proliferative index are important factors in the prognostic evaluation of G3 GEP NEN of pancreatic and non-pancreatic origin. Ki67 remains the most reliable prognostic factor and further work is required to refine optimal Ki67 cutoffs in the G3 GEP NEN cohort to guide prognosis and treatment.

Legal entity responsible for the study: Aimee Hayes.

Funding: Has not received any funding.

Disclosure: C. Thirlwell: Advisory board, Speaker honoraria: Ipsen. C. Toumpanakis: Speaker honoraria: Ipsen, Novartis and AAA. M. Caplin: Advisory Board, Speaker honoraria: Novartis, Ipsen, AAA, Lexicon. All other authors have declared no conflicts of interest.

1321P Surgical resection of primary tumor is prolonged survival in metastatic pancreatic neuroendocrine carcinoma

T. Feng

Abdominal Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China

Background: Most of pancreatic neuroendocrine carcinoma (PanNEC) present with distant metastases. Removal of the primary tumor is not recommended for metastatic PanNEC patients considering the limited survival benefit compared to well differentiated grade patients. However, published data to support these recommendations regarding PanNEC are scarce. The aim of this study was to assess whether resection of the primary tumor in patients with stage IV PanNEC has an impact on survival.

Methods: Patients with stage IV PanNEC registered in the Surveillance, Epidemiology, and End Results database between 1973 and 2014 were identified. The specific criteria are as follows:1 The histologic subtypes and their ICD-O-3: large cell neuroendocrine carcinoma(8013), small cell carcinoma(8041) and neuroendocrine carcinoma (8246); 2 histologic differentiation grade: poorly differentiated and undifferentiated; 3 Diagnostic confirmation is "Positive histology"; 4 the age $\geq$ 18 years and $\leq$ 85 years; 5 "SEER historic stage" variable is"distant"or AJCC stage IV;6.Survival months flag is "Complete dates are available and there are more than 0 days of survival". Overall (OS) and cancer-specific survival (CSS) of patients who did and did not undergo resection of their primary tumor were compared by means of risk-adjusted Cox proportional hazard regression analysis and propensity score matched analysis.

Results: We identified 461 patients with metastatic PanNEC and survival data. 15.8% (73/461) of patients had surgical removal of their primary tumor. Median survival of patients undergoing primary tumor resection was 28 (95% CI: 4.751-51.249) versus 6 (95% CI: 4.672-7.328) months for those without resection ($p < 0.0001$). Patients underwent primary tumor resection showed a significant benefit in both OS (HR of death=0.296, 95%CI 0.206–0.424, $p < 0.001$) and CSS (HR of death=0.329, 95 % CI 0.219–0.493, $p < 0.001$) in unadjusted multivariate Cox regression analysis; the benefit persisted after propensity score adjustment.

Conclusions: The recent recommendations judging resection of the primary as inadvisable and the accompanying trend towards fewer palliative resections of the primary tumor in IV stage PanNEC have to be contested.

Legal entity responsible for the study: Fengtingting.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1322P The commonwealth neuroendocrine tumour collaboration (CommNETs) and North American neuroendocrine tumor society (NANETS) endorsement and update of European neuroendocrine tumor society (ENETS) best practice consensus for lung neuroendocrine tumors (LNET)

E. Segelov[1], E. Bergsland[2], C. Card[3], T. Hope[4], P. Kunz[5], D. Laidley[6], B. Lawrence[7], S. Leyden[8], M. Michael[9], L. Modahl[10], S. Myrehaug[11], S. Padda[12], R. Pommier[13], R. Ramirez[14], M. Soulen[15], J. Strosberg[16], A. Thawer[17], B. Wei[18], S. Singh[11]

[1]Oncology, Monash University and Monash Health, Clayton, Australia, [2]Division of Hematology/Oncology, University of California, San Francisco, CA, USA, [3]Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada, [4]Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA, [5]School of Medicine, Stanford University, California, CA, USA, [6]Division of Nuclear Medicine, London Health Sciences Centre, London, ON, Canada, [7]Oncology, University of Auckland Faculty of Medical & Health Sciences, Auckland, New Zealand, [8]Unicorn Foundation, Blairgowrie, Australia, [9]Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia, [10]Auckland City Hospital, Auckland Radiology Group, Auckland, New Zealand, [11]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [12]Stanford Cancer Institute, Stanford University School of Medicine, California, CA, USA, [13]Oncology, Oregon Health & Science University, Portland, OR, USA, [14]Oncology, Ochsner Medical Centre, Jefferson, LA, USA, [15]University of Pennsylvania, Abramson Cancer Centre, Philadephia, PA, USA, [16]GI Oncology, H. Lee Moffitt Cancer Center University of South Florida, Tampa, FL, USA, [17]Odette Cancer Center, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [18]Oncology, University of Alabama-Birmingham Medical Centre, Birmingham, AL, USA

Background: Despite LNETs increasing in incidence and prevalence, little data exists about natural history and response to various therapies. Management is often based on expert opinion and extrapolation from other NETS. CommNETS and NANETS undertook a rigorous consensus process to endorse and update the 2015 ENETS guidelines (1).

Methods: An endorsement approach based on the AGREE II processes (2) was undertaken by a 4 nation, 22 member CommNETS/NANETS panel, including experts from: surgery, pulmonology, medical and radiation oncology, nuclear medicine, pathology, pharmacy and patients/advocates. Two members assessed content and quality of the 52 ENETS statements using the Rigour of Development subscale. A systematic literature and abstract search since 2013 was conducted. Topic experts reviewed relevant ENETS statements and new data, using a patient-centered care perspective and a LNET-specific focus, to provide justification for endorsement or modification and to define a single important unanswered question. Statements were subsequently discussed by the entire panel at a face-to-face meeting and graded using Oxford criteria (3).

Results: 230 relevant new studies were identified. Of the 20 ENETS statements relating to management strategies, 4 were endorsed, 16 modified and 3 added (see table). A set of important unanswered questions will inform future studies.

Table: 1322P

Therapy	Main change
Surgery	updated techniques for localized disease modified followup protocol expanded indication for liver cytoreduction
Adjuvant	not recommended
Locoregional	optional for slow growing disease
Hormone	prophylaxis of carcinoid crisis added
PRRT	broadened to all SSTR-expressing tumours
Chemotherapy	newer data on temozolomide-based regimens included
Targeted	evidence for everolimus upgraded new statement, not supporting use of anti-angiogenics
Radiotherapy	palliative use for local symptoms added

Conclusions: Through the consensus process, guidelines for LNETS were updated to include recent evidence and practice changes. The guidelines provide clear, evidenced based statements to harmonise treatment of LNETS internationally. Refs: 1.Caplin, Ann Oncology (2015):1604-1620. 2. http://www.agreetrust.org/resource-centre/agree-ii-as-a-practice-guideline-development-framework/ (30.4.18) 3. http://www.cebm.net/index.aspx?o=5653 (30.4.18).

Legal entity responsible for the study: Australian Gastrointestinal Trials Group.

Funding: Ipsen Pty Ltd.

Disclosure: E. Segelov: Attendeded Advisory board: Ipsen Global. Ipsen funds CommNETS through an unrestricted grant to AGITG. This work was carried out by CommNETS. There was no involvement of Ipsen in any aspect of this research. All other authors have declared no conflicts of interest.

1323P Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) in patients with pulmonary carcinoid tumours: Prevalence and prognosis of an under-recognised disease

A.R. Hayes[1], J. Banks[2], H. Shah[2], T.V. Luong[1], S. Navalkissoor[1], A. Grossman[1], D. Mandair[1], C. Toumpanakis[1], M. Caplin[1]

[1]Neuroendocrine Tumour Unit, Royal Free Hospital, London, UK, [2]Medical School, University College of London, London, UK

Background: DIPNECH is considered a rare condition and the natural history is poorly described. Its prevalence is likely underestimated given the absence of routine reporting on histopathology and often insufficient background lung parenchyma in the setting of lung biopsy. It is thought to give rise to pulmonary carcinoids (PCs) (>5 mm) or tumourlets (≤5 mm). We aimed to assess the prevalence and characteristics of DIPNECH in the PC population and to investigate predictors of progression-free (PFS) and overall survival (OS).

Methods: We identified patients with PCs plus histologically-proven DIPNECH and/or high suspicion of DIPNECH on imaging. The relationship between baseline characteristics and PFS and OS was analysed using the Kaplan-Meier method and curves were compared using the logrank test.

Results: 46/233 (20%) patients with well-differentiated PCs and DIPNECH were identified (91% female, 52% never smokers, 50% cough and/or dyspnoea at time of diagnosis, 76% typical carcinoids (TC), 24% atypical carcinoids (AC), 9% both TC and AC) had median follow-up 37 mo (range 2-138 mo). Multicentric carcinoids were demonstrated in 11 (24%) patients on histopathology and a further 26 (57%) patients had synchronous carcinoids suggested on enhanced CT (multiple nodules >5 mm). Median PFS was 10.4 years. Six (13%) patients developed regional or distant metastases after a median of 25 months (8-125 mo) and most patients had higher proliferative indices on biopsy of metastases compared to histopathology at diagnosis. Atypical carcinoid morphology (PFS p-value 0.0006, OS p-value 0.03) and carcinoid TNM stage (PFS p-value $p < 0.0001$, OS p-value 0.006) was associated with shorter PFS and poorer OS. Of the entire cohort, ten year survival rate was 87%. Median OS was not reached.

Conclusions: DIPNECH may be more prevalent in the PC population than previously appreciated, especially in women. Whilst our results confirm DIPNECH is predominantly an indolent disease associated with TCs, up to one quarter of patients may develop ACs and these patients may warrant closer observation. Median PFS is long and lifelong follow-up is recommended.

Legal entity responsible for the study: Aimee Hayes.

Funding: Has not received any funding.

Disclosure: A. Grossman: Lecture fees: Novartis, Ipsen, HRA Pharma, Pfizer, but none for the past 12 months. C. Toumpanakis: Speaker honoraria: Ipsen, Novartis, AAA. M. Caplin: Advisory board and speaker honoraria: Novartis, Ipsen, AAA, Lexicon. All other authors have declared no conflicts of interest.

1324P The role of modulation of somatostatin analogues (SSAs) in association to peptide receptor radionuclide therapy (PRRT) after SSAs progression disease (PD) in advanced well-differentiated (WD) entero-pancreatic neuroendocrine tumours (EP-NETs)

N. Prinzi[1], E. Seregni[2], A. Raimondi[1], M. Maccauro[2], F. Corti[1], G. Lo Russo[1], F. Nichetti[1], M. Torchio[1], J. Coppa[3], G. Peverelli[1], F. Pagani[1], M. Di Bartolomeo[1], V. Mazzaferro[3], F. de Braud[1], S. Pusceddu[1]

[1]Medical Oncology Department, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [2]Nuclear Medicine Department, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Gastrointestinal Surgery and Liver Transplantation Department, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

Background: The NETTER-1 trial has recently shown the efficacy of ^{177}Lu-DOTATATE in association with Octreotide (OCT) in somatostatin receptor positive midgut NETs, progressing to OCT. The aim of this analysis was to evaluate the role of SSA in association to PRRT beyond PD or after switch to other SSA at PD.

Methods: Out of 107 WD EP-NETs, treated with PRRT (^{90}Y-DOTATOC/DOTATATE and/or ^{177}Lu-DOTATOC/DOTATATE) at the Istituto Nazionale Tumori of Milan, from 2008 to 2017, 69 patients (pts) treated with the combination of PRRT and SSA (OCT or Lanreotide, LAN) after SSA treatment failure, were evaluated for present analysis. We identified 2 groups: S1, pts who kept the same SSA treatment beyond first PD; S2, pts who switched the SSA with another SSA after first PD. Median Progression Free Survival (mPFS) (from the start of first SSA) and Overall Survival (OS) have been evaluated using the Kaplan-Maier method.

Results: In S1 ($n = 47$) and S2 ($n = 22$) groups median age and sex were 58 ys (range 29-78) and 59.5% males vs 52.5 ys (range 35-78) and 45.4% males, respectively. We had a P-NETs percentage of 34% vs 40.9% in the S1 vs S2 groups, respectively. The most of pts (82.9% in S1 and 86.3% in S2) received PRRT with alternate radionuclides (^{90}Y/^{177}Lu). Overall the median number of PRRT cycles was 4.2 in S1 and 4.8 in S2 ($p = 0.09$). In the S1 (SSA beyond PD) group PRRT was associated with OCT in 74.5% and LAN in 25.5% of pts. In the S2 group (SSA switched with other SSA) PRRT was associated with OCT in 27.3% and LAN in 72.7% of pts. In the overall population the mPFS and OS were 70 (CI95% 52.8-87.1) and 82 (CI95% 66.7-97.2) months (mo), respectively. The difference on mPFS was 53 and 127 mo in S1 and S2, respectively ($p = 0.001$; HR: 0.31; CI95% 0.15-0.63). In S1 group the OS was 69 mo vs 150 mo in S2 ($p = 0.004$; HR: 0.32; CI95% 0.14-0.71).

Conclusions: Despite the retrospective nature of the analysis and the low number of pts, we found a significant difference on mPFS and OS between S1 and S2 groups. In pts with advanced WD EP-NETs treated with PRRT plus SSA after SSA failure, the "switch" strategy of SSA after PD, might improve PFS and/or OS.

Legal entity responsible for the study: Sara Pusceddu.

Funding: Has not received any funding.

Disclosure: N. Prinzi: Italfarmaco, Novartis: Consultancies. G. Lo Russo: AstraZeneca, BMS, MSD: Consultancies. S. Pusceddu: Novartis, Ipsen, Italfarmaco, Pfizer and advanced accelerator applications (AAA). All other authors have declared no conflicts of interest.

1325P Prognostic importance of lymph node (LN) yield after curative resection of gastroenteropancreatic neuroendocrinetumours (GEP NETs)

J. Chiramel[1], R. Almond[2], A.E. Slagter[3], A. Khan[1], K.H.J. Lim[1], B. Chakrabarty[4], A. Minicozzi[5], A. Lamarca[6], W. Mansoor[1], R. Hubner[1], J.W. Valle[6], M.G. McNamara[1]

[1]Medial Oncology, The Christie NHS Foundation Trust, Manchester, UK, [2]Analytics and Development, The Christie NHS Foundation Trust, Manchester, UK, [3]Radiation Oncology, NKI-AVL, Amsterdam, Netherlands, [4]Pathology, The Christie NHS Foundation Trust, Manchester, UK, [5]Surgery, The Christie Hospital NHS Foundation Trust, Manchester, UK, [6]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK

Background: Surgery is the main stay of treatment for GEP NETs, but there is no consensus on optimal number of resected LNs. The effect of LN status and yield on relapse-free (RFS) and overall survival (OS) in patients (pts) with resected GEP NETs were evaluated.

Methods: Data on pts who underwent curative resection for GEP-NETs (Jan 02-Mar 17) were retrospectively analysed. Grade III tumours (Ki67>20%) were excluded. Kaplan-Meier and univariate/multivariable Cox-proportional hazard analyses were performed. Cut-point analysis was assessed to distinguish a binary categorisation of total LNs retrieved associated with RFS.

Results: Of 217 pts, median (med) age was 59 yrs: 51% male. Primary tumour sites: small bowel (42%), pancreas (25%), appendix (18%), rectum (7%), colon (3%), gastric (2%), others (2%); grade 1 (G1): 77%, G2: 23%. LN cut-point value associated with RFS was 8; ≥8 LNs were retrieved in 106 pts, <8 in 45, and 0 or no record/documentation of LN retrieval in 66. Relapse was reported in 50 pts; 35 deaths. Med follow up times for all pts were 41 months (95% CI 36-51) and 71 months (95% CI 63–76) for RFS and OS respectively. On univariate analysis, there was no effect of LN ratio (number involved/number retrieved) on RFS: $p = 0.1$ or OS: $p = 0.75$. On univariate analysis, tumour necrosis ($p = 0.021$) and perineural infiltration ($p = 0.016$) were the only two variables significantly associated with OS; G ($p = 1$), TNM staging ($p = 0.19$) and surgical margin ($p = 0.69$) were not significantly associated with OS. Multivariable analysis for RFS included 4 variables of interest: perineural infiltration, LNs retrieved, positive LNs and localisation (Table).

Table: 1325P

Variable	Hazard Ratio	(95% CI)	p
Perineural infiltration	1.46	(0.74 - 2.69)	0.277
≥8 lymph nodes retrieved	2.70	(1.07 - 6.84)	0.036
Any lymph nodes positive	2.71	(0.88 - 8.30)	0.081
Pancreas (relative to 'other')	27.33	(2.54 - 294.08)	0.006
Small Bowel (relative to 'other')	32.44	(2.92 - 360.58)	0.005

Conclusions: Removal of ≥ 8 LNs is associated with greater risk of relapse in G1 & G2 GEP NETs; localisation also has a significant association with RFS, necessitating stricter surveillance. Larger prospective studies are required to validate these findings.

Legal entity responsible for the study: The Christie Hospital NHS Trust, Manchester, Uk.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1326P Evaluation of the efficacy and safety of everolimus as a first-line treatment in newly diagnosed patients with advanced gastroenteropancreatic neuroendocrine tumors

A. Koumarianou[1], D.G. Pectasides[2], K. Manousou[3], D. Dionysopoulos[4], G.A. Kaltsas[5], D. Kolomodi[6], C. Poulios[3], M. Skondra[2], E. Samantas[7], G. Pentheroudakis[8], G. Fountzilas[3]

[1]Hematology Oncology Unit, Fourth Department of Internal Medicine, Athens Greece, Attikon University Hospital, Athens, Greece, [2]Oncology Unit, Henry Dynan General Hospital, Athens, Greece, [3]Data Office, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece, [4]Oncology Clinic, Papageorgiou Hospital Aristotle University of Thessaloniki, Thessaloniki, Greece, [5]1st Department of Propaedeutic Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece, [6]Radiology, Vioiatriki, Athens, Greece, [7]Oncology Clinic, General Oncological Hospital of Kifisia "Agioi Anargyroi", Kifisia, Attica, Greece, [8]Oncology Clinic, University Hospital of Ioannina, Ioannina, Greece

Background: The purpose of this study was to explore the efficacy and safety of everolimus administered as first-line treatment in newly diagnosed patients (pts) with metastatic or inoperable gastroenteropancreatic neuroendocrine tumors (GEPNETs).

Methods: This phase II, multicenter, single-arm clinical trial, included pts with advanced GEPNET of well or moderate differentiation and a Ki67<20%. Everolimus 10mg/day was administered until disease progression. All pts' tumors were non-functioning; 18 pts (72%) received concomitantly octreotide long-acting release (LAR) 30mg/month. Endpoints of the study included progression-free survival (PFS), objective response to treatment (RECIST 1.1) and safety.

Results: After a median follow-up of 53 months, twenty-five pts (G1:11 pts, G2:14 pts; Ki67≤2%:11 pts, Ki67=3-19%:14 pts; pancreas:10 pts, GI:15 pts) received a median of 5 treatment cycles per patient. Centrally assessed radiographic responses in 23 evaluable patients included 43% PR, 48% SD and 9% PD. Of the 18 pts receiving octreotide LAR and everolimus, 9 patients had SD and 9 PR. The median PFS was 14.6 months, while the 15-months PFS rate was 48%. No fatal reaction occurred. Twenty-three grade 3-4 events were recorded (14 pts; 56%). Among them, 19 events were assessed as related to treatment and included stomatitis (G3: 3 pts; 12%), diarrhea (G3: 2 pts; 8%), CPK increase (2 pts; 8%), GGT increase (2 pts; 8%), hypokalemia/hypomagnesemia (1 pt; 4%), neutropenia (G3:1 pt; 4%), anemia (G3: 1 pt; 4%), and hyperglycemia (G3:1 pt; 4%). 8 serious adverse reactions to everolimus (6 pts; 24%) occurred. 6 (5 pts; 20%) were grade 3-4, namely mucositis G3/ bacteremia G3 (1 pt; 4%), pneumonia G3 (1 pt; 4%), diarrhea G3 (1 pt; 4%), and CPK G3 (1 pt; 4%) and G4 (1 pt; 4%). Baseline chromogranin A < 4x ULN was found to be associated with improved PFS as compared to higher values (HR = 0.34, 95% CI 0.11-1.02, Wald's p = 0.055).

Conclusions: This prospective phase II study confirms everolimus's efficacy as upfront therapy and provides for the first time high rates of partial responses in advanced GEPNETs attributed to the combined effect of everolimus and octreotide LAR.

Clinical trial identification: NCT01648465.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group.

Funding: Hellenic Cooperative Oncology Group, Novartis.

Disclosure: A. Koumarianou, D.G. Pectasides, G.A. Kaltsas, E. Samantas, G. Pentheroudakis: Honoraria for advisory board: Novartis. All other authors have declared no conflicts of interest.

1327P Improved quality of life in patients with GEP-NETs treated with 177Lu-dotatate

B. Saravana-Bawan[1], M. Wieler[2], T. McMullen[1], A. McEwan[2]

[1]Department of Surgery, University of Alberta, Edmonton, AB, Canada, [2]Department of Oncology, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada

Background: The incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) has been increasing over recent decades. Lutetium therapy is now established as a treatment with benefit towards progression-free survival (PFS) in patients with metastatic GEP-NETs with median PFS of up to 36 months. However, the effect of ^{177}Lu-DOTATATE on quality of life (QoL) is not yet well understood with few studies evaluating the impact on symptom control and patient function. Our study sought to evaluate the change in QoL for patients with progressive GEP-NETs treated with ^{177}Lu-DOTATATE.

Methods: Our study was conducted as a part of the Phase II open label clinical trial at the Cross Cancer Institute in Edmonton. Patient enrollment started in March of 2014 and is ongoing. Treatment consisted of induction phase of 5.55 GBq administered at four treatments, 10 weeks apart. For patients without toxicity or progression on treatment, a maintenance phase was entered consisting of 2.78 GBq every 6 months for up to 4 years and maximum of 12 total treatments. QoL over ^{177}Lu-DOTATATE treatment was assessed with EORTC QLQ-C30 and QLQ-GI.NET 21 QoL questionnaires at baseline and subsequent to each treatment. Planned interim analysis of QoL was completed in all patients having completed induction therapy. Repeated measures ANOVA was performed. A p value of < 0.05 was considered significant and change in EORTC score of ≥ 5 points was considered to be clinically significant.

Results: In total 85 patients met inclusion criteria for interim analysis: tumor of gastroenteric or pancreatic origin and completion of four ^{177}Lu-DOTATATE treatments. Primary analysis revealed statistically significant change and clinically significant improvement in mean insomnia (36.43 to 25.58), endocrine symptom (20.37 to 14.81) and GI symptom scores (22.28 to 16.67) from baseline to post fourth treatment. Overall global health status was maintained over treatment course with no improvement but also no statistically significant deterioration in QoL.

Conclusions: ^{177}Lu-DOTATATE is not only effective in improving PFS for patients with metastatic GEP-NETs but also maintains overall quality of life and importantly provides patients with improvement in specific symptoms such as insomnia, endocrine and GI symptoms.

Clinical trial identification: NCT01876771.

Legal entity responsible for the study: Alberta Health Services.

Funding: Alberta Cancer Foundation, Alberta Heritage Foundation for Medical Research, Canadian Institutes of Health Research, Canada Foundation for Innovation.

Disclosure: All authors have declared no conflicts of interest.

1328P Unmet needs in the management of neuroendocrine tumours (NETs): A global survey of patients, patient advocates and healthcare professionals

C.V. Bouvier[1], M. Caplin[2], S. Conroy[3], P. Davies[4], S. Dureja[5], M. Falconi[6], P. Ferolla[7], G.A. Fisher[8], G. Goldstein[9], R.J. Hicks[10], R. Hollander[11], T. Kolarova[12], B. Lawrence[13], S. Leyden[14], Y. Majima[15], D. Metz[16], D. O'Toole[17], P. Ruszniewski[18], B. Wiedenmann[19]

[1]NET Patient Foundation, NET Patient Foundation, Leamington Spa, UK, [2]Neuroendocrine Tumour Unit, Royal Free Hospital School of Medicine, London, UK, [3]Unicorn Foundation, Auckland, New Zealand, [4]Neuroendocrine Tumour Unit, Royal Free London NHS Foundation Trust, London, UK, [5]Nuclear Medicine, Fortis Memorial Research Institute, Gurgaon, India, [6]Department of Surgery, IRCCS San Raffaele, Milan, Italy, [7]Umbria Regional Cancer Network, Perugia, Italy, [8]Medical Oncology, Stanford University Medical Center, Stanford, CA, USA, [9]The Carcinoid Cancer Foundation, New York, NY, USA, [10]Nuclear Medicine, Peter MacCallum Cancer Center, Melbourne, Australia, [11]Neuroendocrine Tumor Research Foundation NET, Boston, MA, USA, [12]International Neuroendocrine Cancer Alliance (INCA), Boston, MA, USA, [13]Faculty of Medical & Health Sciences, University of Auckland Faculty of Medical & Health Sciences, Auckland, New Zealand, [14]Unicorn Foundation, Blairgowrie, Australia, [15]NPO PanCAN Japan, Tokyo, Japan, [16]Division of Gastroenterology, University of Pennsylvania, Philadelphia, PA, USA, [17]Neuroendocrine Tumour Clinic, St Vincents University Hospital, Dublin, Ireland, [18]Division of Gastroenterology and Pancreatology, Hôpital Beaujon, Clichy, France, [19]Division of Hepatology and Gastroenterology, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany

Background: The International Neuroendocrine Cancer Alliance (INCA) supports NET patients (and their families) by advocating on their behalf to improve diagnosis, care and research. The current survey was undertaken to identify and describe unmet needs in good quality care for NET patients.

Methods: Patients and family, healthcare professionals (HCPs) and patient advocates were surveyed online (Feb-Mar 2017) completing 35 questions covering: Information; Standards of care; Diagnostics and treatment; Research.

Results: 443 responses from 26 countries were collected: 338 patient/family; 70 HCPs; 35 advocates. Patients reported several information gaps at diagnosis, which were not perceived by HCPs (Table). 46% of patients felt their needs about treatment options were fully/mostly met, compared with 88% of HCPs. Many patients (70%) sought information via patient association websites, with 62% feeling this fully/mostly met their needs. 32% of patient advocates felt appropriate standards of care are not met, particularly in terms of psychological (76%) and mental health (71%) care and holistic support (e.g. diet, exercise; 65%). While 90% of HCPs stated MDT care was always/sometime provided, only 66% of patients reported seeing a MDT. Access to Gallium-68-DOTATATE/DOTATOC PET/CT (patients 72%; HCPs 86%; advocates 85%) and PRRT (42%; 77%; 95%) were the major unmet diagnostic and treatment needs. More involvement by patients in research was desired (patients 53%; HCPs 57%; advocates: 82%), particularly in clinical trials and in raising the profile of NET research. The research priority for patients and advocates was in earlier, more accurate diagnosis, while HCPs prioritised clinical trials to improve treatment.

Table: 1328P Informational needs not met at diagnosis

	Patient	HCP
Relevant clinical trials	53%	6%
NETs research	53%	6%
Psychological care	48%	13%
Signposting to patient associations	44%	4%
Advice on how to manage the condition	34%	1%

Conclusions: The INCA survey has highlighted areas for improvement related to information provision, access to gold standard care and attention, focus and patient involvement in research.

Editorial acknowledgement: Strategen Limited provided editorial support.

Legal entity responsible for the study: The International Neuroendocrine Cancer Alliance.

Funding: Neuroendocrine Tumor Research Foundation.

Disclosure: All authors have declared no conflicts of interest.

1329P Efficacy and safety of vandetanib for patients with advanced and progressive medullary thyroid cancer (MTC) as systemic treatment beyond first-line therapy

J. Hernando Cubero[1], E. Grande[2], P. Jimenez Fonseca[3], C. Villabona[4], J.M. Trigo Perez[5], J. Martinez Trufero[6], I. Pajares Bernad[7], C. Lopez[8], T. Alonso[9], J. Biarnes[10], T. RamónY Cajal[11], M. Duran[12], J.J. Grau[13], S. Arevalo Lobera[14], R. Mesia Nin[15], M. Llanos[16], E. Dalmau Portulas[17], C. Alvarez[18], C. Zafon[19], J. Capdevila[1]

[1]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [2]Head of Medical Oncology Department, MD Anderson Cancer Center Center Espana, Madrid, Spain, [3]Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain, [4]Medical Oncology, Hospital Universitario de Bellvitge, Barcelona, Spain, [5]Medical Oncology, Hospital Universitario Virgen de la Victoria, Málaga, Spain, [6]Medical Oncology Department, Hospital Miguel Servet, Zaragoza, Spain, [7]Medical Oncology, Hospital Miguel Servet, Zaragoza, Spain, [8]Medical Oncology, Marques de Valdecilla University Hospital, Santander, Spain, [9]Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain, [10]Medical Oncology, Hospital Universitario Doctor Josep Trueta, Gerona, Spain, [11]Breast Cancer, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [12]Medical Oncology, Hospital Universitario Rey Juan Carlos, Madrid, Spain, [13]Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [14]Medical Oncology, Hospital Donostia, San Sebastian, Spain, [15]Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain, [16]Medical Oncology, Hospital Universitario de Canarias, Santa Cruz De Tenerife, Spain, [17]Medical Oncology, Hospital de Sabadell Corporacis Parc Tauli, Sabadell, Spain, [18]Medical Oncology, Hospital Universitario La Paz, Madrid, Spain, [19]Endocrinology, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Vandetanib has demonstrated efficacy in advanced MTC in a large phase III trial (ZETA trial, JCO 2012). However, the study had several limitations that impact in the daily clinical practice, such as the efficacy in patients (pts) with documented disease progression or beyond first-line therapy who have a worse prognosis.

Methods: Pts with advanced unresectable MTC with previous radiologically documented disease progression were included in the Spanish National Database of the Rare Cancer Working Group (GETHI). Pts started treatment with vandetanib 300mg qd as initial dose, with dose reductions allowed as per toxicity. Baseline characteristics, progression free survival (PFS), response rate (RR), correlation with biomarkers and toxicity data were reviewed retrospectively in first, second and third line setting. The program was validated by regulatory authorities and all patients signed and informed consent form.

Results: 59 pts (med age:48y; male 61%) were included. 14% had RET mutations. Vandetanib was given as first line in 61%, second-line in 22% and third-line therapy in 17% of pts. RR and median PFS in first, second and third-lines were 47%, 53% and 40% (p 0.85%) and 16.8, 13.6 and 11.5 months (p 0.94) respectively. No correlation was found between calcitonin or CEA reduction and RR. However, CEA level decrease (30% versus baseline) appeared to predict PFS longer than 11 months (p 0.028). Treatment was well tolerated and dose reduction was needed in 23% to handle toxicity. Main side effects were grade 1-2 including fatigue (22%), skin rash (19%), hypertension (14%) and diarrhea (14%). Most frequent grade 3 toxicity was oral mucositis (3%).

Conclusions: Probability of tumor shrinkage with vandetanib is maintained throughout treatment lines despite of a trend of reduced benefit in PFS beyond first-line in a cohort of pts with a worse prognosis. CEA reduction may predict longer PFS. Safety is maintained regardless prognosis and prior therapies.

Legal entity responsible for the study: Spanish Rare Cancer Working Group (GETHI).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1330P Development and validation of neuroendocrine tumor marker panel in small biopsies using multiplexed mass spectrometry

S. Thyparambil[1], E. An[1], S. Sellappan[1], E.R. Wertheimer[1], S. Landolfi[2], J. Capdevila[2], F. Cecchi[1], P.G. Nuciforo[3], R. Heaton[1], T. Hembrough[1]

[1]R&D, NantOmics, LLC, Rockville, MD, USA, [2]Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron University Hospital, Barcelona, Spain, [3]Molecular Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Neuroendocrine tumors (NET) occur throughout the body but are not commonly suspected in breast, prostate or colorectal cancers. Morphologic evidence of neuroendocrine differentiation may prompt testing for neuroendocrine markers, but such testing is not routine. Now that NET-specific therapies can increase patient survival, distinction of NET from non-NET is essential. We developed a multiplexed mass spectrometry-based screening tool to measure tumor expression of 3 common neuroendocrine (NE) proteins. We tested and validated this NET panel in clinical biopsies of NET and non-NET.

Methods: Formalin-fixed-paraffin-embedded (FFPE) NET were microdissected and solubilized to tryptic peptides for mass spectrometric analysis using selected reaction monitoring. Synthetic versions of chromogranin A (CHGA), synaptophysin (SYP) and CD56 peptides were used to develop the assay. Using mass spectrometry with stable isotope labeled internal standards, these 3 NE proteins were quantitated in FFPE tumor biopsies of NET and non-NET.

Results: In the test set, 20 of 20 previously diagnosed NET (of the lung and gastroenteropancreatic tract) expressed $\geq$2 of the 3 NE protein markers (positive predictive value=100%), and 47 of 50 non-NET (non-small cell lung cancer) expressed none of the markers, with only one sample expressing $\geq$2 markers (negative predictive value=98%.). NET positivity was therefore defined as expression of $\geq$ 2 markers. In a validation set of 16 NET, the proteomic panel confirmed 13 cases. Of the 3 discordant cases, one of these was a small-cell lung cancer with mixed NE and squamous histology. When used to screen 614 consecutive clinical samples of multiple tumor types, the panel found 16 tumors that unexpectedly expressed $\geq$2 NE markers. Upon pathology review, 5 of these were confirmed as NET, thus revealing new treatment options for 5 patients.

Conclusions: A mass spectrometry-based screening tool can identify NET with sensitivity and specificity similar to that of immunohistochemistry. Such proteomic testing can identify NE proteins simultaneously with dozens of therapeutically relevant biomarkers (eg, HER2, EGFR) to inform treatment decision making without the need for additional FFPE sections.

Legal entity responsible for the study: NantOmics.

Funding: NantOmics.

Disclosure: S. Thyparambil, E. An, S. Sellappan, E.R. Wertheimer, F. Cecchi, R. Heaton, T. Hembrough: Employee: NantOmics. All other authors have declared no conflicts of interest.

1331P Tumour growth rate (TGR) when using lanreotide Autogel® (LAN) before, during and after peptide receptor radionuclide therapy (PRRT) in advanced neuroendocrine tumours (NETs)

V. Prasad[1], R. Srirajaskanthan[2], C.M. Grana[3], S. Baldari[4], T. Shah[5], A. Lamarca[6], F. Courbon[7], K. Scheidhauer[8], E. Baudin[9], X-M. Truong-Thanh[10], A. Houchard[11], L. Bodei[12]

[1]Department of Nuclear Medicine, Universitaetsfrauenklinik Ulm, Ulm, Germany, [2]Gastroenterology and Neuroendocrine Tumours, Kings College Hospital, London, UK, [3]Nuclear Medicine, European Institute of Oncology, Milan, Italy, [4]Nuclear Medicine Unit, University of Messina, Messina, Italy, [5]Hepatocellular Carcinoma/Neuroendocrine Tumours, Queen Elizabeth Hospital Birmingham, Birmingham, UK, [6]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [7]Nuclear Medicine, Institut Claudius Regaud, Toulouse, France, [8]Klinikum r.d. Isar, Technical University Muenchen, Munich, Germany, [9]Institut de Cancérologie, Gustave Roussy, Villejuif, France, [10]Global Medical Affairs, Ipsen Pharma France, Boulogne-Billancourt, France, [11]Clinical Statistics, Ipsen Pharma France, Boulogne-Billancourt, France, [12]Nuclear Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Background: ^{177}Lu-DOTATATE is licensed for gastroenteropancreatic (GEP-)NETs. PRELUDE is an international retrospective study (NCT02788578) to describe LAN use with ^{177}Lu-PRRT (LAN–PRRT) in advanced NETs. Here we report effectiveness results, including a post hoc TGR analysis to complement RECIST-based progression measures.

Methods: Analysis of patients (pts) receiving LAN with ^{177}Lu-DOTATATE/DOTATOC followed by LAN only. Key inclusion criteria: metastatic/locally advanced, grade 1/2, somatostatin receptor-positive GEP-/lung NET, progressive disease (PD) within 12 mo and within 6 mo before LAN–PRRT start (assessed locally), $\geq$1 LAN injection 8 wks before LAN–PRRT start, continuous LAN use during LAN–PRRT, cumulative PRRT activity $\geq$500 mCi. Primary endpoint: progression-free survival (PFS) rate at end of last LAN–PRRT cycle (RECIST v1.1, central review). Key secondary endpoints: PFS rate at last available follow-up (RECIST v1.1 central review), best overall response (OR; RECIST v1.1 central review). Post hoc analysis: TGR (% variation of tumour volume/mo) calculated from sum of longest diameter of target lesions between two MRI/CT scans during: prebaseline/baseline (within 12 mo and within 6 mo before baseline), baseline/end of last LAN–PRRT cycle (within 6 mo before baseline and end of last LAN–PRRT cycle), and end of last LAN–PRRT cycle/last available follow-up visit.

Results: Enrolment terminated early (insufficient recruitment): 40 pts (GEP n = 39; lung n = 1) (full analysis set: GEP n = 23, lung n = 1). LAN exposure and effectiveness results in GEP-NETs are shown in the table. Waterfall plots of prebaseline/baseline TGR showed individual progressions and regressions, with a mean of 0 [–1.4; 1.5].

Table: 1331P

	Patients with GEP-NETs (n = 23)
Median (range) LAN exposure, mo Overall Prior to LAN–PRRT During LAN–PRRT During LAN only follow-up	37.0 (16.7–90.0) 10.5 (0.7–61.7) 14.2 (7.0–24.0) 12.6 (6.1–32.5)
PFS rate [95% CI] at end of last LAN–PRRT cycle	91.7% [53.9; 98.8]
PFS rate [95% CI] at last available follow-up (up to 12 mo post-treatment)	95.0% [69.5; 99.3]
Best OR [95% CI] RECIST v1.1	Partial response (PR): 34.8% [18.8; 55.1] Stable disease: 60.9% [40.8; 77.8] PD: 4.3% [0.8; 21.0]
Mean [95% CI] TGR: Prebaseline/baseline Baseline/end of last LAN–PRRT cycle End of last LAN–PRRT cycle/last available follow-up visit	0.0% [−1.4; 1.5] −1.6% [−2.7; −0.4] −0.2% [−1.3; 0.9]

Conclusions: Effectiveness data were encouraging in this small selected population. TGR suggested tumour regression during LAN–PRRT. Despite low baseline TGR, 35% pts had RECIST PR on central assessment.

Clinical trial identification: PRELUDE: NCT02788578.

Editorial acknowledgement: Writing and editorial/submission support provided by Tom Vizard, PhD, and Richard McDonald (Watermeadow Medical), funded by Ipsen.

Legal entity responsible for the study: Ipsen.

Funding: Ipsen.

Disclosure: V. Prasad: Honoraria: Bayer, Ipsen, ITG; Consultant: Bayer, Ipsen, ITG. C.M. Grana: Consultant: Norgine; Other: Ipsen, Novartis, Iason. T. Shah: Honoraria: Ipsen; Consultant: Ipsen. A. Lamarca: Speaker's bureaux: Ipsen. F. Courbon: Advisory board member: Norgine; Grant recipient: AAA, Bayer; Speaker's bureaux: AAA, Bayer, GEHC, Ipsen, Novartis; Other: Cyclopharma. K. Scheidhauer: Honoraria: Ipsen, Shire. Consultant: Eisa, Ipsen, Novartis, Shire. E. Baudin: Honoraria: Ipsen, Novartis, Pfizer; Consultant, Grant recipient: AAA, Ipsen, Novartis, Pfizer. X.-M. Truong-Thanh: Employee, Stock owner: Ipsen. A. Houchard: Grant recipient, Employee, Stock owner: Ipsen. L. Bodei: Honoraria, Consultant, Speaker's bureaux: AAA, Ipsen. All other authors have declared no conflicts of interest.

1332P Detection of mutations and copy number alterations in circulating DNA from pancreatic neuroendocrine tumor patients

G. Boons[1], K. Op de Beeck[1], T. Vandamme[1], M. Beyens[2], G. Roeyen[3], K. Janssens[2], K. Zwaenepoel[1], G. van Camp[2], M. Peeters[1]

[1]MIPRO, University of Antwerp/Antwerp University Hospital, Edegem, Belgium, [2]MEDGEN, University of Antwerp/Antwerp University Hospital, Edegem, Belgium, [3]Hepatobiliary, Transplantation and Endocrine Surgery, Antwerp University Hospital, Edegem, Belgium

Background: Chromogranin A, the most frequently used circulating biomarker for diagnosis and follow-up of pancreatic neuroendocrine tumor (PNET) patients, has several limitations. Research in other tumor types has indicated the biomarker potential of circulating tumor DNA (ctDNA). However, ctDNA remains unexplored in PNETs. In this study, we aimed to detect and profile ctDNA in plasma of PNET patients.

Methods: Tumor tissue, perioperative blood samples and clinicopathological data were prospectively collected from 10 PNET patients undergoing surgery for their primary tumor at the Antwerp University Hospital. An additional blood sample was collected from one case during follow-up, when patient had disease progression. Whole exome sequencing was performed on tumor and germline DNA to identify somatic variants and copy number alterations (CNAs). For every patient a somatic single nucleotide variant (SNV) was selected and a digital droplet PCR assay was developed to detect this SNV in DNA isolated from plasma. Shallow whole genome sequencing (sWGS) was performed on plasma DNA to identify CNAs.

Results: In two patients, the somatic SNV could be detected in the perioperative plasma sample at variant allele fractions (VAFs) of 19% and 21%. Interestingly, both patients had metastatic disease and succumbed within two years after surgery, while the other eight patients presented with localized disease and are currently disease-free. The follow-up plasma sample of one of the positive cases showed an increase in VAF to 57%. Next, sWGS was performed on ctDNA-positive plasma to detect CNAs. A significant correlation ($p < 0.01$) was found between CNAs in primary tumor and CNAs in perioperative plasma sample. The CNA profile of the follow-up sample showed increased genetic instability.

Conclusions: We provide evidence for the presence of ctDNA in patients with a metastatic PNET. Non-metastatic cases were ctDNA-negative. An increase in VAF and genetic instability were found in the follow-up sample of one of the metastatic cases, suggesting potential for ctDNA as follow-up marker. Furthermore, CNAs in primary tumor and plasma sample were significantly correlated, proposing ctDNA as an alternative for molecular profiling of tissue in metastatic patients.

Legal entity responsible for the study: Antwerp University Hospital.

Funding: Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society; Research Foundation – Flanders (FWO).

Disclosure: All authors have declared no conflicts of interest.

1333TiP CAPTEM or FOLFIRI as second-line therapy in neuroendocrine carcinomas and exploratory analysis of predictive role of PET imaging and biological markers (SENECA study)

A. Bongiovanni[1], S. Pusceddu[2], S. Leo[3], G. Di meglio[4], F. Gelsomino[5], F. Pucci[6], R. Berardi[7], S. Ricci[8], I. Lolli[9], F. Bergamo[10], D. Campana[11], D. Santini[12], S. Tamberi[13], D. Pastorelli[14], M. Cives[15], N. Silvestris[16], A. Russo[17], A. Buonadonna[18], F. Foca[19], T. Ibrahim[20]

[1]Osteoncology and Rare Tumors Center, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori I.R.S.T. IRCCS, Meldola, Forlì-Cesena, Italy, [2]Department of Medical Oncology, Fondazione IRCCS Istituto Naz, Milan, Italy, [3]Medical Oncology, Ospedale Vito Fazzi, Lecce, Italy, [4]Medical Oncology, Hospital of Bolzano, Bolzano, Italy, [5]Medical Oncology, University Hospital of Modena, Modena, Italy, [6]Medical Oncology, Department of Medicine and Surgery, University Hospital of Parma, Parma, Italy, [7]Clinical Oncology, Dept. of Internal Medicine, AOU Ospedali Riuniti Ancona Università Politecnica delle Marche, Ancona, Italy, [8]Medical Oncology 1 Unit, Azienda Ospedaliero-Universitaria S.Chiara, Pisa, Italy, [9]Medical Oncology Unit, IRCCS Saverio de Bellis, Castellana Grotte, Italy, [10]Medical Oncology Unit 1, Department of Clinical and Experimental Oncology, Veneto Institute of Oncology IOV - IRCCS, Padula, Italy, [11]Medical Oncology, Policlinico Sant'Orsola-Malpighi, Bologna, Italy, [12]Oncology, Campus Bio-Medico di Roma, Rome, Italy, [13]Oncology, Ospedale degli Infermi, Faenza, Ravenna, Italy, [14]Oncology Unit, Ospedale Civile, Feltre, Italy, [15]GI Oncology, University of Bari, Bari, Italy, [16]Oncology, Ospedale Oncologico "Giovanni Paolo II"- IRCCS, Bari, Italy, [17]Oncology Unit, AOU Policlinico "Paolo Giaccone", Palermo, Italy, [18]Oncology, CRO di Aviano, Aviano, Italy, [19]Biostatistic Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori I.R.S.T. IRCCS, Meldola, Italy, [20]Osteoncology and Rare Tumors Center, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

Background: Patients with metastatic or locally advanced, non-resectable, grade 3 neuroendocrine carcinoma (NEC) of the lung or gastroenteropancreatic system (GEP NEC) are usually treated with first-line platinum-based chemotherapy. There is no standard second-line treatment when progression occurs. Different second-line chemotherapy combinations have been evaluated retrospectively, but with poor results. FOLFIRI was evaluated in a retrospective monocentric study, showing a disease control rate (DCR) of 62%. In another retrospective study, temozolomide-based chemotherapy obtained a DCR of 71%. There is growing evidence that the current grading system for NECs has a number of inconsistencies, highlighting the need for more accurate biomarkers to better understand the natural history of this very aggressive disease.

Trial design: SENECA study is a randomized, non-comparative, multicenter phase II trial designed to evaluate the efficacy and safety of FOLFIRI or capecitabine plus temozolomide (CAPTEM) after failure of first-line treatment in lung and GEP NECs. Primary aim is to assess DCR of the regimens, with safety as a co-primary. Secondary aims are the evaluation of overall survival (OS), progression-free survival (PFS) and quality of life. It is also planned to assess Gallium-PET/CT and tissue and circulating biomarkers as prognostic and predictive factors. Eligibility criteria are age $\geq$18 years, metastatic or locally advanced, non-resectable, lung or GEP NEC, and documented evidence of progressive disease during or after first-line platinum-based chemotherapy (cisplatin/carboplatin and etoposide; FOLFOX4 or CAPOX). Each patient is randomized to receive FOLFIRI or CAPTEM, considering Ki-67 (21-55 % vs > 55%) and primary tumor site (lung vs. GEP) as stratification factors. The randomized study design allows for two active treatments to be evaluated in a comparable patient population. Analysis will be performed for each regimen separately. 56 patients will be enrolled in each arm of the study (total of 112 patients). Sixteen centers are taking part in the study and recruitment is ongoing. The first patient was randomized on March 6, 2017.

Clinical trial identification: IRST100.22

Legal entity responsible for the study: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), IRCCS, Meldola, FC, Italy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1334TiP A phase I study of oncolytic immunotherapy of metastatic neuroendocrine tumours using intralesional rose bengal disodium

T.J. Price[1], G. Cehic[2], I. Kirkwood[3], G. Maddern[4], E.A. Wachter[5], D. Sarson[6], R. Sebben[7], L. Leopardi[4], J. Reid[4], S.J. Neuhaus[8]

[1]Medical Oncology, The Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia, [2]Nuclear Medicine, The Queen Elizabeth Hospital, Woodville, Australia, [3]Nuclear Medicine, Royal Adelaide Hospital, Adelaide, Australia, [4]Surgery, The Queen Elizabeth Hospital, Woodville, SA, Australia, [5]Development, Provectus Pharmaceuticals, Knoxville, TN, USA, [6]Development, Provectus Biopharmaceuticals, Sydney, Australia, [7]Radiology, The Queen Elizabeth Hospital, Woodville, Australia, [8]Surgical Oncology, University of Adelaide, Woodville, Australia

Background: Neuroendocrine tumours (NET) associated with the gastrointestinal tract are frequently indolent but problematic as a result of potential endocrine secretory properties and metastasis often to the liver. Metastases (mNET) located in the midgut and liver often secrete vasoactive products, giving rise to the "carcinoid Syndrome,"; flushing, diarrhoea, wheezing, abdominal cramps and peripheral oedema. Treatment options for mNET include surgical resection, chemoablation, and use somatostatin analogues (e.g. octreotide, lantreotide) or radio-labelled analogues (e.g. Lutate/Lutathera, ^{177}Lu DOTA-octreotate). However there is a need for additional options for mNET patients. There has been a paradigm shift in anti-cancer therapy over the last decade with the introduction of immunotherapy treatments. Intralesional rose bengal disodium (PV-10) is undergoing clinical development as an oncolytic immunotherapy and is the subject of this phase 1 study examining potential use of PV-10 for treatment of symptomatic mNET of the liver (NCT02693067).

Trial design: This phase 1 study is evaluating the safety, tolerability and reduction of biochemical markers and symptoms resulting from image guided percutaneous administration of PV-10 in up to 12 participants with mNET of the liver not amenable to resection or other potentially curative therapy. The Target Lesion(s) as defined by the interventional radiologist must be a uni-dimensionally measurable lesion with longest diameter between 1.0cm and 3.9cm as measured. The primary endpoint is safety. Secondary endpoints include objective response rate (ORR), target lesion SSTR and biochemical response. ORR is assessed by contrast enhanced CT and ^{68}Ga-DOTATATE PET standardised uptake value (SUV) allows SSTR expression to be used as a surrogate for tumour viability. In addition to characterizing direct effect of PV-10 in injected lesions, response of uninjected bystander lesions is evaluated by CT and PET to characterize potential systemic benefit. Integration of patient-reported outcome (QLQ-GI.NET21), serum biomarker (CgA) and objective response (PET) data will allow testing of concordance between independent indicators of clinical benefit.

Clinical trial identification: NCT02693067.

Legal entity responsible for the study: Provectus Biopharmaceuticals.

Funding: Provectus Biopharmaceuticals.

Disclosure: E.A. Wachter, D. Sarson: Employment: Provectus Biopharmaceuticals. All other authors have declared no conflicts of interest.

1335TiP COMPETE trial: Peptide receptor radionuclide therapy (PRRT) with 177Lu-edotreotide vs. everolimus in progressive GEP-NET

M.E. Pavel[1], A. Rinke[2], R.P. Baum[3]

[1]Gastroenterology and Hepatology, Endocrinology & Metabolic Diseases, Universitätsklinik Erlangen, Erlangen, Germany, [2]Klinik für Gastroenterologie und Endokrinologie, University Hospital of Marburg Klinik für Innere Medizin, Marburg, Germany, [3]Theranostics Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik Bad Berka GmbH, Bad Berka, Germany

Background: There are only limited treatment options for metastasized gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Current standard therapies include somatostatin analogs and targeted drugs such as everolimus and sunitinib. While these treatments rarely induce objective tumor remission, disease stabilization may be achieved for limited periods of time. Median PFS with everolimus in prospective phase III trials is 11 months. A subset of patients may have a benefit of systemic chemotherapy. PRRT has recently emerged as a promising option providing more durable response and potentially higher objective response rates. This therapy uses IV-infused radiolabeled somatostatin analogues to deliver radioactivity directly to metastases, destroying tumor cells but sparing most of the surrounding tissue. A first retrospective study on ^{177}LuEdotreotide PRRT in metastasized GEP-NET reported a median PFS of 34.5 months in patients who received $\geq$2 treatment cycles.

Trial design: COMPETE is a prospective, randomised, controlled, open-label, multicentre phase III study to evaluate the efficacy and safety of ^{177}Lu-Edotreotide PRRT in comparison with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR^{+}) GEP-NET. The study is ongoing in 11 countries & 40 centres worldwide, and currently recruiting patients. 300 patients will be randomized with progressive GEP-NET: 200 will receive max. 4 cycles of ^{177}Lu-Edotreotide PRRT (7.5 GBq/cycle) every 3 months or until diagnosis of progression; 100 will receive 10 mg everolimus daily for 24 months, or until diagnosis of progression. Study duration per patient will be 24 months. The primary endpoint is PFS. Diagnosis of progression and hepatic tumor burden will be established based on radiological information from morphological imaging (MRI and/or CT) according to RECIST 1.1. Key secondary endpoints are objective response rate (ORR), defined as % of patients achieving partial or complete response (PR/CR) as best outcome, and median duration of disease control (mDDC). Other secondary variables include safety and tolerability, dosimetry measures, overall survival, and quality of life.

Clinical trial identification: NCT03049189.

Legal entity responsible for the study: ITM Solucin GmbH.

Funding: ITM Solucin GmbH.

Disclosure: All authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii479–viii482, 2018
doi:10.1093/annonc/mdy294

NEW DIAGNOSTIC TOOLS

1336O Unbiased genomewide screening of circulating plasma DNA for cancer detection

L. Lenaerts[1], N. Brison[2], M. Neofytou[2], H. Che[2], L. Dehaspe[3], M. Verheecke[1], C. Maggen[4], B. Dewaele[2], S. Vanderschueren[5], V. Vandecaveye[6], P. Vandenberghe[7], J. Vermeesch[2], F. Amant[8]

[1]Department of Oncology, KU Leuven, Leuven, Belgium, [2]Department of Human Genetics, KU Leuven, Leuven, Belgium, [3]Department of Human Genetics, University Hospitals Leuven, Leuven, Belgium, [4]Department of Oncology, KU Leuven - University of Leuven, Leuven, Belgium, [5]Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium, [6]Department of Imaging & Pathology, KU Leuven, Leuven, Belgium, [7]Haematology, University Hospitals Leuven, Leuven, Belgium, [8]Gynaecology Unit, University Hospitals Leuven, Leuven, Belgium

1337P Predictive models for CEUS of the breast: Is it feasible in improved performance of BI-RADS evaluation of critical breast lesions?

L. Jun[1], Q. Chen[1], L. Tang[2], L. Yang[3], E. Han[4], Y. Chen[5], L. Yuan[6]

[1]Ultrasound Department, Sichuan Provincial People's Hospital, Chengdu, China, [2]Ultrasound Department, Fujian Provincial Cancer Hospital, Fuzhou, China, [3]Ultrasound Department, Yunnan Tumor Hospital Third Affiliated Hospital of Kunming Medical University, Kunming, China, [4]Ultrasound Department, Huangshi Central Hospital, Huangshi, China, [5]Ultrasound Department, Chengdu First People's Hospital, Chengdu, China, [6]Ultrasound Department, Tangdu Hospital, Xian, China

Background: This prospective study is to determine whether predictive model for contrast-enhanced ultrasound (CEUS) of the breast can improve the precision of BI-RADS.

Methods: A total of 1060 breast lesions classified as BI-RADS 4 or 5 on ultrasound were evaluated. CEUS was performed before core needle biopsy or surgical resection and a revised BI-RADS classification was assigned based on 6 predictive models for CEUS of malignant and benign breast lesions as follows: malignant predictive models : (1) hyper-enhancement with enlarged size; (2) hyper-enhancement with perfusion defect; (3) hyper- or iso-enhancement, present penetrating vessels or crab claw-like pattern. Benign predictive models: (4) rapid wash-in with hyper-enhancement, clear margin after enhancement without enlarged size; (5) synchronous or slow wash-in with iso-enhancement, and cannot distinguish margin and shape after enhancement; and (6) synchronous or slow wash-in with hypo-enhancement, with equal or smaller size after enhancement. To evaluate the diagnostic performance of CEUS-based BI-RADS assignment with pathological examination as reference criteria.

Results: The CEUS-based BI-RADS evaluation classified 287/1060 (27.08%) lesions into category 3, 195 (18.40%), 124 (11.7%) and 144 (13.58%) lesions into categories 4A, 4B and 4C, respectively, and 310 (29.24%) into category 5, compared with 423/1060(39.91%), 348(32.83%), 150(14.15%) and 139(13.11%) in BI-RADS 4A, 4B, 4C. and 5 based on conventional ultrasound and mammography. Selecting CEUS- based BI-RADS category 3 as an appropriate cut-off gave accuracy, sensitivity, specificity, positive and negative predictive values of 69.25%, 98.06%, 49.47%, 58.99% and 96.86%, respectively for the diagnosis of malignant disease. The cancer-to-biopsy yield was 60.16% with CEUS-based BI-RADS 3 selected as the biopsy threshold compared with 43.86% otherwise, while the biopsy rate was only 72.92% compared with 100% otherwise (Figure 2). Overall, only 1.94% of invasive cancers were misdiagnosed as BI-RADS 3 we use nowadays.

Conclusions: This study suggests that evaluation of BI-RADS 4 or 5 breast lesions with CEUS result in reduced biopsy rates and increased cancer-to-biopsy yields.

Clinical trial identification: 2016-14-1 release date: 9/9/2016.

Legal entity responsible for the study: Ultrasound Department of Sichuan Provincial People's Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1338P Tracking VSV-IFNβ-NIS oncolytic virus (OV) activity in patients (pts) with advanced solid tumors: The iodide symporter gene (NIS) as a pharmacodynamic (PD) marker using SPECT/CT imaging of OV therapy

J. Merchan[1], M.R. Patel[2], S.F. Powell[3], J. Strauss[4], T.P. Cripe[5], M.O. Old[6], R.M. Diaz[7], S.J. Russell[8], A.S. Bexon[9], L. Suksanpaisan[10], M.K. O'Connor[11], K.W. Peng[12]

[1]Oncology, Miami School of Medicine, Miami, FL, USA, [2]Hematology, Oncology and Transplantation, Minnesota Medical School, Minneapolis, MN, USA, [3]Hematology and Oncology, Sanford Health, Sioux Falls, SD, USA, [4]Oncology, Mary Crowley Medical Research Center, Dallas, TX, USA, [5]Hematology/Oncology/BMT, Nationwide Children's Hospital, Columbus, OH, USA, [6]Arthur James Cancer Hospital, The Ohio State University, Columbus, OH, USA, [7]Regulatory and Clinical Affairs, Vyriad, Rochester, MN, USA, [8]Vyriad, Rochester, NY, USA, [9]Vyriad, Rochester, NY, USA, [10]Diagnostics, Imanis Life Sciences, Rochester, NY, USA, [11]Nuclear Medicine, Mayo Clinic, Rochester, MN, USA, [12]CTO, Vyriad, Rochester, NY, USA

Background: VSV-IFNβ-NIS (Voyager V1; VV1) is a VSV-derived OV with low human seroprevalence. In addition to its tumor-selective and immune-stimulatory properties, VV1 encodes the human thyroidal sodium iodide symporter NIS to allow imaging of virus-infected tumors with IV ^{99m}Tc pertechnetate. Preclinical studies show increasing ^{99m}Tc uptake correlates with virus dose and allows spatial and temporal tracking of virus.

Methods: Single-photon emission computerized tomography (SPECT/CT) is used to assess virus replication and spread. In a phase 1 study, VV1 is given intratumorally into 1 target lesion on Day 1 (D1). SPECT/CT imaging is performed 45 minutes after 20 mCi IV ^{99m}Tc at baseline and D3. If there is uptake in injected tumor on D3, SPECT/CTs are also done D8 and D15. Imaging requirements include: gamma camera, low energy high resolution collimators with standard acquisition protocols and iterative image reconstruction. All images are read locally and centrally.

Results: SPECT/CT has been performed on 12 patients at 4 VV1 dose levels (DL). ^{99m}Tc uptake was not detected at the first 2 DLs but was seen in injected lesions of 2/4 pts at DL 3 (3e7 $TCID_{50}$) in pts with metastatic colorectal and pancreas cancer, and 1/2 to date at DL 4. PD analysis revealed SPECT/CT-positive pts had peak uptake in injected lesions between D3 and D8. Tumor biopsy samples are being analyzed to correlate SPECT/CT with viral RNA. Spread to uninjected lesions was not yet visualized, but viral RNA was recovered in cystic fluid from the lesion with the strongest signal in a pancreas cancer pt.

Conclusions: This novel therapeutic and diagnostic approach allows PD visualization of the investigational oncolytic virotherapy, VV1, replicating within the injected lesion. Positive images at dose levels 3-4 indicate we have reached a viral dose that allows sufficient viral replication for potential clinical activity. Further objectives include correlation of SPECT/CT positivity with clinical response, viremia, immune infiltrates, and genetic markers of susceptibility to OV therapy.

Clinical trial identification: NCT02923466.

Legal entity responsible for the study: Vyriad.

Funding: Vyriad.

Disclosure: R.M. Diaz: Paid consultant running the trial: Vyriad. S.J. Russell: CEO and own equity: Vyriad. A.S. Bexon: Paid consultant and CMO: Vyriad. K.W. Peng: CTO and own equity: Vyriad. All other authors have declared no conflicts of interest.

1339P mRNA expression of ER, PR, HER2 and Ki67 are concordant to central ihc and predict clinical outcome: A validation study from the ABCSG-6 biomarker cohort

M. Filipits[1], M. Rudas[1], C. Singer[2], Z. Bago-Horvath[3], R. Greil[4], M. Balic[5], S.F. Lax[6], N. Wu[7], S. Zhao[8], J. Weidler[9], M. Bates[9], D. Hlauschek[10], M. Gnant[11], P. Dubsky[11]

[1]Department of Medicine I, Comprehensive Cancer Center, Institute of Cancer Research, Medical University of Vienna, Vienna, Austria, [2]Department of Gynecology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, [3]Department of Pathology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, [4]3rd Medical Department, Salzburg Cancer Research Institute, Cancer Cluster Salzburg, Paracelsus Medical University Salzburg, Salzburg, Austria, [5]Department of Internal Medicine, Division of Oncology, Medical University Graz, Graz, Austria, [6]Department of Pathology, Medical University Graz, Graz, Austria, [7]Research and Development, Oncology, Cepheid, Sunnyvale, CA, USA, [8]Data Management and Analytics, Cepheid, Sunnyvale, CA, USA, [9]Medical and Scientific Affairs and Strategy, Oncology, Cepheid, Sunnyvale, CA, USA, [10]Clinical Statistics, Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria, [11]Department of Surgery, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

Background: Central immunohistochemistry (IHC) is the clinical gold standard for assessing ER, PR, HER2 and Ki67 in FFPE breast cancers, however limitations still exist concerning (pre) analytic validity. mRNA expression assays provide an alternative approach to measuring these biomarkers. Xpert® Breast Cancer STRAT4 is a CE-IVD, cartridge-based test performed on the GeneXpert platform which semi-automates sample preparation and RT-qPCR detection of ESR1, PGR, ERBB2 and MKi67 mRNA in FFPE tissues. Here we demonstrate the concordance of STRAT4 mRNA in comparison to central IHC in women treated within the phase III ABCSG-6 adjuvant endocrine therapy trial.

Methods: We evaluated ESR1, PGR, ERBB2 and MKi67 mRNA expression by STRAT4 and ER, PR, HER2 and Ki67 by IHC (FISH for HER2 IHC 2+) in 525 surgical FFPE specimens from ABCSG-6. All STRAT4 and IHC/FISH testing was performed by a central academic reference laboratory. Concordance (overall percent agreement) between STRAT4 and IHC for each marker was the predetermined primary objective. The effect of binary parameters (positive vs negative) obtained by IHC and by STRAT4 on distant recurrence free interval (DRFI) was analyzed by Cox models and described by hazard ratios (HR).

Results: In this study, concordance between STRAT4 and IHC was 98.6% for ER, 92.6% for PR, 98.4% for HER2, and 88.7% for Ki67 (excluding intermediate IHC 10-20% staining). In univariate Cox regression analyses, PR (HR 0.29, $P < 0.001$), HER2 (HR 2.62, $P = 0.005$), and Ki67 (HR 3.45, $P = 0.001$) tested by central IHC and PGR (HR 0.48,$P = 0.007$), ERBB2 (HR 2.29, $P = 0.037$) and MKi67 (HR 3.87, $P < 0.001$) tested by STRAT4 were all significantly associated with DRFI whereas neither ER by IHC, (HR 0.35, $P = 0.077$, nor ESR1 by STRAT4 (HR 0.73, $P = 0.597$), was associated with DRFI.

Conclusions: We demonstrate high concordance between centrally assessed IHC and mRNA measurements of the four main biomarkers routinely assessed in early breast cancer. This was corroborated by the similar prognostic values observed for protein versus mRNA assessments for each marker. Future investigations of the clinical utility of mRNA based measurements by STRAT4 in breast cancer cohorts are warranted.

Legal entity responsible for the study: ABCSG Austrian Breast and Colorectal Cancer Study Group.

Funding: Cepheid.

Disclosure: M. Filipits: Personal fees: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Ratiopharm, Roche outside the submitted work. M. Rudas: Funding: Cepheid/Danaher to ABCSG. R. Greil: Grants and personal fees: Roche, Celgene, Merck, AstraZeneca, Novartis, Amgen, Abbvie, BMS, MSD, Takeda; Honoraria, Consultant, advisory role, research funding, travel accomodations and expenses outside the submitted work: Sandoz. N. Wu, S. Zhao, J. Weidler, M. Bates: N. Employment and stock ownership: Cepheid (during the conduct of the study and outside the submitted work). D. Hlauschek: Employee: ABCSG which receives study funding from Cepheid. M. Gnant: Grants: AstraZeneca, Novartis, Pfizer and Roche; Personal fee: Accelsiors, Amgen, AstraZeneca, Celgene, Elli Lilly, Ipsen, NanoString Technologies, Novartis, Pfizer, Roche. P. Dubsky: Funding: Cepheid/Danaher to ABCSG. All other authors have declared no conflicts of interest.

1340P Clinical utility of complex multi-platform profiling in metastatic cancer patients

J. Garcia Foncillas[1], P.G. Aftimos[2], P. Barthelemy[3], J. Bellmunt[4], G. Berchem[5], C. Camps[6], R. de las Peñas[7], A. Finzel[8], J.P. Hervonen[9], T. Joensuu[9], A. Kong[10], J. Mackay[11], C. Mikropoulos[12], K. Mokbel[13], J-L. Mouysset[14], T-J. Perren[15], G. Guitti[16], J-F. Laes[8]

[1]Medical Oncology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [2]Oncology, Institute Jules Bordet, Brussels, Belgium, [3]Medical Oncology, C.H.U. Strasbourg-Nouvel Hopital Civil, Strasbourg, France, [4]Medical Oncology, Hospital del Mar, Barcelona, Spain, [5]Medical Oncology, Centre Hospitalier de Luxembourg, Luxembourg, [6]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain, [7]Medical Oncology, Consorcio Hospitalario Provincial de Castellón, Castellón, Spain, [8]Scientific, OncoDNA, Gosselies, Belgium, [9]Medical Oncology, International Comprehensive Cancer Centre Docrates, Helsinki, Finland, [10]Medical Oncology, The University of Birmingham Institute for Cancer Studies, Birmingham, UK, [11]Medical Oncology, University College London Cancer Institute, London, UK, [12]Medical Oncology, Kent Oncology Centre, Kent, UK, [13]Medical Oncology, The Princess Grace Hospital, London, UK, [14]Medical Oncology, Clinique Rambot-Provençale, Aix-en-Provence, France, [15]Medical Oncology, St. James's University Hospital Leeds, Leeds, UK, [16]OncoDNA, Gosselies, Belgium

Background: Precision medicine using multi-platform profiling of metastatic cancers is becoming increasingly used. However, its clinical utility in guiding patients' treatment remains unknown.

Methods: Here we assessed whether molecular profiling helps physicians in their treatment decision by analysing the molecular profile of 1657 advanced cancer patient samples who had failed at least one standard of care treatment using a combination of next generation sequencing (NGS), immunohistochemistry (IHC) and other specific tests. The results were interpreted, and personalized treatments for each patient were suggested. After a minimum of three months, using internet surveys, we investigated how our recommendations influenced treatment choice of the oncologist.

Results: Our data showed that NGS alone provided the oncologist with useful information in 10-50% of cases (depending on cancer type), whereas the addition of IHC/other tests extensively increased the usefulness of the information provided. For patients who were still alive after the provision of the molecular information (76.8%), 60.4% of their oncologists followed our recommendations. Most decisions (93.4%) were made based on the combination of NGS and IHC/other tests, and an approved drug -rather than clinical trial enrolment- was the main treatment choice. Most common reasons given by physicians to explain the non-adherence to recommendations were drug availability and cost, which remain barriers to precision medicine. Finally, we observed that 27% of patients treated with the suggested therapies had an overall survival >12 months.

Conclusions: Our study demonstrates that the combination of NGS and IHC/other tests provides the most useful information in aiding treatment decisions by oncologists in routine clinical practice. However, barriers to full implementation of this approach remain, and include drug availability, cost and low participation in clinical trials.

Legal entity responsible for the study: OncoDNA, S.A.

Funding: OncoDNA SA.

Disclosure: A. Finzel, G. Guitti, J-F. Laes: Employee: OncoDNA. All other authors have declared no conflicts of interest.

1341P Comparison of tissue-based and liquid biopsy genomic tests to guide lung cancer therapy: Asian experience

M-L. Nairismägi[1], K-C. Tung[2], Y-T. Yang[2], Y-J. Lu[2], R-S. Jhou[2], P-N. Yu[2], Y-T. Liu[2], Y-L. Hsieh[2], S.L. Poon[1], S-J. Chen[2], K.T. Tan[2]

[1]Medical Affairs, ACT Genomics (Singapore) Pte. Ltd., Singapore, [2]Medical Informatics, ACT Genomics Co., Ltd., Taipei, Taiwan

Background: Liquid biopsies are rapidly changing the diagnostics in oncology; however, their usability to guide treatment selection remains unknown. Here we explored the differences between liquid biopsy and tissue-based genomic tests in Asian lung cancer patients.

Methods: 226 formalin-fixed, paraffin-embedded (FFPE) and 274 plasma clinical samples were subjected to next-generation sequencing using the Ion Torrent Proton System with mean sequencing depth $\geq 700\times$ and $7{,}000\times$, respectively. FFPE samples were profiled using a 35-gene and circulating tumor DNA samples a 11-gene hotspot panel for base substitutions (single nucleotide variants/small indels) and copy number variants (CNV; for FFPE only).

Results: Actionable variants were identified in 47% (129/274) of liquid biopsies. Actionability was higher in tissue-based tests – 76% (172/226) – with 64% (111/172) derived from base substitutions, 9% (15/172) from CNVs and 27% (46/172) from both. EGFR mutations, indicating the use of tyrosine kinase inhibitors (TKI), were detected in 38% (105/274) and 49% (110/226) of liquid biopsy and tissue-based tests, respectively. Identification of TKI resistance mechanisms via EGFR T790M/C797S or the downstream KRAS, BRAF, PIK3CA, ERBB2 and MET mutations was also higher for tissue testing – alterations were discovered in 38% (86/226) and 27% (75/274) of samples, affecting a total of 35% (78/226) and 24% (65/274) patients, respectively, for tissue and liquid biopsy tests. Tissue testing detected additional CNV-originating TKI

resistance mechanisms (EGFR, MET and HER2 amplifications) in 24% (53/226) samples affecting an additional 13% (30/226) patients on top of those harboring mutation-based resistance mechanisms. RAF and MEK inhibitor indications were identified in 12% (28/226) and 3% (8/274), and mTOR blockade indications in 8% (19/226) and 7% (19/274) of tissue and liquid biopsy tests, respectively.

Conclusions: Although liquid biopsy tests are able to identity a large proportion of lung cancer patients with indications for targeted therapy, tissue-based testing outperforms liquid biopsies for most therapeutic indications. Inclusion of CNV analysis could potentially increase the detection rate in liquid biopsies.

Legal entity responsible for the study: ACT Genomics Co., Ltd.

Funding: ACT Genomics Co., Ltd.

Disclosure: M-L. Nairismägi, K-C. Tung, Y-T. Yang, Y-J. Lu, R-S. Jhou, P-N. Yu, Y-T. Liu, Y-L. Hsieh, S.L. Poon, K.T. Tan: Employee: ACT Genomics. S-J. Chen: Employee and shareholder: ACT Genomics.

1342P 68Ga-PSMA-PET/CT imaging for locally advanced, recurrent and metastatic adenoid cystic carcinoma and salivary duct carcinoma

W. van Boxtel[1], S. Lütje[2], I. van Engen- van Grunsven[3], G. Verhaegh[4], J. Schalken[4], M. Janssen[2], J. Nagarajah[2], M. Gotthardt[2], C.M.L. van Herpen[1]

[1]Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands, [2]Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, Netherlands, [3]Pathology, Radboud University Medical Center, Nijmegen, Netherlands, [4]Urology, Radboud University Medical Center, Nijmegen, Netherlands

Background: Salivary gland cancer (SGC) is a rare cancer with few treatment options. Adenoid cystic carcinoma (ACC) and salivary duct carcinoma (SDC) are major subtypes of SGC which often show immunohistochemical expression of prostate-specific membrane antigen (PSMA). In prostate cancer, PSMA ligands labeled with radioisotopes such as ^{68}Ga or ^{177}Lu, are used for imaging or therapy. The aim of this study was to evaluate ^{68}Ga-PSMA ligand uptake in patients with locally recurrent and/or metastatic ACC and SDC and to establish the diagnostic value of ^{68}Ga-PSMA-PET/CT imaging compared to full-dose CT imaging.

Methods: ^{68}Ga-PSMA-HBED-CC PET/CT scans were performed in 14 ACC patients and 10 SDC patients including a full-dose CT scan of the neck, chest and abdomen. ^{68}Ga-PSMA ligand uptake was evaluated in local recurrences and metastatic lesions. Detected lesions were compared to CT results. Maximum standardized uptake values (SUV_{max}) were determined. The study protocol was approved by the local medical ethical committee and a written informed consent was obtained from all patients.

Results: Moderate to intense PSMA ligand uptake was observed in local recurrences and distant metastases in all ACC patients and 40% of SDC patients. In addition, PSMA-PET imaging detected additional bone metastases in 2 ACC patients and additional lymph node metastases in 1 ACC patient which were not detected on a full-dose CT scan. In 1 ACC patient a local recurrence of a vulvar ACC was suspected on CT but PSMA-PET imaging was negative, which turned out to be scar tissue, eventually.

Conclusions: PSMA-PET imaging showed moderate to intense ligand uptake in local recurrences and distant metastases of all ACC patients and 40% of SDC patients. Based on the high uptake, these patients may be promising candidates for ^{177}Lu-PSMA radioligand therapy in future. Moreover, PSMA-PET imaging has added diagnostic value compared to full-dose CT imaging.

Clinical trial identification: NCT03319641.

Legal entity responsible for the study: Radboud university medical center, Nijmegen, the Netherlands.

Funding: Adenoid Cystic Carcinoma Research Foundation (ACCRF) and the Dutch Salivary Gland Cancer Patient Platform.

Disclosure: All authors have declared no conflicts of interest.

1343P Histology and detectability on ring-type dedicated breast PET in breast cancer

Y. Kimura[1], S. Sasada[1], N. Goda[1], K. Kajitani[1], A. Emi[1], N. Masumoto[1], T. Kadoya[1], R. Haruta[1], T. Kataoka[1], M. Okada[2]

[1]Breast Surgery, Hiroshima University Hospital, Hiroshima, Japan, [2]Surgical Oncology, Hiroshima University, Hiroshima, Japan

Background: Although dedicated breast PET (DbPET) visualizes sub-centimeter breast cancer lesions and intratumoral heterogeneity, the impact of histology on the detectability of DbPET remains unknown.

Methods: This study included 455 patients with breast cancer, who underwent whole-body PET (WBPET) and ring-type DbPET between January 2016 and March 2018. The relationship of histology and sensitivities of WBPET and DbPET for breast cancer was assessed.

Results: The median patient age was 57 years and histology was as follows: 82 (18.0%) noninvasive carcinoma, 18 (4.0%) microinvasive carcinoma, 305 (67.0%) invasive carcinoma with no special type, 9 (2.0%) invasive lobular carcinoma, and 41 (9.0%) other types. The sensitivity of WBPET and DbPET was 74.5% and 93.2%, respectively. The sensitivities of each histology on WBPET/DbPET were 41.5%/78.0%, 72.2%/100%, 83.9%/96.7%, 44.4%/88.9%, and 78.0%/95.1%, respectively (Table). The sensitivity was low on WBPET in noninvasive, microinvasive, invasive lobular, mucinous and tubular carcinomas. Lobular carcinoma in situ had low sensitivity on both WBPET and DbPET imaging. In the multivariate analysis, undetectable tumor factors on WBPET were sub-centimeter tumor size (Odds ratio [OR] = 6.04, P < 0.001) and histology (OR = 1.69, P = 0.08); for DbPET, Ki-67 labeling index was an undetectable tumor factor (OR = 4.32, P = 0.039).

Table: 1343P Sensitivities of whole-body and dedicated breast PET according to histology

	N	Sensitivity (%)		P
		WbPET	DbPET	
Total	455	339 (74.5)	424 (93.2)	< 0.001
Noninvasive carcinoma	82	34 (41.5)	64 (78.0)	< 0.001
Ductal carcinoma in situ	72	32 (44.4)	61 (84.7)	< 0.001
Lobular carcinoma in situ	8	1 (12.5)	2 (25.0)	1
Others	2	1 (50.0)	1 (50.0)	1
Microinvasive carcinoma	18	13 (72.2)	18 (100)	0.046
Invasive carcinoma of no special type	305	256 (83.9)	295 (96.7)	< 0.001
Invasive lobular carcinoma	9	4 (44.4)	8 (88.9)	0.131
Others	41	32 (78.0)	39 (95.1)	0.048
Mucinous carcinoma	19	13 (68.4)	18 (94.7)	0.09
Tubular carcinoma	5	3 (60.0)	4 (80.0)	0.444
Carcinoma with apocrine differentiation	5	5 (100)	5 (100)	1
Invasive micropapillary carcinoma	5	5 (100)	5 (100)	1
Others	7	6 (85.7)	7 (100)	1

Conclusions: Breast cancers with the specific histological subtypes are hard to detect on WBPET. DbPET can overcome the factors for weak WBPET detectability, such as tumor size and histology, and might prevent the overdiagnosis of lobular carcinoma in situ.

Legal entity responsible for the study: Hiroshima University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1344P Thermal liquid biopsy as a new tool for lung cancer patients diagnostic: Pilot study

A. Rodrigo[1], O. Abian[2], A. Velazquez-Campoy[3], A. Callejo[4], S. Vega[5], A. Fernandez[6], O. Sánchez-Gracia[2], P. Iranzo Gomez[6], M. Cruellas[6], E. Quilez Bielsa[6], D. Isla[6]

[1]Medical Oncology, Hospital Arnau de Vilanova, Lleida, Spain, [2]Research, IACS-ISS Aragón, Zaragoza, Spain, [3]Research, ARAID Foundation, Zaragoza, Spain, [4]Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [5]Research, BIFI institute-University of Zaragoza, Zaragoza, Spain, [6]Medical Oncology, Hospital Clinico Universitario Lozano Blesa, Zaragoza, Spain

Background: Thermal Liquid Biopsy (TLB) is based on Differential Scanning Calorimetry (DSC, calorimetric thermogram analysis of serum samples) as a new clinical approach for diagnostic assessment of lung cancer patients. DSC is highly sensitive and it studies the unfolding transitions in proteins by thermal denaturation. The DSC profile of blood serum has been previously proposed as a novel approach for diagnosis and monitoring several diseases. Our main objective is to determine the TLB capacity to differentiate between Healthy Controls (HC) and Lung Cancer Patients (LCP).

Methods: Blood samples from HC and LCP were analyzed with a high sensitivity microcalorimeter VP-DSC (MicroCal-Malvern). The data were processed by Origin 7 software. Thermograms acquired were analyzed with a multiparametric method developed by our research group, procuring some indicators to interpret the results. The Area Under the Curve (AUC) was analyzed and the Youden's Index obtained from ROC curves, allowing to construct the contingency tables. Odds Ratio (OR) was also calculated by binary logistic regression.

Results: 117 samples from LCP (Average age 64.6±8.7, 83.0% men) stage distribution (II: 5.2%, III: 25.9%; IV: 69.0%), smoking status (63.8% smoking, 6.5% non-smoking) histology distribution (37.1% Adenocarcinoma, 28.4% Squamous, 30.2% small cell) compared to 123 HC from a blood bank with homogeneous distribution. 10 out of 28 parameters of our multiparametric method showed statistical differences between HC and LCP. After developing ROC curves, AUC higher than 0.75 were observed in these 10 parameters, exceeding 0.85 in 3 of them. The Youden's index was calculated for all, finding sensitivity and specificity values higher than 75.0-90.0% (for the best parameter

both were more than 85.0%). Comparing HC to LCP, we calculated OR obtaining 10 parameters over 10, showing a high positive association between clinical parameters and DSC results.

Conclusions: High positive association between clinical groups and TLB parameters offers advantages over current diagnosis techniques (CT imaging), providing a powerful diagnostic approach with a minimally-invasive, low-risk, low-cost clinical test for LCP. Future promising applications, such as screening programs, could be developed from TLB.

Legal entity responsible for the study: Instituto Investigación Sanitaria de Aragón (ISS).

Funding: Institute Carlos III (Spain).

Disclosure: All authors have declared no conflicts of interest.

1345P Data-mining of 110 172 electronic patient records with the ConSoRe tool: An analysis of second primary cancer in a comprehensive cancer center

P. Heudel[1], T. Durand[1], B. Fervers[1], F. Gomez[1], M. Rivoire[1], T. Bachelot[2], L. Claude[1], C. Chassagne-Clement[1], F. Pilleul[1], T. Mognetti[1], Y. Devaux[1], J-L. Soubirou[1], C. Lasset[1], D. Perol[1], G. Chvetzoff[1], C. Pezet[1], S. Beaupere[1], P. Zrounba[1], J-Y. Blay[2]

[1]Centre Léon Bérard, Lyon, France, [2]Medical oncology, Centre Léon Bérard, Lyon, France

Background: We report a data-mining analysis of 110,172 electronic patient records (EPR) of the Leon Berard Comprehensive Cancer Center (CLB) over a 10 years period to identify characteristics of second primary cancers (SPC).

Methods: ConSoRe is a new generation data analytics solution using natural language processing to search aggregated data and perform advanced data mining. It was used for data extraction from EPR of 110,172 patients (pts), 47,257 men (M) and 62,915 women (W), treated at the CLB from 2007 to 2017. Patient characteristics, treatment and survival were extracted.

Results: Data extraction identified 88,622 pts with at least one cancer. Among them 7,430 (8.4%) had a SPC: 9% (3,475/38,554) in M and 7.9% (3955/50068) in W ($p = 3\ 10^{-9}$). Of interest, only 4,296 SPC (57%) were already documented manually by the physicians in the dedicated forms. Mean age at diagnosis of first cancer (FC) is 55.1 years (y) in M and 51.8 y in W. Mean interval (MI) from diagnosis of FC to SPC is 5.3 years (4.4 in M, 6.1 in W; T test $p = 4\ 10^{-23}$). Proportions of SPC among specific localization FC are: For M, head & neck cancer (n = 484/5,277, MI: 3.4 y), lymphoma (n = 336/5,611, MI: 5.1 y), prostate cancer (n = 334/4,643, MI: 6.1 y);for W, breast cancer (n = 1,502/21,447, MI: 8.6 y), soft tissue sarcoma (n = 321/3,683, MI: 4.5 y), lymphoma (n = 293/4,432, MI: 6.3 y). Time to SPC differ significantly depending on FC (Anova: $p = 2\ 10^{-18}$).Pts with SPC were more likely to have received chemotherapy (31.1%) for their FC treatment compared to pts without SPC (20.8%; $p = 1.6\ 10^{-94}$). Also, pts with SPC treated by chemotherapy for their FC had shorter MI than pts who did not (3.2 y versus 5.6 y). In multivariate analysis, time from diagnosis of FC to SPC is significantly linked to FC site and shorter when FC was treated with chemotherapy. SPC was significantly correlated to a worth survival: 19% of death with FC at the time of analysis, versus 27.6% of those with SPC ($p = 9.7\ 10^{-57}$).

Conclusions: Screening over 100,000 EPR with ConSoRe enabled to retrieve SPC more exhaustively than the physician forms. ConSoRe will be validated in a broader series of 300,000 EPR and used to study SPC risk factors to enable prevention and early detection.

Legal entity responsible for the study: Leon Berard Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1346P Real world cfDNA collection in EGFR-mutant NSCLC

N. Marcoux[1], L.V. Sequist[1], A. Hata[1], M. Banwait[1], I. Dagogo-Jack[1], R. Nagy[2], R.B. Lanman[2], A. Muzikansky[3], S.R. Digumarthy[4], Z. Piotrowska[1]

[1]Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA, [2]Medical Affairs, Guardant Health, Redwood City, CA, USA, [3]Biostatistics, Massachusetts General Hospital, Boston, MA, USA, [4]Thoracic Radiology, Massachusetts General Hospital, Boston, MA, USA

Background: Plasma cell-free DNA (cfDNA) assays are increasingly used in clinic. Despite their rapid adoption, best practices for use and interpretation need better definition. We assessed key clinically-relevant questions using a prospectively collected cohort of EGFR-mutant pts.

Methods: Starting in 2015, serial cfDNA testing via Guardant360 NGS was obtained from MGH pts with advanced EGFR-mutant NSCLC across multiple lines of therapy in an IRB-approved project. Medical records were analyzed retrospectively, tissue was genotyped by institutional NGS (SNaPshot), scans were assessed by RECIST. Correlations were tested by Wilcoxon Rank-Sum.

Results: 372 plasma samples were collected from 89 pts, covering 150 therapy regimens including 26 drugs (targeted, immune, cytotoxic). To assess genotype correlation, we examined matched cfDNA and tissue biopsies at clinical progression for 60 regimens (51 pts). cfDNA-tissue concordance was 73% for founder EGFR mutations (n = 60), 72% for T790M (n = 60) and 89% for MET amp (n = 53). Excluding 15 samples without detectable founder mutation (presumed "non-shedders"), concordance for T790M=89% and MET=90%. To assess if relative change in cfDNA allelic fraction (AF) correlates with radiographic response, we examined 21 regimens (19 pts) with cfDNA samples at baseline and $\leq$ 30 days, and 3 aspects of the Guardant360 report. 12/21 regimens yielded PR by scans. Decrease in cfDNA AF in the 1st month of therapy correlated with ultimate PR whether assessing the change in AF of founder EGFR ($p = 0.03$), largest AF regardless of gene ($p = 0.02$) or sum of all detected AFs ($p = 0.02$).

Conclusions: CommercialcfDNA assays are readily available, facilitate serial AF monitoring and provide clinically-relevant data at acquired resistance. Among EGFR pts, we found real world cfDNA-tissue correlation of founder mutations and T790M was high and resistance mutation (T790M, MET) results in cfDNA may be most reliable when founder EGFR mutations are detected. Importantly, MET amp had high cfDNA-tissue concordance, which was unexpected. Early AF decrease (within 1st month of therapy) significantly correlates with radiographic response regardless of which aspect of the Guardant360 report is considered. Further investigation is needed to inform optimal use and interpretation of cfDNA assays.

Legal entity responsible for the study: MGH Cancer Center.

Funding: Guardant Healthcare, Lungevity.

Disclosure: N. Marcoux: Honoraria: Bristol-Myers Squibb. L.V. Sequist: Consulting fees: AstraZeneca, Pfizer, Genentech; Institutional research funding: AstraZeneca, Novartis, Merck, Boehringer Ingelheim, Genentech, Merrimack, Incyte. A. Hata: Research/grant support: Novartis, Amgen, Relay Therapeutics. I. Dagogo-Jack: Honoraria: Foundation Medicine; Consulting: Boehringer Ingelheim. R. Nagy, R.B. Lanman: Stock ownership and employee: Guardant Health, Inc. Z. Piotrowska: Consulting/honoraria: AstraZeneca, Ariad/Takeda, GuardantHealth, Novartis, AbbVie; Research support (to institution): Novartis. All other authors have declared no conflicts of interest.

1347TiP Proof-of-concept study evaluating a new tool for standardising radiological assessment of tumour response to treatment in routine clinical practice

C. Mastier[1], C. de la Fouchardière[2], J. Fayette[2], M. Sarabi[2], P. Heudel[2], A. Coulon[1], N. Banaste[1], E. Mercier-Bischoff[1], M. Barma[1], M. Brahmi[2], P. Cassier[2], S. Couchon Thaunat[1], L. Eberst[2], G. Fournier-Garin[3], P. Metral[3], F. Pilleul[1], J-Y. Blay[2]

[1]Department of Radiology, Centre Léon Bérard, Lyon, France, [2]Department of Medical Oncology, Centre Léon Bérard, Lyon, France, [3]Department of Clinical Research and Innovation, Centre Léon Bérard, Lyon, France

Background: Accurate and timely radiological assessment of solid tumour response to treatment is essential to optimise patient outcomes in oncology. Evaluation of tumour response according to Response Evaluation Criteria In Solid Tumors (RECIST) is constantly performed in clinical trials and more occasionally in routine clinical practice. Radiological reporting is not usually standardised. MIRIO (ON'COHUB), a newly developed tool, streamlines interactions between oncologists and radiologists to optimise and ease response evaluation according to RECIST in routine practice. It applies to reading computed tomography scans and magnetic resonance imaging, and allows switching between evaluation criteria (RECIST 1.1, iRECIST and modified RECIST). MIRIO also provides a standardised radiological report, improving communication between oncology and radiology teams to guide treatment decisions. An ongoing proof-of-concept study is evaluating the feasibility of using MIRIO to assess tumour response according to RECIST in routine clinical practice and identify the benefits it may provide to clinical oncology teams and patients.

Trial design: Oncologists specialised in sarcomas, breast, lung, colorectal and head and neck cancers, plus radiologists, will use MIRIO to assess tumours at baseline and tumour response according to RECIST for all new patients seen at Centre Léon Bérard, Lyon, France during the study period. Approximately 80 patients in clinical trials and 320 patients in routine clinical practice will be included. Study duration will be 6 months, with the first patients included in March 2018. All investigators will receive training on MIRIO before including patients in the study. A sample of 20 patient records will be peer-reviewed to determine if MIRIO can improve concordance of assessments made by the radiologist and the oncologist. Other outcome measures include assessments of the quality of data in radiology reports with MIRIO versus standard practice, user satisfaction, integration of the tool into routine practice and improvements in therapeutic follow-up for patients.

Editorial acknowledgement: Gail Rickard; Complete HealthVizion.

Legal entity responsible for the study: Deeplink Medical.

Funding: WeHealth by Servier.

Disclosure: C. Mastier, C. de la Fouchardière: Medical consulting: Deeplink Medical. All other authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii483–viii487, 2018
doi:10.1093/annonc/mdy290

NSCLC, EARLY STAGE

1348PD Genomic landscape and its correlation with TMB, CD8 TILs and PD-L1 expression in Chinese lung squamous cell carcinoma

C. Zhou, T. Jiang

Medical Oncology, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China

1349PD Gene expression signature of DNA damage response to predict the prognosis of early stage lung adenocarcinoma

Z. Wang[1], C. Xu[2], J. Zhao[3], X. Zhao[3], S. Cai[3], Y. Song[4], J. Wang[1]

[1]Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, [2]Department of Pathology, Fujian Cancer Hospital, Fuzhou, China, [3]The Medical Department, Shanghai 3D Medicines.Inc, Shanghai, China, [4]Department of Respiratory Medicine, Jinling Hospital, Nanjing, China

1351P Impact of the 8th edition AJCC classification in early stage lung cancer

A.S. Cortegoso Mosquera[1], M. Vieito Villar[2], C. Rodriguez Lopez[1], V. Varela Pose[1], V. Cebey Lopez[1], J. Alvarez Fernandez[1], M. Perez Martelo[1], S. Aguin Losada[1], U. Anido Herranz[1], L. Leon Mateos[1], F.J. Baron Duarte[3], J.J. Garcia Gonzalez[1]

[1]Medical Oncology, Complejo Hospitalario Universitario de Santiago de Compostela SERGAS, Santiago de Compostela, Spain, [2]Oncology, Vall dHebron Institute of Oncology (VHIO), Barcelona, Spain, [3]Medical Oncology, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

Background: Lung cancer is the main cause of cancer death worldwide. Even in early stages the cancer-specific survival is poor due to disease relapse. The TNM classification is the strongest prognostic tool. The 8th AJCC edition has changed the cutpoints for stage, leading to a "stage shift" or a "stage decrease", mainly reflecting changes in the prognostic score attributed to the tumor diameter. We have reviewed a cohort of patients that were treated before the benefit of adjuvant chemotherapy was proved, in order to corroborate which of the two classifications represents better the risk of recurrence.

Methods: Retrospective analysis of a cohort of 182 patients with lung cancer treated with complete resection and no adyuvant chemotherapy, between 1999 and 2006. Evaluation criteria: overall survival.

Results: 1. Patient characteristics: median diagnostic age 68 years (39-86), 90% males, 48% current and 42% former smokers, 37% diagnosed of COPD. 2. Tumor characteristics:

- Histology: squamous 57%, adenocarcinoma 36%.

- Grade: 47% moderately differentiated, 33% undifferentiated. - Pathological staging by TNM edition.

Table: 1351P

7th edition n (%)		8th edition n (%)	
IA	44 (24)	IA1	5 (2.7)
		IA2	23 (12.6)
		IA3	26 (14.3)
IB	69 (38)	IB	30 (16)
IIA	20 (11)	IIA	27 (15)
IIB	49 (26)	IIB	46 (25)
IIIA	0	IIIA	25 (14)

3. median OS in our cohort of patients = 79 months (IC95% = 58-100) log Rank test p=NS me OS by pathological stage defined by 8th ed. AJCC: IA1 97 m (IC95% 37-158) IA2 108 m (IC95% 54-162) IA3 139 m (IC95% 13-266) IB 71 m (IC95% 45-96) IIA 35 m (IC95% 19-51) IIB 62 m (IC95% 34-90) IIIA 56 m (IC95% 0-141) 4. OS stage I vs II - by 7th edition: 93 vs 66 m, log Rank test, p = 0.016 - by 8th edition: 97 vs 70 m, log Rank test, p = 0.026 5. COPD as an adverse prognostic factor: meOS = 111 vs 55 months, log Rank test, p = 0.002

Conclusions: In our cohort of patients, the 8th edition of AJCC classification identifies better than the previous edition a group of patients with worse prognosis regarding to a higher size of the tumour and shiftening their pathological stage. Due to the small sample, we couldn't prove a more accurate prognostic information for the new stage I

categories in the 8th edition. COPD is confirmed in our serie as an adverse prognostic clinical factor.

Legal entity responsible for the study: IDIS.

Funding: IDIS.

Disclosure: All authors have declared no conflicts of interest.

1352P A serum miRNA biomarker panel for the detection of early stage non-small cell lung cancer

L. Ying[1], R. Zou[2], L. Du[3], L. Shi[4], N. Zhang[1], J. Jin[1], J. Wu[1], F. Zhang[1], K. Chen[1], M. Huang[1], Y. Zhang[5], A. Lin[6], H. Yu[7], L. Zhou[2], W. Mao[8], D. Su[9]

[1]Zhejiang Cancer Hospital, Zhejiang Cancer Research Institution, Hangzhou, China, [2]MIRXES (hangzhou) Biotechnology Co, MIRXES (hangzhou) Biotechnology Co, Hangzhou, China, [3]Zhejiang Cancer Hospital, Zhejiang Cancer Center, Hangzhou, China, [4]Zhejiang Cancer Hospital, Radiology Department, Hangzhou, China, [5]Zhejiang Cancer Hospital, Department of Clinical Laboratory, Hangzhou, China, [6]Taizhou Hospital of Zhejiang Province, Human Tissue Bank/Medical Research Center, Taizhou, China, [7]University of Hawaii Cancer Center, University of Hawaii Cancer Center, Hawaii, USA, [8]Zhejiang Cancer Hospital, Department of Thoracic Surgery, Hangzhou, China, [9]Zhejiang Cancer Hospital, Department of Pathology, Hangzhou, China

Background: Non-small cell lung cancer is the most prevalent cancer and leading cause of cancer death worldwide. Low-dose spiral computed tomography (LDCT) scan is being recommended as a screening test for smokers in the US. However, the poor specificity of LDCT has raised significant concerns about its high chance of false positive results. This study aimed to develop a blood miRNA based molecular diagnostic test for the detection of early stage lung cancer.

Methods: The three-phase study was designed with a total of 948 cancer-free controls, and 768 patients with NSCLC. In the discovery phase, more than 400 miRNAs were profiled with MiRXES's qPCR based high throughput assay platform through a highly defined Chinese male smoker case-control cohort (n = 424) where the cases were collected from Zhejiang Cancer Hospital and the controls were collected form the LDCT screening program in Zhejiang province, China. Differentially expressed miRNAs were further validated in another Chinese case-control cohort (n = 432) collected from similar sources and a white case-control cohort (n = 218) collected from the EU and US. Finally, the identified miRNAs were further assessed in three additional Asian cohorts: a Chinese cohort collected from the similar sources (n = 237), a Chinese cohort collected from independent sources (n = 340), and a Singaporean cohort (Chinese, Malay and Indian population) (n = 65).

Results: 29 miRNA biomarkers with p-value (FDR) <0.01 and more than one z-score (standardized score) difference were identified in the discovery phase. With multiple time of two-fold cross-validation, 5 miRNAs were found to be minimally required to form the biomarker panel for the accurate prediction of early stage lung cancer and the panel gives 0.936 (95% CI, 0.912-0.957) AUC for the Chinese validation cohort and 0.970 (95% CI, 0.939-0.986) AUC for the white validation cohort. The 5-miRNA biomarker panel were then further validated in three additional Asian cohorts, giving 0.973 (95% CI 0.950-0.986) AUC for similarly sourced Chinese cohort, 0.916 (95% CI, 0.852-0.949) AUC for the independently sourced Chinese cohort, and 0.911 (95% CI, 0.822-0.963) AUC for the Singaporean cohort, respectively.

Conclusions: The five-miRNA panel in serum may serve as a potential non-invasive biomarker in detecting early stage NSCLC.

Legal entity responsible for the study: Zhejiang Cancer Hospital & Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology of Zhejiang Province.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1353P Split-lobe resections versus lobectomy for stage IA-IB peripheral non-small cell lung cancer

A. Levitckii[1], D. Chichevatov[2], M. Ter-Ovanesov[1], E. Sinev[2]

[1]Thoracic Oncology, City Clinical Hospital, Moscow, Russian Federation, [2]Thoracic Oncology, Regional Cancer Center, Penza, Russian Federation

Background: To compare left-upper, right and left inferior split-lobe procedures with the same lobectomies for surgical treatment of peripheral non-small cell lung cancer of stage IA-IB, originating from the large pulmonary lobes.

Methods: We analyzed the results of the treatment of 116 patients, who underwent surgical procedures for clinical stage IA-IB non-small cell lung cancer. Patients were divided into two groups, based on the type of procedure performed. Lobectomies were performed in 78 (67,2%) patients, split-lobe resections of the large pulmonary lobes in 38 (32,8%): upper left trisegmentectomy (S1,2,3) in 14 patients, resection of the lingula (S4,5) in 7, anatomical segmentectomy S6 in 15, resection of basal segments in 2 patients. Radical mediastinal lymph node dissection was performed in all cases. The primary end-points of the analysis were relapse-free survival (RFS), overall survival (OS) and rate of recurrence (RR).

Results: There were no significant differences in morbidity between lobectomy and split-lobe resection groups (7,7% vs. 5,3%; p=NS). RR was registered in 9 patients in the lobectomy group vs 7 patients from split-lobe group (11,5% vs. 18,4%; p=NS). Regional recurrence in hilar lymph nodes was confirmed only in one patient from split-lobe group 28 months after right anatomical segmentectomy S6. Survival analysis did not show significant differences between lobectomy and split-lobe groups. Overall 5-year survival was 82,0% (95% confidence interval, 70,3-93,7%) in lobectomy group versus 74,8% (95% confidence interval, 57,5-97,1%) in split-lobe group (p = 0,369). Relapse-free 5-year survival was 85,2% (95% confidence interval, 76,8-94,6%) in lobectomy group versus 76,2% (95% confidence interval, 59,6-92,8%) in split-lobe group (p = 0,353). Cox regression analysis with multiple factors demonstrated statistical significance for overall (p = 0,03) and relapse-free (p = 0,025) survival only for pT1-T2 tumour descriptors.

Conclusions: Split-lobe procedures and lobectomy have equivalent in-hospital morbidity and long-term results for patients with clinical stage IA-IB peripheral non-small cell LC. In the future split-lobe resection can be recommended as a standard procedure for early stage peripheral non-small cell LC.

Legal entity responsible for the study: City Clinical Hospital no. 40.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1354P Patient reported outcomes after the treatment of early stage non-small cell lung cancer by stereotactic body radiotherapy compared to surgery

L. Alberts[1], H.B. Wolff[2], E.A. Kastelijn[1], F.J. Lagerwaard[3], S. Senan[3], S.Y. El Sharouni[4], F.M.N.H. Schramel[1], V.M.H. Coupe[2]

[1]Pulmonology, St. Antonius Ziekenhuis, Nieuwegein, Netherlands, [2]Epidemiology and Biostatistics, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [3]Radiation Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [4]Radiotherapy, University Medical Center Utrecht, Utrecht, Netherlands

Background: As survival seems to be equal after either stereotactic body radiotherapy (SBRT) or surgery for patients with stage I non-small cell lung cancer (NSCLC), treatment impact on the quality of life (QoL) after is essential for well-informed decision making. After a surgical resection, deterioration of QoL is often observed in the early post-treatment period, whereas QoL is reported to be maintained after SBRT. The aim of this study is to compare QoL in the first year after SBRT and surgery.

Methods: QoL was assessed by using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the lung cancer-specific supplementary questionnaire (QLQ-LC13) at baseline and 3, 6 and 12 months after treatment. Two prospectively collected databases of patients with clinically proven stage I NSCLC, from two large hospitals in the Netherlands, were pooled (n = 306; 256 patients were treated with SBRT and 41 patients with surgery). This observational study design is susceptible to selection bias. To correct for confounding, propensity-scores were calculated using forward stepwise logistic regression, to be selected for surgical treatment. For the final model, age, dichotomized ECOG score and FEV1% predicted scores were selected.

Results: The 41 surgical patients were matched to 41 SBRT patients on propensity score with a 1:1 ratio. At baseline, patients in the surgery group report a lower health related-QoL compared to patients in the SBRT group. However, during the first year after treatment, no clinical meaningful differences in social-, role, physical, emotional and cognitive domains were observed between patients treated using either modality. Furthermore, no clinical meaningful differences in QLQ-LC13 scores (dyspnea, pain, fatigue) after treatment were observed.

Conclusions: This study comparing a matched cohort, revealed no clinical significant differences in QoL following either SBRT or surgery for an early stage NSCLC.

Legal entity responsible for the study: Leonie Alberts and Harold Wolff.

Funding: Has not received any funding.

Disclosure: H.B. Wolff, V.M.H. Coupe: Research funding: Novartis. Novartis Pharma B.V. was not involved in the data collection, data analysis, or reporting. F.J. Lagerwaard: Honoraria, Speaker's bureau: Viewray inc USA. S. Senan: Honoraria, Consulting/advisory role company: Lilly Oncology, AstraZeneca; Research funding: Varian Medical systems. All other authors have declared no conflicts of interest.

1355P miR-200s in operated NSCLC: Main drivers of epithelial to mesenchymal transition and independent prognostic factors

A. Legras

Thoracic Surgery, Assistance Publique - Hopitaux De Paris, Paris, France

Background: Epithelial-to-mesenchymal transition (EMT) plays essential roles in non-small cell lung cancer (NSCLC) progression and was related to TWIST1 reactivation. Among regulators of EMT, microRNAs are extensively studied. This work aimed at identifying microRNAs that might be important regulators of TWIST1 and EMT in NSCLC.

Methods: We performed miRSeq in a series of EGFR-mutated lung adenocarcinomas (n = 24, series A) and identified a set of miRNAs (n = 12) associated to TWIST1 reactivation. These miRNAs and additional EMT-related miRNAs selected from the

literature and from TCGA public data were reanalysed by Fluidigm® technology on the same series. Two miRNAs were significantly associated with TWIST1 reactivation. We then quantified these two miRNAs in a series of 176 consecutive operated NSCLC (series B), in addition to E-cadherin, Jup, N-cadherin, Zeb1, Snai1, Twist1, Vimentin, TCF3 and CD44 using qPCR. Results were validated using TCGA public data.

Results: MiR-200a-3p and miR-429 were significantly associated with TWIST1 reactivation ($p = 0.018$) in series A, not confirmed by the 16 EGFR-mutated lung adenocarcinomas of series B, but by TCGA analysis ($p = 0.03$). In series B, miR-200a-3p and miR-429 expression levels were highly correlated ($p < 0.001$) together and associated to Twist1 up-regulation ($p = 0.02$ and $p = 0.07$, respectively), EMT ($p = 0.003$) and stem cell features ($p < 0.05$). Low miR-200a-3p and miR-429 expression levels were significantly associated with overall survival in multivariate analyses (Cox; $p = 0.008$ and $p = 0.01$, respectively), thus identified as independent prognostic factors. TCGA overall survival multivariate analyses confirmed this finding ($p < 0.02$).

Conclusions: This study provides new insights on the clinical impact of miR-200 family members down-regulation in localized NSCLC. EMT targeting should be considered as a therapeutic option for a subset of NSCLC patients.

Legal entity responsible for the study: Assistance Publique des Hôpitaux de Paris.

Funding: Site de la Recherche Intégrée sur le Cancer (SIRIC) Cancer Research for Personalized Medicine (Carpem).

Disclosure: The author has declared no conflicts of interest.

1356P The level of circulating NKp46+ CD56dim CD16+ natural killer cells predicts distinct survival in non-small cell lung cancer

E. Picard[1], Y. Godet[1], C. Laheurte[2], L. Boullerot[1], E. Lauret Marie Joseph[1], M. Jacquin[3], V. Kaulek[4], G. Eberst[4], B. Gaugler[1], P. Jacoulet[4], M. Gainet-Brun[4], J. Lahoucarde[4], H. Almotlak[4], F. Le Pimpec-Barthes[5], E. Fabre-Guillevin[6], C. Borg[1], V. Westeel[4], O. Adotevi[1]

[1]Univ. Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire et Génique, LabEx LipSTIC,, Besançon, France, [2]INSERM CIC-1431 Clinical Investigation Center in Biotherapies, Plateforme de Biomonitoring, Besançon, France, [3]CIC-1431, University Hospital of Besançon, Besançon, France, [4]University Hospital of Besançon, Department of Pneumology, Besançon, France, [5]Service de Chirurgie Thoracique, AP-HP, Hôpital Européen Georges Pompidou, Paris, France, [6]Service d'Oncologie Médicale, AP-HP, Hôpital Européen Georges Pompidou, Paris, France

Background: Natural killer (NK) cells are innate effector lymphocytes involved in cancer immunosurveillance. Here we investigated the distribution, function and prognosis role of circulating NK cell subsets in non-small cell lung cancer (NSCLC).

Methods: Blood samples from 176 NSCLC patients were collected before any treatment and from 41 healthy donors (HD) as control. The phenotype and cytotoxic functions of NK cells were performed by multicolor flow cytometry. Kaplan–Meier method was used to estimate survival.

Results: NSCLC patients exhibited three distinct NK cell subsets in blood such as $CD56^{dim}$ $CD16^{+}$, $CD56^{dim}$ $CD16^{-}$ and $CD56^{bright}$ NK cells. However, a lower rate of $CD56^{dim}$ $CD16^{+}$ NK cells and a higher rate of $CD56^{dim}$ $CD16^{-}$ NK cells were found in patients as compared to HD. Unsupervised clustering analysis of activating receptors expression such as NKG2D, NKp30, NKp44, and NKp46 identified four groups of patients with distinct circulating NK cell profiles. We showed that the rate of circulating $NKp46^{+}$ NK cells was inversely correlated with overall survival (OS). Consistently, the median OS in high versus low level $NKp46^{+}$ NK cell group was 16 and 27 months respectively ($P = 0.04$). This effect was mainly driven by $NKp46^{+}$ $CD56^{dim}$ $CD16^{+}$ NK cells subset ($P = 0.02$). Finally, blocking NKp46 receptor in vitro was able to restore antitumor T cell immunity suggesting an inhibitory role of $NKp46^{+}$ NK cells.

Conclusions: Altogether, our results show a distinct pattern of circulating NK cell subsets in NSCLC and also support the immune regulatory property of $NKp46^{+}$ NK cell subsets. This study provides important insights on circulating $Nkp46^{+}$ NK cell subsets as potential prognosis factor in lung cancer.

Legal entity responsible for the study: Olivier Adotévi.

Funding: Assistance Publique des Hôpitaux de Paris, La Ligue Contre le Cancer, and the Conseil Régional de Franche-Comté.

Disclosure: All authors have declared no conflicts of interest.

1357P A positive correlation between the EZH2 and PD-L1 expression in patients with resected lung adenocarcinoma

G. Toyokawa[1], K. Takada[2], R. Hamamoto[3], Y. Yamada[4], T. Tagawa[2], F. Shoji[1], K. Yamazaki[1], Y. Oda[4], S. Takeo[1]

[1]Department of Thoracic Surgery, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan, [2]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [3]National Cancer Center, Division of Molecular Modification and Cancer Biology, Tokyo, Japan, [4]Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Background: Enhancer of zeste homolog 2 (EZH2) is reported to be involved in lung cancer pathogenesis via the epigenetic regulation of various genes. Recently, EZH2 was shown to control mechanisms of adaptive resistance to immunotherapy in melanoma; however, the association between EZH2 and programmed death-ligand 1 (PD-L1), which reflects the tumor microenvironment, remains poorly understood.

Methods: A total of 428 patients with resected lung adenocarcinoma were analyzed for their EZH2 and PD-L1 expression by immunohistochemistry and evaluated to determine the association between the EZH2 and PD-L1 expression.

Results: Among 428 patients, the EZH2 expression was identified in 219 (51.2%), while the PD-L1 expression was observed in 88 (20.6%). The recurrence-free and overall survival (RFS and OS, respectively) were significantly shorter in patients with the EZH2 expression than in those without it. A multivariate analysis showed that EZH2 remained an independent prognosticator for the RFS and OS. Patients with the EZH2-positive lung adenocarcinoma exhibited a significantly higher expression of PD-L1 than those without it. A logistic regression analysis with backward elimination revealed that the presence of lymphatic and vessel invasion and PD-L1 positivity were independently associated with the EZH2 expression, while age over 70, the presence of vessel invasion, wild-type epidermal growth factor receptor, and EZH2 positivity were significantly associated with the PD-L1 expression.

Conclusions: EZH2-expressing lung adenocarcinomas were shown to express PD-L1 protein more frequently than non-expressing lesions. This study provides the first evidence of a possible association between the EZH2 and PD-L1 expression in patients with resected lung adenocarcinoma.

Legal entity responsible for the study: Gouji Toyokawa.

Funding: Japan Society for the Promotion of Science and Kaibara Morikazu Medical Science Promotion Foundation.

Disclosure: All authors have declared no conflicts of interest.

1358P Comprehensive analysis for immune profiles of tumor microenvironment in non-small cell lung cancers: Prognostic effect of immunomodulatory molecules

K. Takamochi[1], M. Hosoya[2], K. Mogushi[2], T. Hayashi[3], M. Ito[4], H. Kawaji[4], Y. Hayashizaki[4], K. Suzuki[1]

[1]Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan, [2]Intractable Disease Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [3]Department of Human Pathology, Juntendo University School of Medicine, Tokyo, Japan, [4]Preventive Medicine and Applied Genomics Unit, Riken Advanced Center for Computing and Communication, Yokohama, Japan

Background: Therapies targeting immune checkpoints have recently shown promising activity in non-small cell lung cancer (NSCLC) patients. T-cell activation is controlled by the balance of co-stimulatory molecules and co-inhibitory molecules (immune checkpoint molecules).

Methods: A comprehensive analysis was performed for immune profiles of tumor microenvironment in NSCLCs using cap analysis of gene expression (CAGE). CAGE is a method used to quantify promoter activities across the whole genome by determining the 5' ends of capped RNA molecules with next-generation sequencing. Gene expressions of PD-L1, PD-L2, co-inhibitory molecules (CTLA-4, PD-1, TIM-3, BTLA, VISTA, and LAG-3), co-stimulatory molecules (CD28, OX40, GITR, CD317, CD27, and HVEM), and markers of immune cells (CD4, CD8, CD25, Foxp3, CD68, and CD204) were quantified using RNA extracted from frozen tumor tissue samples of 100 surgically resected NSCLCs (71 adenocarcinomas (AD), 22 squamous cell carcinomas (SQ), and 7 other histologic types).

Results: NSCLCs in this study were classified into two groups: tumors with high expression of almost all immunomodulatory targets (immunoreactive) and tumors with intermediate or low expression (non-immunoreactive). Co-stimulatory and co-inhibitory molecules were simultaneously highly expressed in immunoreactive tumors. The prognosis of immunoreactive ADs was worse than that of non-immunoreactive ADs regardless of histologic grade or EGFR mutation status ($P = 0.002$). However, an opposite trend was observed in SQs ($P = 0.789$). In ADs, high expression of CD137, TIM-3, and HVEM was an unfavorable prognostic factor. In SQs, high expression of CTLA-4 and LAG-3 was a favorable prognostic factor, and whereas HVEM expression was unfavorable.

Conclusions: NSCLCs can be classified into immunogenic and non-immunogenic tumors. The prognostic effect of immunomodulatory molecules differs according to histologic types and gene expression profiles of immune cells.

Legal entity responsible for the study: Juntendo University School of Medicine.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1359P Association between PD-L1 expression and survival in early stage non-small cell carcinoma

E. Gálvez[1], C. Gálvez Muñoz[2], A. Cotes Sanchís[1], A. Gonzaga López[1], M.M. Llorente Ostiategui[1], M. Montero Gómez[1], I. Aranda López[3], C. Llorca Ferrandiz[1]
[1]Oncología, Hospital General de Elda, Elda, Spain, [2]Cirugía Torácica, Hospital General de Alicante, Alicante, Spain, [3]Anatomía Patológica, Hospital General de Alicante, Alicante, Spain

Background: Programmed death-ligand 1 (PD-L1) is used to predict response to immunotherapy. Temporal variability in the expression of PD-L1 in tumor cells has been reported; we wanted to assess the prevalence and prognostic role of PD-L1 expression in patients with resected non-small cell lung carcinoma (NSCLC) in initial stages with negative ganglia.

Methods: We analyzed tumor tissue of 170 patients with NSCLC stages I and II (pN0), no adjuvant or neoadjuvant therapy. Immunohistochemical staining of PD-L1 (Dako PD-L1 IHC 22C3 pharmDx) was performed on sections of tissue microarrays (TMAs), being able to be carried out in 165 cases (97%). The results were correlated (Ji Square and Fisher test) with clinicopathological variables (gender, age, smoking, pathological stage, histological type, nuclear grade, Ki67). For the analysis of survival (disease-free (DFS) and overall (OS) survival), the curves of Kaplan-Meier were used with the test of the logarithmic ranges (log rank test), and the proportional method of Cox taking the negative values as reference.

Results: The median age was 66 years (IQR 60-73), 135 men and 35 women. Eighty-eight per cent of them were smokers. The median follow-up was 64 months (range 1-163). The distribution by stages was: 51% of pathological stage IA, 31% of IB stage and 18% corresponded to stage II with pN0. Regarding histology there were 57% adenocarcinomas, 34% squamous cell carcinomas and 7% large cell carcinomas. PD-L1 expression was detected in 28.8% of the cases: 19.8% of the adenocarcinoma tumours and 41.3% of the squamous subtypes. We found a PD-L1 expression greater than 5% in 24.7% of cases and 11.8% of the total showed a PD-L1 expression $\geq$ 50%. The median DFS was 59.6 months (IQR 27-85) and OS 64.2 months (IQR 39.9-94.9). A statistically significant association was observed between expression of PD-L1 and younger age (inverse relationship, p = 0,033) and histologic subtype (lower expression in squamous type, p = 0,029). Kaplan-Meier analysis showed less DFS in positive PD-L1 patients. No significant differences were observed in relation to overall survival.

Conclusions: The expression of PD-L1 is associated with morphological data of greater aggressiveness and is a risk factor for relapse in NSCLC in early stages without positive ganglia.

Legal entity responsible for the study: Hospital General de Alicante.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1360P Neoadjuvant pembrolizumab (Pembro) for early stage non-small cell lung cancer (NSCLC): Initial report of a phase I study, MK3475-223

A. Ben Nun[1], N. Golan[1], E. Ofek[2], D. Urban[3], I. Kamer[3], D. Simansky[1], A. Onn[4], A. Ackerstein[3], S.P. Raskin[3], T. Shulimzon[4], N. Zeitlin[1], I. Redinsky[3], S. Halperin[3], M. Jurkowicz[3], J. Bar[3]
[1]Department of Thoracic Surgery, Chaim Sheba Medical Center, Ramat Gan, Israel, [2]Department of Pathology, Chaim Sheba Medical Center, Ramat Gan, Israel, [3]Institute of Oncology, Chaim Sheba Medical Center, Ramat Gan, Israel, [4]Institute of Pulmonology, Chaim Sheba Medical Center, Ramat Gan, Israel

Background: NSCLC is the most common cause of cancer-related death. Even clinical stage I or II tumors that are completely resected harbor a 5-year survival of only 30-50%. Immunotherapy is being investigated now as adjuvant therapy and might improve those results. We hypothesize that neo-adjuvant immunotherapy is a feasible, safe and effective treatment for early stage NSCLC.

Methods: MK3475-223 is a phase I study, testing neoadjuvant Pembro for stage I and II NSCLC. Study design is based on a classical 3 + 3 cohort, but the differences between cohorts are not drug dose but number of treatments (1st cohort 1 treatment, 2nd and 3rd cohorts 2 treatments with a 3 weeks (wk) interval between them) prior to surgery, and interval from last dose to surgery (1st cohort 3 wks, 2nd cohort 2 wks, 3rd cohort 1 wk). All Pembro treatments are 200mg. Primary objectives are to determine safety, recommended phase 2 dose/schedule, pathological and radiological response. Dose limiting toxicities (DLT) were defined as significant surgical complications (bleeding, delayed wound healing, acute respiratory distress syndrome, prolonged air-leak) or a significant delay of surgery. DLT period was defined as 30 days post-surgery.

Results: To date, two cohorts (6 patients (pts)) have been fully recruited and completed the DLT period. No DLT has occurred. Adverse events (AEs) are within the recognized AE profile of Pembro and of thoracic surgical procedures. No significant responses were seen in the 1st cohort (1 Pembro treatment, 3 wks later surgery). Out of 3 pts on the 2nd cohort (2 Pembro treatments, 2 wks later surgery), 2 pts (66.6%) demonstrate near complete pathologic response, with less than 1% of tumor cells left estimated. The study is ongoing and continuing to recruit, currently recruiting the final cohort (2 pembro treatments, 1 wk later surgery), to be followed by an expansion cohort.

Conclusions: Neoadjuvant Pembro is a promising option for early stage NSCLC. Initial data suggest the safety of this approach. The trial will provide initial evidence as well as correlative studies regarding the efficacy of this approach.

Legal entity responsible for the study: Sheba Medical Center.
Funding: MSD.
Disclosure: J. Bar: Consultant fees: Roche, Boehringer Ingelheim, Novartis, BMS, MSD, Pfizer, AstraZeneca, Takada, Abbvie, VBL; Grant support: Boehringer Ingelheim, AstraZeneca, MSD. All other authors have declared no conflicts of interest.

1361P Neoadjuvant chemotherapy with bevacizumab followed by surgery for clinical stage II/IIIA non-squamous non-small cell lung cancer: Survival results from a phase II feasibility study (NAVAL)

Y. Tsutani[1], Y. Miyata[1], K. Suzuki[2], K. Takamochi[2], F. Tanaka[3], H. Nakayama[4], Y. Yamashita[5], M. Oda[6], M. Tsuboi[7], M. Okada[1]
[1]Surgical Oncology, Hiroshima University, Hiroshima, Japan, [2]Thoracic Surgery, Juntendo University, Tokyo, Japan, [3]Thoracic Surgery, University of Occupational and Environmental Health, Kokura, Japan, [4]Thoracic Surgery, Kanagawa Cancer Center, Yokohama, Japan, [5]Thoracic Surgery, Kure Medical Center, Kure, Japan, [6]Thoracic Surgery, Kanazawa University, Kanazawa, Japan, [7]Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: We previously reported that neoadjuvant cisplatin, pemetrexed, and bevacizumab followed by surgery is safe and feasible in patients with clinical stage II/IIIA non-squamous non-small cell lung cancer (NSCLC) (NAVAL study). The purpose of this study is to evaluate survival results, which are secondary endpoints of NAVAL study.

Methods: In a phase II feasibility study of neoadjuvant chemotherapy with cisplatin (75 mg/m^2), pemetrexed (500 mg/m^2), and bevacizumab (15 mg/kg) followed by surgery for resectable clinical stage II/IIIA non-squamous NSCLC, progression-free survival (PFS) and overall survival (OS) were analyzed. Patients who had less than 33% residual viable primary tumor after neoadjuvant chemotherapy were defined as pathologic responders. Others were defined as non-responders.

Results: Among all 30 patients, 25 underwent surgical resection after 3 cycle of neoadjuvant chemotherapy with bevacizumab, and 3 underwent off protocol surgical resection. Two-year PFS rate and 5-year PFS rate were 41.5% and 34.6%, respectively. Two-year OS rate and 5-year OS rate were 70.0% and 60.0%, respectively. Six (20%) patients were classified as pathologic responders, whereas 24 (80%) as non-responders. There was significant difference in PFS between pathologic responders (5-year PFS rate, 100%) and non-responders (5-year PFS rate, 17.5%; P = 0.002). Also, there was significant difference in OS between pathologic responders (5-year OS rate, 100%) and non-responders (5-year OS rate, 43.5%; P = 0.006).

Conclusions: Neoadjuvant cisplatin, pemetrexed, and bevacizumab followed by surgery is effective for clinical stage II/IIIA non-squamous NSCLC. Long-term survival after surgery is expected for pathologic responders, whereas additional therapy will be needed for non-responders.

Clinical trial identification: UMIN000004278, 2010/10/01.

Legal entity responsible for the study: Morihito Okada.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1362P Clinical outcomes and treatment strategies of sarcomatoid carcinoma of the lung

Y. Wang
Thoracic Surgery, Hebei Provincial Tumor Hospital, Shijiazhuang, China

Background: Sarcomatoid carcinoma of the lung is characterized by worse prognosis, and generally felt to be chemo-refractory compared with other non-small cell lung cancer. We conduct this retrospective study to investigate the clinical characteristics of patients with sarcomatoid carcinoma of the lung and determine the optimal treatment strategies.

Methods: We reviewed the medical records of 8176 patients with resected lung cancer in a single high-volume institution between 2008 and 2015. All patients with pathologically diagnosed sarcomatoid carcinoma were evaluated. Clinicopathologic data were analyzed using Kaplan-Meier analysis and Cox regression analysis. Subgroups stratified by pathological stage were analysed to determine the optimal treatment modality. We also conducted subgroup analysis of overall survival among pulmonary sarcomatoid carcinoma and other NSCLC patients.

Results: Kaplan-Meier and Cox regression analyses showed pathological stage (8th edition) is the independent prognostic factor (P = 0.001, HR = 2.601, 95%CI(1.447-4.675)) for pulmonary sarcomatoid carcinoma. Overall survival favored other NSCLC over PSC across subgroups. Male (HR = 0.695, 95%CI(0.505-0.955)), age above 60

years (HR = 0.622, 95%CI(0.417-0.928)), never-smoker (HR = 0.583, 95%CI(0.383-0.888)), patients who had no alcohol abuse history (HR = 0.597, 95%CI(0.416-0.856)), tumor size >5cm (HR = 0.700, 95%CI(0.492-0.995)), tumor stage T1 (HR = 0.383, 95%CI(0.167-0.877)), tumor location in peripheral (HR = 0.577, 95%CI(0.367-0.906)), or in both peripheral and central (HR = 0.626, 95%CI(0.424-0.923)), node stage N0 (HR = 0.599, 95%CI(0.403-0.891)), stage Ia(HR = 0.362, 95%CI(0.131-1.000)), stage Ib(HR = 0.450, 95%CI(0.278-0.729)), surgery alone (HR = 0.712, 95%CI(0.507-0.999)).

Conclusions: Pathological stage (8th edition) is independent prognostic factor for sarcomatoid carcinoma of the lung. Surgery followed by adjuvant chemotherapy should be considered for stage I pulmonary sarcomatoid carcinoma. Further prospective studies are needed to confirm these results.

Legal entity responsible for the study: The Fourth Hospital of Hebei Medical University.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii488–viii492, 2018
doi:10.1093/annonc/mdy291

NSCLC, LOCALLY ADVANCED

1363O Efficacy and safety evaluation based on time from completion of radiotherapy to randomization with durvalumab or placebo in pts from PACIFIC

C. Faivre-Finn[1], D.R. Spigel[2], S. Senan[3], C.J. Langer[4], D. Raben[5], B. Perez[6], M. Özgüroğlu[7], D. Daniel[8], A. Villegas[9], D. Vicente[10], R. Hui[11], S. Murakami[12], L. Paz-Ares[13], L. Poole[14], C. Wadsworth[15], P.A. Dennis[16], S.J. Antonia[6]

[1]Clinical Oncology, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK, [2]Lung Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN, USA, [3]Radiation Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [5]Moores Cancer Center, University of Colorado, Denver, CO, USA, [6]Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA, [7]Medical Oncology, Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey, [8]Medical Oncology, Tennessee Oncology and Sarah Cannon Research Institute, Chattanooga, TN, USA, [9]Medical Oncology, Cancer Specialists of North Florida, Jacksonville, FL, USA, [10]Medical Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, [11]Oncology, Westmead Hospital and the University of Sydney, Sydney, Australia, [12]Department of Respiratory Medicine, Kanagawa Cancer Center, Yokohama, Japan, [13]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain, [14]Department of Statistics, AstraZeneca, Cambridge, UK, [15]Medical Oncology, AstraZeneca, Macclesfield, UK, [16]Medical Oncology, AstraZeneca, Gaithersburg, MD, USA

1364PD Cardiac events in stage III non-small cell lung cancer (NSCLC) treated in daily clinical practice: Is it time for cardiovascular screening and follow-up?

J. Degens[1], D. De Ruysscher[2], B. Kietselaer[3], G. Bootsma[4], A. Schols[1], A-M.C. Dingemans[5]

[1]Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht, Netherlands, [2]Radiation Oncology, Maastricht University Medical Centre (MUMC)-MAASTRO Clinic, Maastricht, Netherlands, [3]Departement of Cardiology, Zuyderland Medical Center, Geleen, Netherlands, [4]Department of Respiratory Medicine, Zuyderland Medical Center, Heerlen, Netherlands, [5]Department of Respiratory Medicine, Maastricht University Medical Center (MUMC), Maastricht, Netherlands

1365PD Screening for brain metastases (BM) in patients (pts) with stage III non-small cell lung cancer (NSCLC), magnetic resonance imaging (MRI) or dedicated contrast-enhanced computed tomography (dCE-CT)? A prospective observational study

J.J.A.O. Schoenmaekers[1], L. Hendriks[2], A-M.C. Dingemans[3], D. De Ruysscher[4], G. Bootsma[5], W. Schreurs[6], M. Westenend[7], R. Houben[8], P. Hofman[9], M. De Booij[10]

[1]Pulmonology, Academisch Ziekenhuis Maastricht (AZM), Maastricht, Netherlands, [2]Pulmonary Diseases, Maastricht University Medical Center (MUMC), Maastricht, Netherlands, [3]Pulmonology, Maastricht University Medical Center (MUMC), Maastricht, Netherlands, [4]Radiation Oncology, Maastricht University Medical Centre (MUMC)-MAASTRO Clinic, Maastricht, Netherlands, [5]Pulmonary Diseases, Zuyderland Medical Center, Heerlen, Netherlands, [6]Nuclear Medicine, Zuyderland Hospital Heerlen, Heerlen, Netherlands, [7]Pulmonology, Viercurie Hospital Venlo, Venlo, Netherlands, [8]Radiotherapy, Maastro, Maastricht, Netherlands, [9]Radiology, MUMC, Maastricht, Netherlands, [10]Radiology, Zuyderland Medical Center, Heerlen, Netherlands

1366P The impact of the new TNM classification on survival of patients in stage III non-small cell lung cancer

M. Vrankar, K. Stanic

Radiotherapy, Institute of Oncology Ljubljana, Ljubljana, Slovenia

Background: In the new 8th TNM classification, stage III non-small cell lung cancer (NSCLC) is divided into three subgroups. Stage IIIA includes T4 N0 M0 and T3/4 N1 M0 tumours as well as T1/T2 N2 M0 tumours. Stage IIIB tumours are either T3/T4 N2 M0 or T1/T2 N3 M0. Stage IIIC involves T3/T4 N3 M0 tumours. Beside new IIIC stage, the greatest change is reclassification of T category based on dimension. Tumours larger than 7 cm that were previously T3 are now staged T4. The anatomic extent of disease is the base of the TNM classification with impact on survival. The aim of this analysis was to determine applicability of the new 8th TNM edition on survival of stage III NSCLC treated with combined radiochemotherapy between 2005 and 2010 in our institution.

Methods: A total of 101 patient with stage III NSCLC treated between September 2005 and November 2010 with induction chemotherapy and radiochemotherapy were included in long term survival analysis of TNM restaging. Results of survival are presented for the 7^{th} and 8^{th} edition in view of the revised T stage.

Results: After a median follow up of 117.5 months, median overall survival (mOS) of stage IIIA patients according to the 7th TNM classification was significantly longer than those of stage IIIB patients (30.8 months and 19.0 months, $p = 0.005$). Redefinition of the stages according to the new 8th TNM classification showed similar mOS for patients in stage IIIA and stage IIIB (21.6 months and 24.9 months), but much shorter mOS for stage IIIC patients with 6.6 months ($p = 0.885$). Of 101 patient 13 were up-graded from T3 to T4 according to new TNM classification. In the 7th TNM classification T3N2 was in stage IIIA and T4N2 in stage IIIB, while in 8th TNM classification both are in stage IIIB. According to 7th TNM classification, mOS of patients in stage T3N2 was significantly longer with 60.0 months than in stage T4N2 with 19.2 months ($p = 0.004$). After the revision there is no difference, mOS of patients with T3N2 was 28.4 months and with T4N2 was 31.4 months ($p = 0.478$).

Conclusions: The statistical difference in survival between subgroups of stage III shown in the old TNM classification did not appear in the new classification. Other factors could affect prognosis that are patient, tumour and treatment related.

Legal entity responsible for the study: Martina Vrankar.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1367P Survival in never-smokers with non-small cell lung cancer: A population-based study from Sweden

L. Löfling[1], S. Bahmanyar[1], A. Karimi[2], H. Kieler[1], M. Lambe[3], K. Lamberg Lundström[2], F. Sandin[3], G. Wagenius[4]

[1]Centre for Pharmacoepidemiology, Medicine Solna, Karolinska Institute, Stockholm, Sweden, [2]Pulmonary Medicine, University Hospital Uppsala, Uppsala, Sweden, [3]Regional Oncologic Centre, Uppsala, Sweden, [4]Oncology, Karolinska University Hospital, Solna, Sweden

Background: Tobacco smoking is the major risk factor for lung cancer. However, approximately 10% of patients diagnosed with lung cancer have never smoked and knowledge of their characteristics and survival remain limited. Specific genetic alterations, e.g. ALK (anaplastic lymphoma kinase) rearrangements and EGFR (epidermal growth factor receptor) mutations, are more common in never-smoking lung cancer patients than in current or former smokers. We aimed to investigate characteristics of patients with different smoking history and estimate their lung cancer-specific survival.

Methods: This study was based on data from the Lung Cancer Database Sweden generated by record linkage between the Swedish National Lung Cancer Register and other population-based registers. Patients diagnosed with primary non-small cell lung cancer between 2002 and 2016 were included. The Kaplan-Meier method was used to estimate lung cancer-specific survival by smoking history (never-smokers, former smokers, and current smokers).

Results: In total, 41,262 patients with lung cancer were included, of those 4,624 (11.2%) had never smoked. Never-smokers were older at time of the diagnosis (median: 73 years, Inter Quartile Range (IQR)=63-80) than current smokers (median: 67 years, IQR=61-73) and former smokers (median: 72 years, IQR=66-78). Women were overrepresented among never-smokers (66%) than among current (49%) and former smokers (43%). Adenocarcinoma was the most frequent histological subtype in all groups, but was proportionally more frequent in never-smokers (77%) compared to current smokers (52%) and former smokers (57%). The estimated overall (all stages) 2-year cause specific lung cancer survival was higher in never-smokers (35.9%, 95% CI 34.4 - 37.5) than among current smokers (29.4%, 95% CI 28.7 - 30.2) and former smokers (30.7%, 95% CI 30.0 -31.4).

Conclusions: The observed longer survival and the difference in histopathology suggest that tumours in never-smokers have a different pathogenesis and a different behaviour than tobacco-associated lung cancer. In further analyses, we will examine observed differences in outcomes in more detail, including the modifying role of other prognostic factors.

Legal entity responsible for the study: Regional Oncologic Centre Uppsala-Örebro and Karolinska Institutet.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1368P Clinical features and prognosis of eighty-five patients with primary pulmonary lymphoepithelioma-like carcinoma

Q.Y. Yin, G.Y. Gao, C.Z. Zhou, Z. Zhu, Y.Q. Liu, X.H. Xie, X.Q. Lin, Z.H. Xie, J.X. Zhang, O.Y. Ming, S.Y. Li, R.C. Chen

State Key Laboratory of Respiratory Disease, National Clinical Research Center of Respiratory Disease, Guangzhou Institute of the Respiratory Disease, The 1st Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

Background: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare subtype of lung cancer that is less reported and not well understood around the world.

Methods: A retrospective analysis of clinical features for 85 patients was conducted to determine the prognostic factors in terms of age, gender, radiographic features, serum tumor markers, TNM stages, pathological features, treatment and prognosis.

Results: PLELC preferentially affects the young (< 60 years old: 71.8%) nonsmokers (72.9%), without significant difference in gender. The median follow-up time was 15 months (1-37 months) for the whole group and most patients were in the early stage with opportunity of operation (50.6%). For the advanced stage group, patients mainly received chemotherapies and radiotherapies, the 0.5-year and 1.5-year PFS rates were 61% and 29%, respectively. The TNM stage ($P = 0.014$) and performance status (PS) ($P = 0.040$) were associated with PFS significantly in the univariate analysis, while TNM stage was an independent prognostic factor in multivariate analysis ($P = 0.026$). In the subtype analysis, patients in the advanced stage receiving Gemcitabine plus platinum (GP group) or Paclitaxel plus platinum (TP group) had better PFS than Pemetrexed plus platinum (PP group) ($P = 0.005$).

Conclusions: PLELC had a better prognosis compared with other types of non-small cell lung cancer (NSCLC) and was sensitive to radiotherapy and chemotherapy. The current results recommended that the GP and TP should be used as first-line treatment of PLELC. The TNM stage and PS were predictive in prognosis of PLELC patients.

Legal entity responsible for the study: Y. Qin.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1369P Meta-analysis of prognostic factors of completely resected pathologic N2 stage IIIA non-small cell lung cancer including 11,384 patients

X. Zhan, N. Li
Key Laboratory of Cancer Proteomics of Chinese Ministry of Health, Xiangya Hospital, Central South University, Changsha, China

Background: Patients with IIIA-pN2 non-small cell lung cancer (NSCLC) are a heterogeneous group, So this meta-analysis aimed to determine prognostic factors and compare different postoperative adjuvant therapies on survival.

Methods: MEDLINE, Embase, Web of Science were searched to identify relevant trials up to May 2017. Datas of univariate and multivariate analyses of prognostic factors for overall survival (OS) were extracted and calculated by hazard ratios (HR) and 95% confience intervals (95% CI). Pooled survival curves were constructed by Engauge Digitizer and RStudio.

Results: Overall 26 trials comprising 11,384 patients were included. The subgroup analysis for OS indicated that increased age (HR 1.02, 95%CI 1.02-1.02, $P < 0.00001$), male (HR 1.37, 95%CI 1.25–1.49, $P < 0.00001$), increased pathologic T stage (HR 1.27, 95%CI 1.12–1.45, $P = 0.0003$), multiple N2 metastases (HR 1.53, 95%CI 1.34–1.74, $P < 0.0001$), positive of skip matestasis (HR 2.07, 95%CI 1.25–3.42, $P < 0.0001$), involvement of N1 nodal station (HR 1.42, 95%CI 1.13–1.70, $P = 0.003$), pneumonectomy (HR 1.42, 95%CI 1.16–1.73, $P = 0.0007$), increasing clinical T classification (HR 1.48, 95%CI 1.09–2.02, $P = 0.01$), increasing clinical N classification (HR 1.75, 95%CI 1.23–1.48, $P = 0.002$) were significantly associated with poor OS and N downstaging (HR 0.46, 95%CI 0.37–0.68, $P < 0.0001$), PORT (HR 0.76, 95%CI 0.64–0.72, $P = 0.004$), adjuvant chemotherapy (HR 0.69, 95%CI 0.56–0.85, $P = 0.007$) were significantly associated with better OS. The 5-year disease-free survival rate was 38.9% in postoperative chemoradiotherapy group and 29.5% in postoperative chemotherapy group ($p = 0.001$). Survival was improved in patients with pN2 disease who received postoperative radiotherapy, both in the chemotherapy (5-year survival rate, 65.3% vs. 49.3%) and observation arm (5-year survival rate, 53.3% vs. 32.3%).

Conclusions: The main prognostic factors were age, gender, clinical T stage, pathologic T stage, operation procedure, clinical N status, involved N2 stations, N1 nodes involved, N2 Skip metastasis, N downstaging, postoperative radiotherapy as well as adjuvant chemotherapy. And these should be considered as stratification factors for further trials.

Legal entity responsible for the study: Key Laboratory of Cancer Proteomics of Chinese Ministry of Health, Xiangya Hospital, Central South University.
Funding: China "863" Plan Project.
Disclosure: All authors have declared no conflicts of interest.

1370P The results of treatment of non-small cell lung cancer stage III with a preoperative vinorelbine/carboplatin and personalized adjuvant chemotherapy

E.O. Rodionov[1], S.V. Miller[1], S.A. Tuzikov[1], M.M. Tsyganov[2], N.V. Litviakov[2], L.A. Efteev[1], I.V. Deriusheva[2]
[1]Thoracic and Abdominal Department, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation, [2]Laboratory of Viral Oncology, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation

Background: Individual chemotherapy based on the determination of molecular biomarkers of chemosensitivity is a new way to treat patients with NSCLC. Promising markers for chemosensitivity are monoresistance genes such as BRCA1, RRM1, ERCC1, TOP1, TOP2α, TUBB3, TYMS, and ABCC5.

Methods: We enrolled and analyzed 62 patients with stage III NSCLC. All the patients have received 2 courses of neoadjuvant chemotherapy vinorelbine/carboplatin and surgery. Then patients were randomly assigned (1:1 ratio) to either the personalized adjuvant chemotherapy arm (main group) or the adjuvant chemotherapy vinorelbine/carboplatin arm (control group). In the main group, carboplatin-containing doublets were assigned based on monoresistance gene expression levels ABCC5, RRM1, ERCC1, BRCA1, TOP1, TOP2α, TUBB3 and TYMS. RNA was extracted from tumor after neoadjuvant chemotherapy using "RNeasy Plus Mini Kit" (QIAGEN, Germany). The analysis of monoresistance genes expression was done by qRT-PCR method. A χ^2 test was used to analyze gene expression in relation to clinicopathological parameters. The survival rates were calculated by the Kaplan-Meier method.

Results: The follow-up period was 4 - 76 months. In the main group, the disease progression was observed in 6 patients (19.4%), in the control group - 15 patients (48.4%). Three-year disease-free survival in the main group was 80.7% (median DFS not achieved), in the control group - 51.6%, median DFS - 34 months (HR: 2.56, 95% CI: 1.09 - 6,03); differences are statistically significant: Log-Rank test $\chi 2=4.196$, $p = 0.041$. There was no difference in three-year overall survival (main group: 87.1%, control group: 67.7%, HR: 2.27, 95% CI: 0.79 - 6,47).

Conclusions: Personalized postoperative chemotherapy based on the determination of monoresistance gene expression after neoadjuvant chemotherapy allows significant increase of patients 3-year disease-free survival by 29.1%.

Legal entity responsible for the study: Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1371P Final results of RENO study: Randomized phase II of oral vinorelbine or etoposide with cisplatin & chemo-radiation in stage III NSCLC - SLCG 10/02

M. Provencio Pulla[1], R. de las Peñas[2], N. Martinez Banaclocha[3], R. MarsÉ Fabregat[4], A. Insa Molla[5], T. Moran[6], M.A. Sala Gonzalez[7], B. Massuti Sureda[8], P. Mut Sanchis[9], A.L. Ortega Granados[10], J.M. Jurado[11], J. Gomez Codina[12], A. Artal-Cortes[13], F. Vazquez[14], V. Gutierrez Calderon[15], P. Diz Tain[16], N. Vinolas Segarra[17], I. Maestu Maiques[18], C. Camps[19], M.D. Isla Casado[20]
[1]Servicio de Oncología Médica, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain, [2]Medical Oncology, Consorcio Hospitalario Provincial de Castellón, Castellón, Spain, [3]Medical Oncology, Hospital General Universitario de Elche, Elche, Spain, [4]Medical Oncology, Hospital Universitario Son Espases, Palma De Mallorca, Spain, [5]Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain, [6]Medical Oncology, ICO Badalona, Badalona, Spain, [7]Medical Oncology, Hospital de Basurto, Bilbao, Spain, [8]Medical Oncology, Hospital General Universitario de Alicante, Alicante, Spain, [9]Medical Oncology, Sona Llätzer Hospital, Palma De Mallorca, Spain, [10]Oncología Médica, Complejo Hospitalario de Jaen - Universidad de Jaen, Jaen, Spain, [11]Medical Oncology, Hospital Clinico San Cecilio, Granada, Spain, [12]Oncologia, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [13]Medical Oncology, Hospital Miguel Servet, Zaragoza, Spain, [14]Medical Oncology, Complejo Hospitalario Universitario de Santiago de Compostela SERGAS, Santiago de Compostela, Spain, [15]Medical Oncology, Universitary and Regional Hospital of Málaga, Málaga, Spain, [16]Medical Oncology, Hospital Universitario de León, Leon, Spain, [17]Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [18]Medical Oncology, Hospital Dr. Peset Aleixandre, Valencia, Spain, [19]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain, [20]Medical Oncology, H. Clínico Zaragoza, Zaragoza, Spain

Background: This study aims to compare efficacy and safety of two widely used combinations of cisplatin (P) in this setting: as etoposide (E) and vinorelbine. This last, in its oral formulation (oV) which has achieved comparable results as the IV formulation and patients (pts) prefer it.

Methods: Pts between 18-75years, with histologically proven untreated and unresectable locally-advanced NSCLC (LA-NSCLC), adequate respiratory function, V20≤35% and ECOG-PS 0-1, were randomized 1:1 to oV-P arm: 2 induction cycles (cy) of oV-P followed by 2 cy more with RT; or to E-P arm: 2 cy of E-P concomitants to RT. Both arms with a total radiation dose of 66Gy administered 2 Gys daily. Primary endpoint was progression free survival (PFS) by RECIST 1.1. Secondary endpoints: overall response rate (ORR), overall survival (OS) and safety. With α-error of 0.05 (one-tailed test) and 0.1 β-error, median PFS unacceptable for the oV-P arm of 10 months (m) (p0) and a very acceptable of 15 m (p1), 122 eligible pts were required.

Results: 140 pts from 23 institutions of SLCG were randomized between 08/2011-12/2014. 134 pts were treated (66 in oV-P and 68 in E-P arms). Results based on this 134 pts are presented. Median age 62 years [39-76]; PS 0/1, 45%/55%; current smoker 51%; squamous cell 51%; stage IIIB 54%. 244 and 131 cy were given in the oV-P and E-P arms, respectively. All irradiated pts in oV-P arm received at least 60Gy, 7 pts in the E-P arm received less than 60Gy (4 due to toxicity). 1 pt (1.5%) in oV-P arm and 12 pts (17.6%) in E-P arm presented esophagitis G3/4 ($p = 0.002$). ORR were 39 (61.9%) and 41 pts (65.1%) in the oV-P and E-P arms, respectively ($p = 0.711$). After 26.3 m [0.03-61] of follow-up, 77.9% pts progressed and 58.6% pts died. Median PFS was 10.8 m (CI95%; 7.5-14) in oV-P arm and 9.1 m (CI95%; 5.5-12.7) in E-P arm ($p = 0.389$). Median OS was 38 m (CI95%; 21.3-58.8) in oV-P and 27.1 m (CI95%; 19.3-34.9) in E-P arm ($p = 0.547$).

Conclusions: Clearly both regimens achieve similar efficacy however oV-P has less toxicity, especially esophagitis G3/4.

Clinical trial identification: EudraCT 2010-022927-31.

Legal entity responsible for the study: Spanish Lung Cancer Group.
Funding: Spanish Lung Cancer Group.
Disclosure: All authors have declared no conflicts of interest.

1372P Survival update in randomized phase II trial of S-1/cisplatin (SP) or docetaxel/cisplatin (DP) with concurrent thoracic radiotherapy for inoperable stage III non-small cell lung cancer (NSCLC)-TORG1018

Y. Takiguchi[1], K. Yamada[2], H. Tanaka[3], K. Kubota[4], K. Kishi[5], T. Shimokawa[6], H. Saito[7], Y. Hosomi[8], T. Kato[7], N. Nogami[9], S. Igawa[10], T. Kasai[11], Y. Nakamura[11], T. Yamanaka[12], H. Okamoto[13]

[1]Medical Oncology, Chiba University, School of Medicine, Chiba, Japan, [2]Respirology, Neurology, and Rheumatology, Kurume University, Kurume, Japan, [3]Thoracic Oncology, Niigata Cancer Center, Niigata, Japan, [4]Division of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan, [5]Respiratory Medicine, Toranomon Hospital, Tokyo, Japan, [6]Respiratory Medicine, Yokohama Municipal Citizen's Hospital, Yokohama, Kanagawa, Japan, [7]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan, [8]Department of Thoracic Oncology & Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [9]Thoracic Oncology, Shikoku Cancer Center, Matsuyama, Japan, [10]Respiratory Medicine, Kitasato University School of Medicine, Kanagawa, Japan, [11]Respiratory Medicine, Tochigi Cancer Center, Utsunomiya, Japan, [12]Biostatistics, Yokohama City University Hospital, Yokohama, Japan, [13]Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Yokohama, Japan

Background: Treatment with an immune checkpoint inhibitor (ICI) on completion of concurrent chemoradiotherapy (CCRT) for pts with inoperable stage III NSCLC significantly prolongs the PFS; however the best chemotherapy regimen in CCRT has not been established. This study was conducted to evaluate whether SP or DP, both with concurrent thoracic radiotherapy, in pts with inoperable stage III NSCLC showed a favorable 2-year OS rate with less toxicity in the SP arm as presented previously (J Clin Oncol 2017; 35, suppl; abstr 8534). An update of survival, relapsed sites and post-treatment information with prolonged follow-up has been awaited.

Methods: Pts with inoperable stage III NSCLC were randomized to SP (S-1 40 mg/m^2 bid on days 1-14 and 29-42 plus cisplatin 60 mg/m^2 on days 1 and 29) or DP (docetaxel 50 mg/m^2 and cisplatin 80 mg/m^2 on days 1 and 29), with concurrent radiotherapy beginning on day 1 (60 Gy/30 fr) followed by two additional cycles of the chemotherapy. Primary endpoint was 2-year OS rate, and secondary endpoints included OS, PFS and safety.

Results: Among 110 pts enrolled, 106 (53 in each arm) were evaluable, with male/female 83/23; median age 65 (range 42-74); performance status 0/1 59/47; IIIA/IIIB 59/47. With a median follow-up of 48.1 months, 2-year survival and median OS were 79% (95% CI: 68-90%) and 55.2 months in the SP and 69% (95% CI: 57-82%) and 50.8 months in the DP arm, respectively. 5-year PFS rates in SP and DP arms were 23.2 (95% CI: 11-35) and 23.6% (95% CI: 11-36), and 5-year OS rates were 48.8 (95% CI: 34-64) and 42.3% (95%CI: 24-61), respectively. Hematological and non-hematological toxicities were less in the SP arm. Relapsed site in the RT field and in the CNS were similar between the two arms. Post-treatment chemotherapy for pts with progression was delivered in 92.5% and 71.1% pts in SP and DP arms, respectively.

Conclusions: Because of favorable 2-year OS with less toxicity, we choose SP in CCRT as a future reference regimen. High 5-year PFS and OS rates shown here should be considered in designing further studies where CCRT is followed by ICI.

Clinical trial identification: UMIN000005993.

Legal entity responsible for the study: NPO Thoracic Oncology Research Group (TORG).

Funding: Has not received any funding.

Disclosure: Y. Takiguchi, K. Yamada, K. Kubota, K. Kishi, Y. Hosomi, T. Kato, N. Nogami, T. Kasai, Y. Nakamura, T. Yamanaka, H. Okamoto: Lecture fee, Research funds: Taiho Pharmaceutical Co. H. Tanaka, T. Shimokawa, H. Saito, S. Igawa: Lecture fee: Taiho Pharmaceutical Co.

1373P Identification of subjects with locally advanced lung cancer who are likely to respond to standard-of-care chemoradiotherapy by a longitudinal monitoring of circulating tumor DNA (ctDNA) using a comprehensive ultra-sensitive NGS assay

P. Vitazka[1], N. Tikoo[2], A. Balasubramanyam[2], L. Xi[3], S. Yaung[3], E. Kwok[4], A. Lovejoy[5], D. Klass[5], M. Heibeck[6], K. Probst[7], A. Rehfeldt[7], E. Meldgaard[8], A. Madsen[9], M. Clement[9], J. Palma[10], B. Sorensen[9], P. Meldgaard[8]

[1]Clinical Science, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [2]Biometrics, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [3]Bioinformatics, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [4]Clinical Operations, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [5]Development, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [6]Biometrics, Roche Sequencing Solutions, Inc., Potsdam, Germany, [7]Clinical Operations, Roche Sequencing Solutions, Inc., Potsdam, Germany, [8]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [9]Clinical-Biochemistry, Aarhus University Hospital, Aarhus, Denmark, [10]Medical Scientific Affairs, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA

Background: Only ~20% of patients with locally advanced non-small cell lung cancer (NSCLC) have long term benefit from chemoradiation treatment. Analysis of ctDNA may be superior to other conventional approaches (e.g. CT imaging) in early detection of recurrent disease and can facilitate personalization of treatment strategies. Here we evaluate association between ctDNA levels and survival in subjects with locally advanced NSCLC using an ultra-sensitive next-generation sequencing (NGS) assay.

Methods: Treatment naive tumor and longitudinally collected plasma specimens were analyzed using a 197-gene NGS assay (AVENIO ctDNA Surveillance Kit and AVENIO Tumor Tissue Surveillance Kit prototype, Research Use Only). Mutations detected in pre-chemotherapy tumor specimens and in pre-chemotherapy or pre-radiation therapy plasma specimens were monitored in post-treatment plasma samples by measuring the number of Mutant Molecules Per Milliliter-of-plasma (MMPM). MMPM values were correlated with disease control (as evaluated by RECIST1.1). Kaplan-Meier curves and Cox proportional hazards models were used to assess association of tumor burden with subject survival.

Results: We sequenced 36 tumor and 160 plasma specimens from 40 subjects. At least one mutation reporter was identified in 92% (n = 27/33) of tumor and in 100% (n = 31/31) of pre-chemo or 100% (n = 37/37) of pre-radiation plasma specimens. The best predictive performance of the assay was observed using tumor pre-treatment reporters and MMPM cutoff of 8 in plasma samples collected at completion of the scheduled chemoradiation regimen. Subjects with MMPM below the cutoff had a mean overall survival (OS) benefit of 18.5 months (n = 27, Tarone p-value=0.013, HR = 3.73, 95%CI = 1.37-10.12). A similar trend was observed using plasma pre-chemo reporters (n = 31, Tarone p-value=0.024, HR = 2.08, 95%CI = 0.91-4.74).

Conclusions: Circulating tumor DNA monitoring with an ultra-sensitive NGS-based assay identifies subjects with a locally advanced NSCLC who will have a more favorable outcome when treated with a stand-of-care chemoradiation therapy.

Legal entity responsible for the study: Roche.

Funding: Roche.

Disclosure: P. Vitazka, A. Balasubramanyam, L. Xi, S. Yaung, E. Kwok, A. Lovejoy, M. Heibeck, K. Probst, A. Rehfeldt: Employment: Roche. N. Tikoo, J. Palma: Employment and stocks: Roche. D. Klass: Employment: Roche; Royalties for ctDNA detection: IP; Former shareholder: CAPP Medical. B. Sorensen, P. Meldgaard: Research support: Roche; Advisory board: Roche. All other authors have declared no conflicts of interest.

1374P Correlations between Ape1/Ref-1, ICAM-1 and IL-17A levels in serum and radiation pneumonitis for local advanced non-small cell lung cancer patients

L. Guo

Radiotherapy Department, Henan Cancer Hospital, Zhengzhou, China

Background: The main manifestations of radiation pneumonitis are injury of alveolar epithelial and endothelial cells, abnormal expression of cytokines, abnormal proliferation of fibroblasts and synthesis of fibrous matrix. The occurrence of radiation pneumonitis is associated with multiplecytokine level abnormality. These cytokines can also be used as bio-markers to predict the occurrence of radiation pneumonitis.

Methods: NSCLC patients (68 cases) were treated with concurrent radiotherapy and chemotherapy, every patient's normal tissue were controlled with a same radation dose. 68 local advanced NSCLC patients with concurrent chemoradiotherapy were detected the levels of Ape1/Ref-1, ICAM-1 and IL-17A in serum by ELISA before radiotherapy and in the 14th week after radiotherapy. Acute and advanced radiation pulmonary injury was graded according to RTOG/EORTC diagnostic and grading criteria. Grade 2 or more radiation pneumonitis was taken as the main end point.

Results: Eighteen cases out of 68 developed radiation pneumonitis, 50 of 68 cases have no radiation pneumonia development. There was no significant change of Ape1/Ref-1 levels before and after radiotherapy in radiation pneumonitis group ($P > 0.05$). There was no significant change of Ape1/Ref-1 concentration in serum after radiotherapy between radiation pneumonitis group and non- radiation pneumonitis group ($P > 0.05$). Compared with before radiotherapy, upregulation degree of ICAM-1 levels in radiation pneumonitis group was higher than that in non- radiation pneumonitis group ($P < 0.05$). There was no significant change of IL-17A concentration before and after radiotherapy in radiation pneumonitis group, but after radiotherapy IL-17A concentration in serum were higher than that in non-radiation pneumonitis group ($P < 0.05$). Correlation analysis found that the change of ICAM-1 before and after radiotherapy has no obvious correlation with the incidence of radiation pneumonitis, and IL–17A change has obvious correlation with the incidence of radiation pneumonitis.

Conclusions: IL-17A in serum could be the predictive factors of radiation pneumonitis for local advanced NSCLC patients with concurrent chemoradiotherapy.

Legal entity responsible for the study: Department of radiotherapy, affiliated Cancer Hospital, Zhengzhou University.

Funding: National Natural Science Foundation of China (No.81372436).

Disclosure: The author has declared no conflicts of interest.

1375P Programmed cell death ligand 1 expression and CD8 positive lymphocytes in stage III non-small cell lung cancer after neo adjuvant concurrent chemoradiotherapy and their relation with prognosis

E. Choe[1], C. Yoon-Jin[2], H-S. Shim[3], C-Y. Lee[4], B.C. Cho[5], H-R. Kim[1]

[1]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Seoul, Republic of Korea, [2]Department of Pathology, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Republic of Korea, [3]Department of Pathology, Yonsei University College of Medicine, Seoul, Republic of Korea, [4]Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea, [5]Medical Oncology, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea

Background: Previous studies in non-small cell lung cancer (NSCLC) on programmed cell death ligand 1 (PD-L1) expression and its role in prognosis led to conflicting results. For treatment plan after CCRT, we sought to analyze PD-L1 expression and CD8+ lymphocyte and their relation with prognosis in stage III NSCLC patients treated with neo adjuvant CCRT followed by surgery with curative aim.

Methods: We retrospectively enrolled 43 patients with stage III NSCLC treated with neo adjuvant CCRT followed by surgery at Yonsei Cancer Center Severance hospital, between June 2008 and October 2010. Immunohistochemistry (IHC) was performed on tissue sections of PD-L1 expression and presence of stromal CD8+ lymphocytes in NSCLC specimens. Weekly standard chemotherapy based on platinum was included in CCRT.

Results: The median age of patients at diagnosis was 62 years. Thirty patients (70%) were males and 13 patients (30%) were females. Never smokers were 17 patients (40%). Twenty-five patients had squamous cell carcinoma (58%). The post-CCRT PD-L1-positive group exhibited a tendency of poorer recurrence free survival (RFS) compared to post CCRT PD-L1-negative group ($p = 0.108$). The overall survival (OS) also showed a similar trend ($p = 0.215$). In the survival analysis with pre-CCRT specimens, both RFS and OS analyses showed no statistically significant differences ($p = 0.423$). Although it was not statistically significant, in a group showed increase in PD-L1 expression after CCRT resulted in the steepest curve in OS analysis ($p = 0.220$). Increase in stromal CD8+ lymphocytes after CCRT exhibited better survival than other groups (decrease or no change) ($p = 0.017$).

Conclusions: Increase in CD8+ lymphocyte density improved OS. Because this study was performed with small number of patients, prognostic value of PD-L1 in this group of patients should be considered for future treatment planning or study design although it was not statistically significant in this study.

Legal entity responsible for the study: Yonsei Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1376P The standard of care for stage III NSCLC in the era of immunotherapy: An Italian national survey on the current pattern of care among Italian thoracic oncologists

A. Bruni[1], F. Grossi[2], F. Katia[3], E. Capelletto[4], L. Buffoni[4], S. Badellino[5], V. Poletti[6], R. Chiari[7], N. Giaj Levra[8], G.L. Banna[9], S. Vagge[10], P. Borghetti[11], E. Baldini[12], E. Bria[13], M. Tiseo[14], M. Paci[15], P. Ciammella[16], M. Taraborrelli[17], U. Ricardi[18], V. Scotti[19]

[1]Oncology and Hematology, Radiotherapy Unit, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy, [2]Department of Oncology, IRCCS AOU San Martino, IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [3]Thoracic and Lung Physiopathology Unit, "Careggi" University Hospital, Florence, Italy, [4]Department of Oncology, Azienda Ospedaliera Universitaria San Luigi Gonzaga, Orbassano, Italy, [5]Department of Oncology, University of Turin, AOU Città della Salute e della Scienza, Turin, Italy, [6]Department of Thoracic Diseases, Pulmonary Operative Unit, "Morgagni-Pierantoni" Hospital, Forlì, Italy, [7]Medical Oncology Unit, Azienda Ospedaliera di Perugia S. Maria della Misericordia, Perugia, Italy, [8]Radiation Oncology Unit, "Sacro Cuore Don Calabria" Hospital, Verona, Italy, [9]Medical Oncology, Cannizzaro Hospital, Catania, Italy, [10]Radiation Oncology Department, IRCCS Policlinico San Martino, Genoa, Italy, [11]Radiation Oncology Department, "Spedali Civili" University Hospital, Brescia, Italy, [12]Department of Oncology, Division of Oncology, S. Luca Hospital, Lucca, Italy, [13]UOC Oncologia Medica, Universitàà Cattolica del Sacro Cuore - Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy, [14]Medical Oncology, AOU di Parma, Parma, Italy, [15]Thoracic Surgery Unit, Azienda Unità Sanitaria Locale - IRCCS, Reggio Emilia, Italy, [16]Radiation Oncology Unit, Azienda Unità Sanitaria Locale - IRCCS, Reggio Emilia, Italy, [17]Department of Radiation Oncology, SS. Annunziata Hospital, G. D'Annunzio, Chieti, Italy, [18]Department of Oncology, Radiotherapy Unit, University of Turin, AOU Città della Salute e della Scienza, Turin, Italy, [19]Radiation Oncology Unit, Oncology Department, Careggi University Hospital, Florence, Italy

Background: Concurrent Chemo-Radiotherapy (cCRT) is standard treatment in "fit patients" (pts) affected with locally advanced (LA) NSCLC, with surgery limited to few selected cases. Despite some improvements, outcomes are still unsatisfactory, with only 15-25% of pts alive at 5 years. Recently, encouraging results were obtained with the addition of immunotherapy (IT) to cCRT. Survey was conducted to evaluate the pattern of care of LA-NSCLC treatment among Italian Thoracic Oncologists (TO) involving pneumologists, thoracic surgeons, radiation and medical oncologists.

Methods: In February 2018, all Italian TO were invited to participate to a "web-based" survey consisting in 15 multiple-choice questions about staging procedures and most appropriate multimodal approach to manage LA-NSCLC. Questions were also focused on diagnostic imaging and histopathological modalities.

Results: 421 responses were analyzed;69% of responders had more than 5 years experience in thoracic oncology. In 72% of Centers, TO regularly attend a weekly multidisciplinary Team (MDT) meeting, while in 28% MDT is not regularly planned. About pathology, cytological/histological morphologic diagnosis of malignancy were considered enough to define a therapeutic approach in 63% of responders. In N2, Stage IIIA, "minimal" pts upfront surgery was considered the preferred option from 43% of responders, while in N2, multi-nodal and/or bulky pts cCRT was recommended. For this latter group ("unresectable") only 54% considered cCRT the most appropriate choice, while 46% preferred a sequential chemo-RT, even in fit pts due to better pts compliance and lower toxicity profiles.

Conclusions: Our analysis showed an inhomogeneous scenario between different specialists regarding the appropriate therapeutic choices for LA-NSCLC treatment. Additionally, some discrepancies were found about a correct selection of pts fit for cCRT. Many efforts have to be put towards the increase of a true multidisciplinarity, since in many Institutions lack of MDT was described. Future investigations and trials are necessary to optimize treatment approaches in LA-NSCLC, in particular considering recent clinical results on combination of cCRT and IT.

Legal entity responsible for the study: Alessio Bruni.

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii493–viii547, 2018
doi:10.1093/annonc/mdy292

NSCLC, METASTATIC

1377O Phase II study of tepotinib + gefitinib (TEP+GEF) in MET-positive (MET+)/epidermal growth factor receptor (EGFR)-mutant (MT) non-small cell lung cancer (NSCLC)

Y. Cheng[1], J. Zhou[2], S. Lu[3], Y. Zhang[4], J. Zhao[5], H. Pan[6], Y-M. Chen[7], C-F. Chian[8], R. Bruns[9], A. Johne[10], J. Scheele[10], Y-L. Wu[11]

[1]Medical Oncology, Jilin Province Cancer Hospital, Changchun, China, [2]Department of Respiratory Disease, Thoracic Disease Center, The First Affiliated Hospital, Zhejiang University, HangZhou, China, [3]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China, [4]Thoracic Medical Oncology, Zhejiang Cancer Hospital, HangZhou, China, [5]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, China, [6]School of Medicine, Sir Run Run Shaw Hospital, Zhejiang Medical University, Zhejiang Sheng, China, [7]Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, [8]Department of Internal Medicine, Tri-Service General Hospital, National Defence Medical Center, Taipei, Taiwan, [9]Biostatistics, Merck KGaA, Darmstadt, Germany, [10]Global Clinical Development, Merck KGaA, Darmstadt, Germany, [11]Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

1378O ARCTIC: Durvalumab + tremelimumab and durvalumab monotherapy vs SoC in ≥ 3L advanced NSCLC treatment

D.M. Kowalski[1], N. Reinmuth[2], S.V. Orlov[3], J.R. Fischer[4], S. Sugawara[5], S. Mandziuk[6], D.M. Medine[7], S. Novello[8], Y. Takeda[9], R.A. Soo[10], K. Park[11], M. McCleod[12], S.L. Geater[13], M. Powell[14], R. May[15], P. Stockman[16], D. Planchard[17]

[1]Department of Lung Cancer and Thoracic Oncology, The Maria Sklodowska-Curie Memorial Institute of Oncology, Warsaw, Poland, [2]Asklepios Fachkliniken Muenchen-Gauting, Asklepios Kliniken GmbH, Gauting, Germany, [3]Oncology, Pavlov Medical University, St. Petersburg, Russian Federation, [4]Oncology, Klinik Loewenstein GmbH Med Klinik II Onkologie, Loewenstein, Germany, [5]Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan, [6]Oncology, Centrum Medyczne Luxmed Sp, Lublin, Poland, [7]Oncology, Hospital Universitari Arnau de Vilanova, Lleida, Spain, [8]Oncology, University of Turin, Orbassano, Italy, [9]Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan, [10]Haematology-Oncology, National University Hospital, Singapore, [11]Division of Heamatology/Oncology, Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [12]Medical Oncology, Florida Cancer Specialists, Fort Myers, FL, USA, [13]Internal Medicine, Prince of Songkla University, Songkhla, Thailand, [14]Biostatistics, AstraZeneca, Gaithersburg, MD, USA, [15]Clinical Research, AstraZeneca, Gaithersburg, MD, USA, [16]Clinical Research, AstraZeneca, Macclesfield, UK, [17]Medical Oncology, Institut Gustave Roussy, Villejuif, France

1379PD **Impact of the EML4-ALK variant on the efficacy of alectinib (ALC) in untreated ALK+ advanced NSCLC (aNSCLC) in the global phase III ALEX study**

R. Dziadziuszko[1], T.S. Mok[2], D.R. Camidge[3], A.T. Shaw[4], J. Noe[5], M. Nowicka[5], T. Liu[6], E. Mitry[6], S. Peters[7]

[1]Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland, [2]Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, China, [3]Medical Oncology, University of Colorado, Aurora, CO, USA, [4]MGH Cancer Center, Massachusetts General Hospital, Boston, MA, USA, [5]Oncology Biomarker Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland, [6]Product Development Oncology, F. Hoffmann-La Roche Ltd., Basel, Switzerland, [7]Multidisciplinary Oncology Center, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland

1380PD Efficacy of lorlatinib in patients (pts) with ROS1-positive advanced non-small cell lung cancer (NSCLC) and ROS1 kinase domain mutations

B.J. Solomon[1], J-F. Martini[2], S-H.I. Ou[3], R. Chiari[4], R.A. Soo[5], A. Bearz[6], S. Li[2], H. Thurm[2], C-C. Lin[7], G.J. Riely[8], T.M. Bauer[9], A.T. Shaw[10]

[1]Peter MacCallum Cancer Center, Melbourne, Australia, [2]Pfizer Oncology, La Jolla, CA, USA, [3]Chao Family Comprehensive Cancer Center, University of California at Irvine Medical Center, Irvine, CA, USA, [4]Azienda Ospedaliera di Perugia, Perugia, Italy, [5]National University Cancer Institute, Singapore, [6]National Institute for Cancer Research, Aviano, Italy, [7]National Taiwan University Hospital, Taipei, Taiwan, [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [9]Sarah Cannon Cancer Research Institute/Tennessee Oncology, Nashville, TN, USA, [10]Massachusetts General Hospital, Boston, MA, USA

1381PD Gefitinib with or without pemetrexed in nonsquamous (NS) non-small cell lung cancer (NSCLC) with EGFR mutation (mut): Final overall survival (OS) results from a randomized phase II study

J.C-H. Yang[1], Y. Cheng[2], H. Murakami[3], P-C. Yang[4], J. He[5], K. Nakagawa[6], J.H. Kang[7], J-H. Kim[8], X. Wnag[9], S. Enatsu[10], T. Puri[11], M. Orlando[12]

[1]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan, [2]Department of Thoracic Oncology, Jilin Provincial Cancer Hospital, Changchun, China, [3]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [4]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [5]Thoracic Department, The First Affiliated Hospital of Guangzhou Medical College, Guangdong, China, [6]Department of Internal Medicine, Kinki University School of Medicine, Osaka, Japan, [7]Department of Oncology, The Catholic University of Korea, Seoul, Republic of Korea, [8]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Gyeonggi-do, Republic of Korea, [9]Asia Pacific Statistical Sciences, Lilly China Drug Development and Medical Affairs Centre, Eli Lilly and Company, Shanghai, China, [10]Oncology Medicine Development Unit, Eli Lilly and Company, Kobe, Japan, [11]Medical Department, Eli Lilly and Company, Gurgaon, India, [12]Department of Oncology, Instituto Alexander Fleming, Buenos Aires, Argentina

1382PD Phase III study of gefitinib (G) versus gefitinib+carboplatin+pemetrexed (GCP) as first-line treatment for patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009)

M. Seike[1], A. Inoue[2], S. Sugawara[3], S. Morita[4], Y. Hosomi[5], S. Ikeda[6], K. Watanabe[7], K. Takahashi[8], Y. Fujita[9], T. Harada[10], K. Minato[11], K. Takamura[12], K. Kobayashi[13], T. Nukiwa[14]

[1]Department of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan, [2]Department of Palliative Medicine, Tohoku University School of Medicine, Miyagi, Japan, [3]Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan, [4]Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [5]Department of Thoracic Oncology & Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [6]Division of Respiratory Medicine, Cardiovascular & Respiratory Center, Yokohama, Japan, [7]Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan, [8]Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan, [9]Respiratory Medicine, Asahikawa Medical Center, Asahikawa, Japan, [10]Department of Pulmonary Medicine, JCHO Hokkaido Hospital, Sapporo, Japan, [11]Department of Pulmonary Medicine, Gunma Prefectural Cancer Center, Ota, Japan, [12]First Department of Medicine, Obihiro Kosei General Hospital, Obihiro, Japan, [13]Department of Pulmonary Medicine, Saitama Medical University International Medical Centre, Saitama, Japan, [14]Tohoku University, Sendai, Japan

1383PD An open-label, multicenter, phase I study of ABBV-399 (telisotuzumab vedotin, teliso-V) as monotherapy (T) and in combination with erlotinib (T+E) in non-small cell lung cancer (NSCLC)

R. Camidge[1], R.S. Heist[2], J. Goldman[3], E. Angevin[4], J. Strickler[5], D. Morgensztern[6], M. Barve[7], T.M. Bauer[8], E.E. Vokes[9], T. Yi[10], M. Motwani[10], A. Parikh[11], J. Wu[10], K. Kelly[12]

[1]Medical Oncology, University of Colorado Hospital, Aurora, CO, USA, [2]Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA, [3]Hematology & Oncology, UCLA, Santa Monica, CA, USA, [4]Medical Oncology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [5]Medical Oncology, Duke University Medical Center, Durham, NC, USA, [6]Medical Oncology, Washington University School of Medicine, St. Louis, MO, USA, [7]Oncology, Mary Crowley Cancer Research, Dallas, TX, USA, [8]Oncology, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [9]Medical Oncology, The University of Chicago Medicine, Chicago, IL, USA, [10]Oncology, AbbVie Inc., North Chicago, IL, USA, [11]Oncology, AbbVie Inc., Redwood City, CA, USA, [12]Hematology/Oncology, University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA

1384PD **Pembrolizumab in performance status 2 patients with non-small cell lung cancer (NSCLC): Results of the PePS2 trial**

G. Middleton[1], K. Brock[2], Y. Summers[3], J. Connibear[4], R. Shah[5], C. Ottensmeier[6], P. Shaw[7], S. Ming-Lee[8], S. Popat[9], C. Barrie[10], G. Barone[11], R. Mant[2], J.S. Savage[2], L. Billingham[2]

[1]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK, [2]Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, UK, [3]The Christie NHS Foundation Trust, Manchester, UK, [4]St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK, [5]Maidstone Hospital, Maidstone and Tumbridge Wells NHS Trust, Maidstone, UK, [6]Southampton General Hospital, University Hospital Southampton NHS Foundation Trust, Southampton, UK, [7]Velindre Cancer Centre, Velindre NHS Trust, Cardiff, UK, [8]University College London Hospitals NHS Foundation Trust, London, UK, [9]The Royal Marsden NHS Foundation Trust, London, UK, [10]Western General Hospital, NHS Lothian, Edinburgh, UK, [11]Lincoln County Hospital, United Lincolnshire Hospitals NHS Trust, Lincoln, UK

1385PD A randomised phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC: The ETOP and EORTC SPLENDOUR trial

S. Peters[1], S.J. Danson[2], B. Hasan[3], N. Reinmuth[4], M. Majem[5], K.G. Tournoy[6], M.T. Mark[7], M. Pless[8], M. Cobo[9], D. Rodriguez-Abreu[10], L. Falchero[11], B. Massutí[12], L. Coate[13], R. von Moos[14], C.C. Zielinski[15], E. De Maio[3], M. O'Brien[16], H. Roschitzki-Voser[17], U. Dafni[18], R.A. Stahel[19]

[1]Département d'Oncologie, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, [2]University of Sheffield, Weston Park Hospital, Sheffield, UK, [3]European Organisation for Research and Treatment of Cancer (EORTC), Headquarters, Brussels, Belgium, [4]Asklepios Kliniken GmbH, Asklepios Fachkliniken Muenchen-Gauting, Gauting, Germany, [5]Medical Oncology Department, Hospital De La Santa Creu I Sant Pau, Barcelona, Spain, [6]Onze-Lieve-Vrouw Ziekenhuis (OLV) Aalst and, Faculty of Medicine and Life Sciences, Ghent University, Ghent, Belgium, [7]Medical Oncology, Kantonsspital Graubünden, Chur, Switzerland, [8]Medical Oncology and Hematology, Kantonsspital Winterthur, Winterthur, Switzerland, [9]Oncología Médica, Hospital Regional Universitario Carlos Haya, Málaga, Spain, [10]Servicio Oncología Médica, Hospital Insular De Gran Canaria, Las Palmas, Spain, [11]Medical Oncology, Hopital Nord-Ouest Villefranche, Gleizé, France, [12]Spanish Lung Cancer Group (SLCG) and, Hospital Universitario Alicante - ISABIAL Oncologia Médica, Alicante, Spain, [13]Cancer Trials Ireland, University Hospital Limerick, Limerick, Ireland, [14]Swiss Group for Clinical Cancer Research (SAKK) and, Kantonsspital Graubünden, Chur, Switzerland, [15]Central European Cooperative Oncology Group (CECOG), Comprehensive Cancer Center, Medical University, Vienna, Austria, [16]Medical Oncology, Royal Marsden Hospital, Sutton, UK, [17]European Thoracic Oncology Platform (ETOP), Coordinating Office, Bern, Switzerland, [18]Frontier Science Foundation-Hellas and, National and Kapodistrian University of Athens, Athens, Greece, [19]Department of Haematology and Oncology, Division of Oncology, University Hospital Zürich, Zurich, Switzerland

1386PD IMpower150: Clinical safety, tolerability and immune-related adverse events in a phase III study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous NSCLC

M. Reck[1], T. Wehler[2], F. Orlandi[3], N. Nogami[4], C. Barone[5], D. Moro-Sibilot[6], M. Shtivelband[7], J.L. González Larriba[8], J. Rothenstein[9], M. Frueh[10], G. Shankar[11], A. Lee[11], Y. Deng[12], H. Patel[13], C. Kelsch[13], W. Lin[14], M.A. Socinski[15]

[1]Medical Oncology, LungenClinic Grosshansdorf, Airway Research Center North (ARCN), German Center of Lung Research, Grosshansdorf, Germany, [2]Klinik für Hämatologie, Onkologie und Palliativmedizin Evangelisches, Evangelisches Krankenhaus Hamm, Hamm, Germany, [3]Medical Oncology, Instituto Nacional del Tórax, Prosalud Oncología, Santiago, Chile, [4]Department of Thoracic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [5]Medical Oncology, Università Cattolica del Sacro Cuore, Rome, Italy, [6]Thoracic Oncology Unit SHUPP, Centre Hospitalier Universitaire de Grenoble Alpes, Grenoble, France, [7]Medical Oncology, Ironwood Cancer & Research Center, Chandler, AZ, USA, [8]Servicio de Oncologia Medica, Hospital Clinico San Carlos, Madrid, Spain, [9]Medical Oncology, Durham Regional Cancer Center, Lakeridge Health, Oshawa, ON, Canada, [10]Department of Medical Oncology/ Hematology, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland, [11]Product Development Oncology, Genentech, Inc., South San Francisco, CA, USA, [12]Biostatistics, Genentech, Inc., South San Francisco, CA, USA, [13]Safety Science, Genentech, Inc., South San Francisco, CA, USA, [14]Global Development Team, Genentech, Inc., South San Francisco, CA, USA, [15]Thoracic Oncology, Florida Hospital Cancer Institute, Orlando, FL, USA

1387P Randomized, double-blind, placebo (P)-controlled phase III non-inferiority study of darbepoetin alfa (D) for anemia in patients (pts) with advanced NSCLC: An ad hoc subgroup analysis of pts with baseline hemoglobin (Hb) ≤ 10.0 g/dL

D. Henry[1], V. Hirsh[2], K. Kubota[3], T. Steinmetz[4], G. Thomas[5], J-H. Kang[6], D. Gordon[7], S. Orlov[8], A.N. Fleishman[9], C. De Oliveira Brandao[10]

[1]Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [2]Oncology, McGill University Health Centre Royal Victoria Hospital, Montreal, QC, Canada, [3]Division of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan, [4]Hematology/Oncology, Outpatient Clinic for Hematology and Oncology, Cologne, Germany, [5]Hematology/Oncology, St Joseph's/Candler and Hilton Head Hospital Oncology, Hilton Head Island, SC, USA, [6]Oncology, The Catholic University of Korea, ST. Mary's Hospital, Seoul, Republic of Korea, [7]US Oncology Research, San Antonio, TX, USA, [8]Oncology, Pavlov Medical University, St. Petersburg, Russian Federation, [9]Biostatistics, Amgen Inc., Thousand Oaks, CA, USA, [10]Oncology, Amgen Inc., Thousand Oaks, CA, USA

Background: In the primary analysis of this study (EudraCT: 2007-005792-34), D dosed to a 12.0-g/dL Hb ceiling was noninferior to P for overall survival (OS) and progression-free survival (PFS) and superior to P for transfusion (TN) or Hb ≤ 8.0 g/dL in anemic pts with advanced NSCLC (screening Hb ≤ 11.0 g/dL).

Methods: Adults with stage IV NSCLC expected to receive ≥2 cycles of myelosuppressive chemotherapy, life expectancy >6 mo, ECOG 0–1, and Hb ≤ 11.0 g/dL were randomized 2:1 to D (500 μg SC) or P Q3W. Pts were stratified by region, histology, and Hb. This ad hoc analysis assessed key study endpoints in pts with baseline Hb ≤ 10.0 g/dL and in subgroups with Hb 9.0–10.0 and <9.0 g/dL. Primary endpoint of the parent study was OS; a Cox proportional hazards model, stratified by randomization factors, was used to evaluate noninferiority (upper confidence limit for hazard ratio [HR] <1.15). Secondary endpoints were PFS (noninferiority) and incidence of TN or Hb ≤ 8.0 g/dL from wk 5 to end of efficacy treatment period (EOETP).

Results: Of 2549 pts enrolled in the trial, 1183 had baseline Hb ≤ 10.0 g/dL (735, Hb 9.0–10.0; 448, Hb < 9.0 g/dL). Pts were well matched between arms for sex, race, and age. Among pts with Hb ≤ 10.0 g/dL, the HRs for OS and PFS were close to 1.0; results were consistent in the subgroups. Odds ratios for TN or Hb ≤ 8.0 g/dL from wk 5 to EOETP were <1.0 and were consistent in the subgroups (Table). TN was more frequent in pts with lower baseline Hb. Safety findings were consistent with previous studies; thrombovascular events were more frequent with D than P (Table).

Conclusions: The results presented here appear mostly consistent with the primary study results, but this ad hoc analysis was not powered to demonstrate noninferiority or superiority, so the results should be interpreted in that context.

Clinical trial identification: NCT00858364; July 17, 2009.

Editorial acknowledgement: The authors would also like to acknowledge James Balwit, MS, CMPP (Complete Healthcare Communications, LLC, an ICON plc company, West Chester, PA), whose work was funded by Amgen Inc., and Micah Robinson, PhD (Amgen Inc.), for assistance in writing this abstract.

Legal entity responsible for the study: Amgen Inc.

Funding: Amgen Inc.

Disclosure: D. Henry: Grants: Amgen Inc.; Consulting fees: Amag; Editor in Chief of the Journal of Community and Supportive Oncology. K. Kubota: Research grants: Boehringer Ingelheim, Ono, Taiho; Consulting fees: Taiho; Speakers' bureau: Chugai, MSD, Boehringer Ingelheim, Ono, Taiho, AstraZeneca, Eli Lilly, Kyowa Hakko Kirin,

Table: 1387P

	Hb < 9.0 g/dL		Hb 9.0–10.0 g/dL		Total	
Efficacy	D	P	D	P	D	P
OS (death), n/N (%)	220/291 (75.6)	126/157 (80.3)	370/486 (76.1)	197/249 (79.1)	590/777 (75.9)	323/406 (79.6)
$HR_{adjusted}$ (95% CI)	1.05 (0.83–1.32)		0.96 (0.80–1.15)		0.98 (0.85–1.13)	
PFS (progression or death), n/N (%)	241/285 (84.6)	141/154 (91.6)	406/468 (86.8)	222/246 (90.2)	647/753 (85.9)	363/400 (90.8)
$HR_{adjusted}$ (95% CI)	0.99 (0.79–1.24)		0.89 (0.75–1.05)		0.93 (0.81–1.06)	
TN or Hb ≤ 8.0 g/dL from week 5 to EOETP, n/N (%)	112/255 (43.9)	71/137 (51.8)	118/438 (26.9)	76/233 (32.6)	230/693 (33.2)	147/370 (39.7)
OR (95% CI)	0.66 (0.42–1.04)		0.77 (0.54–1.09)		0.75 (0.57–0.98)	
Safety	D	P	D	P	D	P
n	292	157	487	248	779	405
All treatment-emergent AEs, %	90.1	90.4	86.0	86.7	87.5	88.1
Serious AEs, %	41.8	44.6	34.1	31.5	37.0	36.5
Fatal AEs, %	15.1	14.6	14.6	13.7	14.8	14.1
AEs leading to discontinuation of blinded drug, %	2.4	5.1	3.5	3.2	3.1	4.0
Arterial embolic and thrombotic events,* %	1.7	0.6	0.6	0.4	1.0	0.5
Venous embolic and thrombotic events,* %	4.5	3.8	3.5	2.0	3.9	2.7

*Standardized MedDRA query.

AEs, adverse events; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

Novartis, Dainippon Sumitomo, Daiichi Sankyo, Eisai. T. Steinmetz: Research grants: Celgene, Novartis; Consulting fees: Amgen Inc., Bristol-Myers Squibb; Speakers' bureau: Amgen Inc., Celgene. G. Thomas: Ownership or partnership: South Carolina Cancer Specialists, P.A.; Consulting fees: Gilead Sciences, Cardinal Health, TRM Oncology, Bayer Oncology; President: South Carolina Oncology Society, 2016–2017; Employee: Hospice Care of the Lowcountry. D. Gordon: Stockholder: Amgen Inc. A.N. Fleishman, C. De Oliveira Brandao: Employee and stockholder: Amgen Inc,. All other authors have declared no conflicts of interest.

1388P Incidence of cardiac toxicities in patients with advanced non-small cell lung cancer treated with osimertinib: A combined analysis of two phase III randomized controlled trials

K.Z. Thein[1], S. Swarup[1], S. Ball[2], M. Quirch[2], Y. Vorakunthada[2], K.K. Htwe[3], N. D'Cunha[1], F. Hardwicke[1], S. Awasthi[1], L. Tijani[1]

[1]Hematology Oncology, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [2]Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [3]Internal Medicine, Kingsbrook Jewish Medical Center, Brooklyn, NY, USA

Background: Osimertinib is an oral, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). In both EGFR-TKI sensitizing and EGFR T790M resistance mutations in advanced non-small-cell lung cancer (NSCLC), osimertinib has shown to improve survival. Nevertheless, cardiac toxicities remain a safety concern. We undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the incidence of cardiac toxicities.

Methods: MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018 were queried. Phase III RCTs that mentioned cardiac failure (CF), decrease in ejection fraction (EF) and ECG QT prolongation as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) and absolute risk difference (RD) with 95% confidence interval (CI). A fixed effects model was applied.

Results: 971 patients with advanced NSCLC from two phase III RCTs were included. Studies compared osimertinib vs carboplatin/cisplatin + pemetrexed and osimertinib vs gefitinib/erlotinib. The I^2 statistic for heterogeneity was 0, and the heterogeneity X^2 (Cochran's Q) was 1 (P = 0.787), suggesting homogeneity among RCTs. The CF incidence was 21 (3.763%) in the osimertinib group vs 6 (1.453%) in control group. The RR for CF was 2.719 (95% CI: 1.094 – 6.755, P = 0.031) and RD was 0.026 (95% CI: 0.006 – 0.046, P = 0.012). The decrease in EF was noted in 16 (2.867%) in study arm vs 5 (1.211%) in control arm. The RR for decrease in EF was 2.502 (95% CI: 0.927 –6.753, P = 0.070) and RD was 0.019 (95% CI: - 0.001 – 0.037, P = 0.037). The QT prolongation was reported in 35 (6.272%) vs 12 (2.906%) in control group with the RR of 2.623 (95% CI: 1.374 –5.007, P = 0.003) and RD of 0.04 (95% CI: - 0.017 – 0.071, P = 0.002).

Conclusions: Chemotherapy-induced cardiotoxicity, a major cause of morbidity and mortality, is one of the most feared complications and affects patients' quality of life and adds financial burden. Our study showed that osimertinib notably increased the risk of cardiac toxicities with a RR of 2.71 for CF and 2.62 for QT prolongation. Prompt monitoring and early intervention is warranted.

Legal entity responsible for the study: Kyaw Zin Thein/ Texas Tech University Health Sciences Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1389P Impact of early steroids use on clinical outcomes of patients with advanced NSCLC treated with immune checkpoint inhibitors

G. Fucà, M. Poggi, G. Galli, M. Imbimbo, G. Lo Russo, D. Signorelli, M. Vitali, M. Ganzinelli, N. Zilembo, F. de Braud, M.C. Garassino, C. Proto

Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: In advanced non-small cell lung cancer (NSCLC), immune checkpoint inhibitors (ICIs) significantly improved patients (pts) prognosis, even if many factors could impair their efficacy. The impact of steroids (well below the immunosuppressant dose) on ICIs outcomes is debatable, although a quite number of pts starts immunotherapy while on, or early recurs to steroids as supportive care medications or for mild AEs. Here, we aimed at assessing the impact of early steroids use on clinical outcomes of ICIs treatment in a series of pts with advanced NSCLC.

Methods: All consecutive pts with advanced NSCLC who started ICIs at our institution from Apr 2013 to Dec 2017 were retrospectively reviewed. Pts with at least one instrumental response assessment were included. Early use of steroids was defined as the use of a daily prednisone-equivalent dose ≥ 10 mg for at least 1 day within 28 days from ICIs initiation. Chi-square test or Fisher's exact test were used to analyze the association of early use of steroids with pts' characteristics. The Kaplan-Meier method and the Cox proportional-hazards model were used for survival analyses.

Results: Out of 151 pts included, 35 (23 %) made early use of steroids. Most of the pts (96%) received single agent anti PD-1/PD-L1, while 6 pts (4%) received combinatorial PD-L1+CTLA-4 blockade. Early use of steroids was negatively associated with disease control (OR 0,32; 95% CI 0.14-0.71, P = .006) and positively associated with ≥2 metastatic sites (OR 3,08, 95% CI 1.33-7.89; P = .01) and ECOG PS ^{3} 2 (OR 4.57; 95% CI 1.10-20.37; P = .03). With a median follow-up of 32.7 months, early use of steroids conferred a worse median progression-free survival (PFS) (1.98 vs 3.94 months; HR 1.80; 95% CI 1.20-2.80; P = .003). In the multivariable model including other covariates significantly associated with PFS (i.e. ECOG PS and PD-L1 status), the early use of steroids was confirmed to be independently associated with poorer PFS (HR 1.88; 95% CI 1.08-3.28; P = .03).

Conclusions: We found that the early use of steroids independently affects clinical outcomes in patients with advanced NSCLC treated with ICIs. If these findings will be further validated, such use in this setting should be carefully evaluated and avoided when not strictly needed.

Legal entity responsible for the study: Giovanni Fucà.

Funding: Has not received any funding.

Disclosure: D. Signorelli: Consultancies: AstraZeneca, Boehringer Ingelheim, BMS. M.C. Garassino: Consultancies: MSD, BMS, AstraZeneca, Eli Lilly. C. Proto: Consultancies: MSD, BMS. All other authors have declared no conflicts of interest.

1390P Dose modification and therapy interruption due to adverse events in treatment with anlotinib for refractory advanced NSCLC: Data from ALTER0303

L. Zhang[1], X. Si[1], H. Wang[1], X. Zhang[1], M. Wang[1], B. Han[2], K. Li[3], Q. Wang[4], J. Shi[5], Z. Wang[6], Y. Cheng[7], J. He[8], Y. Shi[9], W. Chen[10], X. Wang[11], Y. Luo[12], K. Nan[13], F. Jin[14], B. Li[15], Y. Chen[16]

[1]Oncology, Peking Union Medical College Hospital, Beijing, China, [2]Oncology, Shanghai Chest Hospital, Shanghai, China, [3]Oncology, Tianjin Medical University Cancer Hospital, Tianjin, China, [4]Department of Internal Medicine, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China, [5]Oncology, Linyi City Tumor Hospital, Linyi, China, [6]Oncology, Shandong Province Tumor Hospital, Jinan, China, [7]Oncology, Jilin Province Tumor Hospital, Changchun, China, [8]Oncology, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, [9]Oncology, Chinese Academy of Medical Sciences Cancer Hospital, Beijing, China, [10]Oncology, Lanzhou Military General Hospital, Lanzhou, China, [11]Qilu Hospital, Shandong University, Jinan, China, [12]Oncology, Hunan Province Tumor Hospital, Changsha, China, [13]Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University (School of Medicine), Xi'an, China, [14]Oncology, Tangdu Hospital, Xi'an, China, [15]Oncology, Beijing Chest Hospital, Capital Medical University, Beijing, China, [16]Oncology, Jiangxi Province Tumor Hospital, Nanchang, China

Background: Anlotinib is an oral tyrosine kinase inhibitor targeting VEGFR, FGFR, PDGFR and c-kit. Anlotinib showed significantly improvement in overall survival in ALTER0303 trial for refractory NSCLC, a randomized, double-blind, placebo-controlled phase III trial in China. This study reported the tolerance of anlotinib in the ALTER0303.

Methods: The adverse events (AEs), dose modification, and therapy interruption were collected from anlotinib group (n = 294) and placebo group (n = 143) that were enrolled in ALTER0303. AEs were graded using Common Terminology Criteria.

Results: The anlotinb related grade ≥3 AEs reported in ≥ 1% patients were hypertension (13.3%), hyponatremia (4.8%), hand-foot syndrome (HFS) (3.7%), hemoptysis (3.1%), GGT elevation (2.7%), hypertriglyceridemia (2.4%), QT interval prolongation (2.4%), lipase elevation (2.4%), proteinuria (2.4%), oral mucositis (1.0%), diarrhea (1.0%), and hyperbilirubinemia (1.0%). Grade ≥3 hypertension, HFS, and hypertriglyceridemia were significantly more frequent in the anlotinib group than in the control group. Dose reduction and drug interruption were required in 24 (8.16%) (Table) and 31 (10.54%) patients in anlotinib group, respectively. The most common anlotinib-related AEs causing interruption were hemoptysis (2.3%), venous thromboembolism (1.0%), proteinuria (0.7%), interstitial lung disease (0.7%), and pneumothorax (0.7%).

Table: 1390P Dose modification due to anlotinib-related adverse events

Adverse events	No. (%)	Dose modification
Hand-foot syndrome	7 (2.3)	12mg→10mg
Hypertension	3 (1.0)	12mg→10mg
Hypertriglyceridemia	2 (<1)	12mg→10mg
Diarrhea	1 (<1) 1 (<1)	12mg→10mg 12mg→10mg→8mg
Liver dysfunction	1 (<1) 1 (<1)	12mg→10mg 12mg→10mg→8mg
Anorexia	2 (<1)	12mg→10mg
Oral mucositis	2 (<1)	12mg→10mg
Arrhythmia	2 (<1)	12mg→10mg
Fatigue	1 (<1)	12mg→10mg
Dyspnea	1 (<1)	12mg→10mg

Conclusions: It was important to manage hand-foot syndrome, hypertension, diarrhea and hemoptysis, so that patients could benefit from anlotinib.

Clinical trial identification: NCT02388919.

Legal entity responsible for the study: Chia Tai Tianqing Pharmaceutical Group Co., LTD.
Funding: Chia Tai Tianqing Pharmaceutical Group Co., LTD.
Disclosure: All authors have declared no conflicts of interest.

1391P Immune-related adverse events (irAEs) and survival (OS) in metastatic non-small cell lung cancer (mNSCLC) patients (pts) treated with immunotherapy

M. Meliàn Sosa, C. Puchades, J.A. Mendez, A. Torres, C. Rodrigo, G. Gimeno, E. Rama, A. Martínez-Castillo, J. Caballero Daroqui, J. Gomez Codina, O. Juan-Vidal, D. Lorente
Medical Oncology, Hospital Universitari i Politècnic La Fe, Valencia, Spain

Background: Immunotherapy represents a new standard of care in first and second line treatment of advanced NSCLC. Immune related adverse events (irAEs) have been proposed as an indicator of treatment efficacy.

Methods: Retrospective analysis of mNSCLC patients treated with anti-PD/anti-PDL1 with or without anti-CTLA4 therapy. Electronic patient records were reviewed; irAEs were identified and graded according to CTC AE v4.03 criteria. The association with survival was evaluated in uni- (UV) and multivariable (MV) Cox-regression models.

Results: 64 pts were identified; 41 (64.1%) were adenocarcinomas and 27 (42.2%) received immunotherapy in first-line. 44 pts (68.8%) received antiPD1/PDL1 monotherapy, and 20 pts (31.2%) received antiPDL1 + antiCTLA4. 15 pts (25%) developed irAEs: gastrointestinal (17.6%), endocrine (11.8%), cutaneous (17.6%), other (33.3%). Treatment was interrupted in 8 (53.3%) and suspended in 5 (33.3%) pts. 7 (50%) pts received high dose corticosteroids. No toxic deaths occurred. iRAEs were not significantly increased in pts receiving combination therapy (30% vs 20%, p = 0.377). Median OS was 6.5 m (95%CI: 0.24-12.7). Pts experiencing irAEs had a significantly higher OS (HR: 0.2; 95%CI: 0.07-0.58; p = 0.003) in UV analysis, and was independent of other prognostic factors in MV analysis (Table).

Table: 1391P MV Cox-regression survival model

Factor	HR (95%CI)	p-value
irAE (yes vs no)	0.18 (0.06 – 0.53)	0.002
Histology	1.11 (0.99 – 1.24)	0.061
ECOG PS	0.82 (0.42 – 1.59)	0.551
Treatment line (first line vs second or further)	1.06 (0.52 – 2.18)	0.868
Treatment type (monotherapy vs combination)	2.25 (1.02 – 4.99)	0.045

Conclusions: The development of irAEs may identify pts with a higher likelihood of benefitting from immunotherapy in NSCLC. These findings will require prospective validation in well-designed clinical trials.

Legal entity responsible for the study: Instituto Investigación Sanitaria La Fe.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1392P Dose-determination results from a phase Ib/II study of ceritinib (CER) + ribociclib (RIB) in ALK-positive (ALK+) non-small cell lung cancer (NSCLC)

A. Santoro[1], W-C. Su[2], A. Navarro[3], M. Simonelli[4], J.C-H. Yang[5], A. Ardizzoni[6], F. Barlesi[7], J.H. Kang[8], S. Didominick[9], A. Abdelhady[10], B. Goswami[10], A. Crystal[9], E. Felip[3]
[1]Humanitas University and Humanitas Cancer Center, Milan, Italy, [2]National Cheng Kung University Hospital, Tainan, Taiwan, [3]Vall d'Hebron University Hospital, Barcelona, Spain, [4]Department of Biomedical Sciences, Humanitas University and Humanitas Cancer Center, Milan, (MI), Italy, [5]National Taiwan University Hospital, Taipei, Taiwan, [6]University Hospital Bologna, Bologna, Italy, [7]Aix-Marseille University, Assistance Publique Hopitaux de Marseille, Marseille, France, [8]Catholic University of Korea, Seoul, Republic of Korea, [9]Oncology, Novartis Pharmaceutical Corporations, Cambridge, MA, USA, [10]Oncology, Novartis Pharmaceutical Corporations, Hyderabad, India

Background: Preclinical data suggest cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) may improve ALK inhibitor (ALKi) efficacy in ALK+ NSCLC. A Phase Ib/II study (NCT02292550) is assessing CER (ALKi) + RIB (CDK4/6i) in patients (pts) with ALK+ NSCLC; here we report data from the Phase Ib dose-escalation.

Methods: Pts with Stage IIIB/IV ALK+ NSCLC (≥1 prior therapy for advanced NSCLC; no prior CDK4/6i) received escalating doses of CER (starting dose 300 mg once daily [QD]; continuous [cont]) + RIB (starting dose 100 mg QD; 3 weeks [wks] on/1 wk off) under fed conditions. Primary objective: maximum tolerated dose/recommended Phase II dose (RP2D); secondary objectives: safety, pharmacokinetics, and efficacy.

Results: As of Jan 8, 2018, 27 pts were enrolled into 5 dose cohorts (Table); 8 were ALKi naive, 14 had prior crizotinib; 5 had prior 3rd-generation (gen) ALKi. Treatment was ongoing in n = 4; the most common reason for discontinuation was disease progression (n/n; 10/27). One dose-limiting toxicity occurred (CER 450 mg + RIB 100 mg; Grade [G] 2 increased blood creatinine for ≥7 consecutive days); RP2D was CER 300 mg QD (cont) + RIB 200 mg QD (3 wks on/1 wk off). At steady state, CER and RIB exposure (AUC_{0-24h}) each increased by ~1.5–2 fold compared with CER and RIB single-agent exposures under fasting conditions, with considerable variability in the setting of limited pt numbers. G3/4 treatment-related adverse events occurred in 15 pts; the most common (≥10% of pts) were decreased neutrophil count, increased ALT, and

Table: 1392P

	CER 300 mg + RIB 100 mg	CER 450 mg + RIB 100 mg	CER 300 mg + RIB 200 mg	CER 450 mg + RIB 200 mg	CER 450 mg + RIB 300 mg	All
Enrolled (n)	4	7	4	7	5	27
Prior antineoplastic therapy, n (%)						
ALKi naive	3 (75.0)	2 (28.6)	1 (25.0)	1 (14.3)	1 (20.0)	8 (29.6)
Prior crizotinib‡	1 (25.0)	4 (57.1)	2 (50.0)	5 (71.4)	2 (40.0)	14 (51.9)
Prior 3rd-gen ALKi§	0	1 (14.3)	1 (25.0)	1 (14.3)	2 (40.0)	5 (18.5)
Treatment ongoing, n (%)	2 (50.0)	1 (14.3)	1 (25.0)	0	0	4 (14.8)
Discontinuation due to disease progression, n (%)	2 (50.0)	1 (14.3)	1 (25.0)	3 (42.9)	3 (60.0)	10 (37.0)
Most common Grade 3/4 treatment-related adverse events (≥10% of all pts), n (%)						
All	2 (50.0)	5 (71.4)	1 (25.0)	4 (57.1)	3 (60.0)	15 (55.6)
Decreased neutrophil count	0	1 (14.3)	0	2 (28.6)	3 (60.0)	6 (22.2)
Increased ALT	0	2 (28.6)	0	2 (28.6)	0	4 (14.8)
Increased AST	0	2 (28.6)	0	2 (28.6)	0	4 (14.8)
Best overall response, n (%)						
Complete response	1 (25.0)	0	0	0	0	1 (3.7)
Partial response	1 (25.0)	4 (57.1)	2 (50.0)	3 (42.9)	2 (40.0)	12 (44.4)
Stable disease	2 (50.0)	2 (28.6)	1 (25.0)	2 (28.6)	2 (40.0)	9 (33.3)
Progressive disease	0	0	0	0	1 (20.0)	1 (3.7)
Unknown*	0	1 (14.3)	1 (25.0)	2 (28.6)	0	4 (14.8)
ORR,‖ n (%) [90% CI]	2 (50.0) [0.10–0.90]	4 (57.1) [0.22–0.87]	2 (50.0) [0.10–0.90]	3 (42.9) [0.13–0.77]	2 (40.0) [0.08–0.81]	13 (48.1) [0.31–0.65]

*These 4 pts discontinued study treatment prior to completing their first tumor evaluation;
‡Pts received prior crizotinib only;
§Pts received prior 3rd-gen ALKi only (n = 2) or prior 3rd-gen ALKi and crizotinib (n = 3); ‖ORR = complete response + partial response.

increased AST. Efficacy data are shown in the table. ORR (n/n; 90% CI) was 50% (4/8; 0.19–0.80) in ALKi-naive pts; 64% (9/14; 0.39–0.84) in pts with prior crizotinib; 0% (0/5; 0.00–0.45) in pts with prior 3rd-gen ALKi.

Conclusions: RP2D was CER 300 mg QD (cont) + RIB 200 mg QD (3 wks on/1 wk off) in pts with Stage IIIB/IV ALK+ NSCLC. CER + RIB showed a manageable safety profile and preliminary efficacy, including in pts with prior ALKi exposure.

Clinical trial identification: NCT02292550 and November 17, 2014.

Editorial acknowledgement: Editorial assistance was provided by Bhavika Modasia PhD of ArticulateScience Ltd.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: A. Santoro: Advisory board member: Bayer, Takeda, Lilly, Amgen, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Novartis, Roche, Servier, Eisai; Consulting fees: ArQule. J.C-H. Yang: Personal fees: Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech, Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono Pharmaceuticals, Daiichi Sankyo, AstraZeneca, Hansoh Pharmaceuticals, outside the submitted work. A. Ardizzoni: Grants and personal fees: BMS; Personal fees: MSD, Eli Lilly, Boehringer Ingelheim, Pfizer; Grants: Celgene, outside the submitted work. F. Barlesi: Support for the trial: Novartis, during the conduct of the study; Personal fees: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer, Takeda, outside the submitted work. S. Didominick, A. Abdelhady, B. Goswami, A. Crystal: Employee: Novartis, during the conduct of the study. E. Felip: Consultancy/advisory board: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb Celgene, Eli Lilly, Guardant Health, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Merck, outside the submitted work. All other authors have declared no conflicts of interest.

1393P Safety profile and effectiveness of alectinib in the real-world surveillance study of 1251 Japanese patients with ALK-positive non-small cell lung cancer

Y. Ohe[1], N. Yamamoto[2], A. Gemma[3], M. Kusumoto[4], I. Yamada[5], T. Ishii[6], N. Masuda[7]

[1]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan, [2]Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan, [3]Division of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan, [4]Department of Diagnostic Radiology, National Cancer Center Hospital East, Kashiwa, Japan, [5]Department of Pharmacovigilance, Chugai Pharmaceutical Co.,Ltd., Chuo-Ku, Tokyo, Japan, [6]Department of Real World Data Science, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, [7]Division of Clinical Research Center, Izumi City General Hospital, Osaka, Japan

Background: Alectinib is a CNS penetrant and highly selective ALK inhibitor. The Japanese Risk Management Plan based on the phase I/II studies highlighted interstitial lung disease (ILD), liver function disorder, decreased neutrophil cell and white blood cell counts as identified risk in Japanese patients (pts). To investigate the safety and effectiveness of alectinib, including adverse drug reactions (ADR) of particular concern in the real world setting, a large scale surveillance funded by Chugai Pharmaceuticals has been implemented. This study is registered with the UMIN, number UMIN000014989.

Methods: From Sep 2014 to June 2015 all pts with ALK-positive recurrent/advanced NSCLC treated with alectinib, were enrolled in the study. The observation period was 18 months, ADR were collected. Overall survival (OS) was also assessed.

Results: By Jun 2015, a total of 1251 pts were registered. We analysed 1221 pts as the safety population. Baseline characteristics included: female (54% of population), median age (62 years), ECOG PS 3-4 (n = 89) (7%), pts who received first line (18%), second line (32%) or third line or more (50%) treatments, pts who received crizotinib (63%), brain metastases (41%). The overall incidence of ADRs was 53.6% (mostly grade 1/2), the most common were laboratory tests abnormality (27.7%). ILD events were reported in 47 pts (3.8% of population), including grade 3 events in 8 pts and grade 4 events in 1 pt, in which the rate of recovery or improvement was 92%. Events of liver function disorder were reported in 242 pts (19.8%), including grade 3 events in 24 pts, and events of neutrophil cell and white blood cell decrease were reported in 93 pts (7.6%), including grade 3 events in 12 pts and grade 4 events in 2 pts, in which the rates of recovery or improvement were 83% and 93%, respectively. Median OS was not reached. Overall survival rate at 12 months and 18 months were 82.4% and 76.2%, respectively.

Conclusions: These final data from this study in Japanese ALK-positive NSCLC pts provide an acceptable safety and effectiveness profile in the real-world setting. Alectinib was primarily one of the effective therapies for the treatment of ALK-positive NSCLC.

Legal entity responsible for the study: Chugai Pharmaceutical CO., LTD.

Funding: Chugai Pharmaceutical CO., LTD.

Disclosure: Y. Ohe: Consuting or advisory role, honoraria: Chugai Pharm Co., Ltd.; Research funding to institution: Chugai Pharm Co., Ltd. N. Yamamoto: Consuting or advisory role, speakers' bureau, honoraria: Chugai Pharm Co., Ltd. Research funding to instution: Chugai Pharm Co., Ltd. A. Gemma, M. Kusumoto, N. Masuda: Consuting or advisory role: Chugai Pharm CO., LTD. I. Yamada, T. Ishii: Employment: Chugai Pharm Co., Ltd.

1394P A multicenter study of mutational profiling of Chinese ALK+ non-small cell lung cancer patients with acquired resistance to crizotinib using next generation sequencing

C. Xu[1], W. Wang[2], W. Zhuang[3], Z. Song[2], Y. Zhu[4], G. Chen[1], M. Fang[2], T. Lv[5], Y. Song[5]

[1]Pathology, Fujian Cancer Hospital, Fuzhou, China, [2]Chemotherapy, Zhejiang Cancer Hospital, Hangzhou, China, [3]Medical Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China, [4]Thoracic Disease Center, Zhejiang Rongjun Hospital, Jiaxing, China, [5]Respiratory Medicine, Jinling Hospital, Nanjing, China

Background: Anaplastic lymphoma kinase (ALK) rearrangements define a distinct molecular subtype of non-small cell lung cancer. Recently, the therapeutic landscape for advanced ALK+ NSCLC has been transformed by the development of increasingly potent and selective ALK inhibitors. Crizotinib was the first ALK inhibitor to enter clinical development. The mechanism of acquired resistance to crizotinib for the patients with ALK+ NSCLC is not yet fully identified. In this study, we performed mutational profiling in a cohort of 42 ALK+NSCLC patients at diagnosis and following acquired resistance to crizotinib using targeted NGS.

Methods: A total of 42 patients with stage IIIb-IV ALK+ NSCLC underwent tumor biopsies or blood withdrawal by the time of acquiring resistance to crizotinib, including 19 formalin-fixed paraffin-embedded (FFPE) samples, 12 serum samples and 11 serous effusions. We used targeted NGS to detect the gene status of patients.

Results: In total, we identified 92 genetic alterations with a median of 2.2 mutations per patient. 83% of patients still exhibit fusions, and 29% of patients acquired ALK point mutations. Besides other known resistance mechanisms, we identified KRAS mutations in 14% of patients, and EGFR mutations in 12%. Interestingly, we also observed IGF1R, GPR133, CDH18and HSD17B3 mutations in ALK point mutation-negative patients, which were restricted to crizotinib resistance.

Conclusions: Our study uncovered mutational profiles of ALK+NSCLC patients with crizotinib resistance with potential therapeutic implications, and this study also comprehensively depicted the genetic landscape in a Chinese ALK+NSCLC population resistant to crizotinib. Our analysis demonstrates new perspectives for further study of resistance and suggests corresponding relevant tactics against the challenge of disease progression.

Legal entity responsible for the study: Chunwei Xu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1395P Lung cancers carrying distinct ALK fusion variants demonstrate similar responsiveness to ALK tyrosine kinase inhibitors

E.N. Imyanitov[1], N.V. Mitiushkina[1], V.I. Tiurin[1], A.G. Iyevleva[1], M. Holmatov[1], E. Filippova[2], F. Moiseyenko[3], N. Levchenko[4], S. Odintsova[2], A. Lozhkina[2], A.V. Togo[1], N. Karaseva[5], V.M. Moiseyenko[3], S. Orlov[2]

[1]Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, St. Petersburg, Russian Federation, [2]Department of Oncology, Pavlov State Medical University, St. Petersburg, Russian Federation, [3]Department of Chemotherapy, St. Petersburg City Cancer Center, St. Petersburg, Russian Federation, [4]Department of Thoracic Oncology, N.N. Petrov Institute of Oncology, St. Petersburg, Russian Federation, [5]Department fo Thoracic Oncology, City Clinical Oncology Dispensary, St. Petersburg, Russian Federation

Background: Multiple laboratory evidences indicate that distinct variants of ALK translocations differ in their biochemical properties and responsiveness to ALK tyrosine kinase inhibitors (TKI). These data are supported by some Asian clinical studies, which showed improved responses to crizotinib in non-small cell lung cancer (NSCLC) patients carrying particular variants of ALK translocation.

Methods: This study retrospectively considered 64 Russian patients with ALK-rearranged NSCLC, who were treated by crizotinib (n = 23), ceritinib (n = 39) or alectinib (n = 2). ALK fusion variants were genotyped by PCR.

Results: Median progression-free survival (PFS) approached to 18 and 21 months in subjects with "short" (v.3a/b, v.5a/b) vs. "long" (TAPE-domain containing) fusion variants (p = 0.783), respectively; similar data were obtained while comparing EML4/ALK variant 1 vs. other ALK translocations (19 and 21 months, respectively; p = 0.604). Objective response rates were also strikingly similar in the above groups ("short": 88%, "long": 77%, p = 0.479; variant 1: 76%, other translocations: 81%, p = 0.753). Furthermore, ALK variants did not influence the disease outcomes when patients treated by crizotinib and ceritinib were analyzed separately. Overall, PFS on ALK TKI did not depend on whether the drug was administered upfront or after chemotherapy. Ceritinib produced significantly longer PFS than crizotinib (p = 0.022).

Conclusions: This is the first non-Asian study evaluating the relationship between ALK fusion variants and response to ALK TKI. Although being larger in size as compared to published data sets, it failed to confirm the role of the type of ALK translocation in determining the treatment outcome.

Legal entity responsible for the study: Evgeny Imyanitov.

Funding: This study has been supported by the Russian Scientific Fund.

Disclosure: All authors have declared no conflicts of interest.

1396P Efficacy and safety of crizotinib in previously treated patients (Pts) with ALK+ advanced non-small cell lung cancer (NSCLC) aged ≥65 years (y)

D. Moro-Sibilot[1], M-J. Ahn[2], B. Halmos[3], D-W. Kim[4], G.J. Riely[5], A.T. Shaw[6], P-C. Yang[7], S. Lanzalone[8], A. Polli[8], K.D. Wilner[9], J. De Castro Carpeño[10]

[1]Pneumologie, CHU Grenoble-Alpes, Grenoble, France, [2]Samsung Medical Center, Seoul, Republic of Korea, [3]Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY, USA, [4]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [6]Massachusetts General Hospital, Boston, MA, USA, [7]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [8]Pfizer Oncology, Milan, Italy, [9]Pfizer Oncology, La Jolla, CA, USA, [10]Medical Oncology Service, Hospital Universitario La Paz, Madrid, Spain

Background: Crizotinib is an oral tyrosine kinase inhibitor (TKI) approved for treatment of ALK+ advanced NSCLC. We report efficacy and safety from subgroups of pts aged ≥65 y included in PROFILE 1005, the largest clinical trial to date of an ALK TKI in ALK+ NSCLC.

Methods: PROFILE 1005 (NCT00932451) was a multicenter, single-arm phase 2 trial of crizotinib (250 mg twice daily; continuously) in pts with ALK+ NSCLC who had failed ≥1 line of systemic treatment for advanced/metastatic disease. Co-primary endpoints were objective response rate (ORR) per RECIST v1.1 and adverse events (AEs). Other efficacy endpoints included duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

Results: Of 1066 treated pts, 93 (54 female/39 male) and 79 pts (49 female/30 male) were aged 65–70 y and >70 y, respectively, at baseline (overall safety population). 908 out of 1066 pts, including 74 pts in the 65–70 y subgroup and 57 in the >70 y subgroup, were ALK+ by central FISH testing; all were evaluable for response. The table shows investigator-assessed efficacy endpoints for these pts. Most common TRAEs in the 65–70 (n = 93) and >70 y (n = 79) subgroups, respectively, were vision disorder (54.8% & 45.6%), nausea (50.5% & 57.0%), edema (43.0% & 57.0%), vomiting (41.9% & 51.9%) and diarrhea (39.8 % & 48.1%), mostly Grade 1/2, comparable to the safety profile of the overall safety population (n = 1066), but with some higher frequencies seen in the >70 y subgroup. In the 65–70 y and >70 y subgroups, respectively, 24.7% and 27.8% of pts had TRAEs leading to dose reductions (overall safety population, 18.3%), and 9.7% and 13.9% had TRAEs requiring permanent treatment discontinuation (overall safety population, 5.6%).

Conclusions: Efficacy and safety profiles in ALK+ NSCLC pts aged 65–70 or > 70 y were comparable to those previously reported for PROFILE 1005, with some TRAEs occurring at higher frequencies in pts >70 y.

Editorial acknowledgement: Medical writing support was provided by Jade Drummond and Brian Szente of inScience Communications, Springer Healthcare (Chester, UK and Philadelphia, PA, US), and was funded by Pfizer.

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer.

Disclosure: D. Moro-Sibilot: Membership of an advisory board or board of directors: MSD, BMS, Takeda, Roche, AstraZeneca, Ariad, Abbvie, Novartis, Pfizer, Lilly, Boehringer Ingelheim; Corporate sponsored research: Pfizer, Boehringer Ingelheim. M-J. Ahn: Membership of an advisory board or board of directors: AstraZeneca, Lilly, Lyzz. B. Halmos: Membership of an advisory board or board of directors: Pfizer, Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, Genentech, Ignyta; Corporate sponsored research: Merck, Pfizer, Mirati, Boehringer Ingelheim, AstraZeneca, Takeda, Novartis, Eli Lilly; Other: Foundation Medicine, Guardant Health 360, Eli Lilly, Merck. G.J. Riely: Speakers or advisory board: Genetech; Grant/research support: Novartis, Roche/Genetech, Millenium, GlaxoSmithKline, Pfizer, Infinity Pharmaceuticals, Ariad. A.T. Shaw: Membership of an advisory board or board of directors: Blueprint Medicines, KSQ Therapeutics; Consulting or honoraria: Pfizer, Novartis, Genentech, Roche, Takeda, Ariad, Ignyta, Loxo, Blueprint, Natera, Foundation Medicine, EMD Serono. S. Lanzalone, A. Polli, K.D. Wilner: Stock ownership and employment: Pfizer. J. De Castro Carpeño: Advisory board: Roche, Takeda, Pfizer. All other authors have declared no conflicts of interest.

1397P Long-term safety of crizotinib in previously treated patients (pts) with ALK-positive advanced/metastatic non-small cell lung cancer (NSCLC)

L. Crinò[1], M-J. Ahn[2], J-Y. Han[3], X. Liu[4], S-H.I. Ou[5], A.T. Shaw[6], P-C. Yang[7], Y-K. Shi[8], S. Lanzalone[9], A. Polli[9], K.D. Wilner[10], D-W. Kim[11]

[1]Medical Oncology Unit, Istituto Scientifico Romagnolo Per Lo Studio E La Cura Dei Tumori (IRST)- IRCCS, Meldola, Italy, [2]Samsung Medical Center, Seoul, Republic of Korea, [3]Center for Lung Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea, [4]The 307 Hospital of Chinese People's Liberation Army, Beijing, China, [5]University of California Irvine, Irvine, CA, USA, [6]Massachusetts General Hospital, Boston, MA, USA, [7]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [8]National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [9]Pfizer Oncology, Milan, Italy, [10]Pfizer Oncology, La Jolla, CA, USA, [11]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Background: The oral tyrosine kinase inhibitor (TKI) crizotinib is approved for the treatment of pts with anaplastic lymphoma kinase (ALK)+ advanced NSCLC. Here we report safety results for pts who were treated with crizotinib for longer than 1 year (y) in PROFILE 1005, the largest clinical trial to date of an ALK TKI in ALK+ advanced NSCLC.

Methods: The PROFILE 1005 study (NCT00932451) was a single-arm phase 2 trial of crizotinib (250 mg twice daily; continuously) conducted at multiple centers. The study enrolled pts with ALK+ NSCLC who had failed ≥1 line of systemic treatment for locally advanced/metastatic disease. The co-primary endpoints were safety and objective response rate.

Results: A total of 1066 pts were treated; 240 and 248 pts were treated for 1–2 y and >2 y, respectively. Treatment-related adverse events (TRAEs) are summarized by treatment duration subgroup in the table. Most common TRAEs of any grade in the 1–2 y and >2 y subgroups, respectively, were vision disorder (65.8% and 69.4%), nausea (57.5% and 58.1%), diarrhea (54.2% and 61.3%), vomiting (49.6% and 46.4%) and edema (47.1% and 60.1%). The most common grade 3/4 TRAE in both subgroups was neutropenia (17.1% and 23.0%). Two grade 5 TRAEs (interstitial lung disease [n = 1] and cardiac arrest [n = 1; for which other factors could not be excluded]) were reported in the >2 y subgroup; no grade 5 TRAEs were reported in the 1–2 y subgroup. Selected TRAEs of interest based on prior experience with crizotinib included the following, reported in the 1–2 y and >2 y subgroups, respectively: elevated transaminases (35.4% and 37.1%), hepatotoxicity (1.3% and 1.2%), interstitial lung disease (2.1% and 2.4%), ECG QT prolonged (2.5% and 4.8%), bradycardia (13.3% and 16.5%), and renal cysts (2.1% and 7.7%).

Table: 1397P

n (%)	Treatment duration subgroup		
	1–2 y (n = 240)	>2y (n = 248)	Overall (n = 1066)
Pts with TRAEs	239 (99.6)	247 (99.6)	1022 (95.9)
Pts with serious TRAEs	23 (9.6)	34 (13.7)	119 (11.2)
Pts with grade 3 or 4 TRAEs	104 (43.3)	114 (46.0)	425 (39.9)
Pts with temporary discontinuation due to TRAEs	87 (36.3)	103 (41.5)	332 (31.1)
Pts with dose reductions due to TRAEs	54 (22.5)	56 (22.6)	195 (18.3)
Pts permanently discontinued treatment due to TRAEs	2 (0.8)	4 (1.6)	60 (5.6)

Table: 1396P

	Patients With ALK+ NSCLC by Central FISH Testing		
	65–70 y (n = 74)	>70 y (n = 57)	PROFILE 1005 Total (n = 908)
Mean age, years (range)	67 (65–70)	76 (71–84)	52 (19–84)
ORR, % (95% CI)[a]	54.1 (42.1, 65.7)	47.4 (34.0, 61.0)	54.1 (50.8, 57.4)
Median DOR (Kaplan–Meier), months (95% CI)[a]	11.4 (8.3, 16.6)	12.4 (9.6, 14.1)	11.8 (10.4, 12.8)
Median PFS (Kaplan–Meier), months (95% CI)[b]	9.6 (5.5, 16.8)	11.6 (6.9, 15.1)	8.4 (7.1, 9.7)
Median PFS (Kaplan–Meier), months (95% CI)[b]	23.2 (17.6, 31.2)	17.0 (12.2, 22.4)	21.8 (19.4, 24.0)

[a]Calculated using the exact method based on the F distribution

[b]Based on Brookmeyer and Crowley method

Conclusions: No new major safety signals were observed. The long-term safety profile was consistent with the known safety profile of crizotinib.

Editorial acknowledgement: Medical writing support was provided by Jade Drummond and Brian Szente of inScience Communications, Springer Healthcare (Chester, UK and Philadelphia, PA, US), and was funded by Pfizer.

Legal entity responsible for the study: Pfizer, Inc.

Funding: Pfizer.

Disclosure: M-J. Ahn: Membership of an advisory board or board of directors: AstraZeneca, Lilly, Lyzz. S-H.I. Ou: Membership of an advisory board or board of directors: TP Therapeutics; Corporate sponsored research: Pfizer, AstraZeneca, Roche/Genentech, Takeda/Ariad, Ignyta, TP Therapeutics, BluePrint Medicines; Honorarium: Pfizer, Roche/Genentech, AstraZeneca, Takeda/Ariad. A.T. Shaw: Membership of an advisory board or board of directors: Blueprint Medicines, KSQ Therapeutics; Consulting or honoraria: Pfizer, Novartis, Genentech, Roche, Takeda, Ariad, Ignyta, Loxo, Blueprint, Natera, Foundation Medicine, EMD Serono. S. Lanzalone, A. Polli, K.D. Wilner: Stock ownership and employment: Pfizer. All other authors have declared no conflicts of interest.

1398P Real-world progression-free survival of patients on anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) for ALK+ non-small cell lung cancer (NSCLC)

M. Jahanzeb[1], H.M. Lin[2], X. Pan[2], Y. Yin[3], P. Hou[3], B.L. Nordstrom[4], A. Desai[5], M.A. Socinski[6]

[1]Sylvester Comprehensive Cancer Center, University of Miami, Deerfield Beach, FL, USA, [2]Global Outcomes Research, Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, [3]Safety and Observational Statistics, Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, [4]Real World Evidence, Evidera, Waltham, MA, USA, [5]Global Medical Affairs, Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, [6]Florida Hospital Cancer Institute, Orlando, FL, USA

Background: Patients with NSCLC characterized by ALK rearrangements may benefit from ALK TKI therapies. Although ALK TKIs have shown improved efficacy relative to conventional chemotherapy, the prognosis for patients with ALK+ NSCLC remains suboptimal. The present study uses real-world evidence to examine progression-free survival (PFS) among patients with ALK+ NSCLC treated with an ALK TKI.

Methods: Patients with advanced ALK+ NSCLC diagnosed and treated with an ALK TKI in 2011-2017 were identified from the Flatiron Health Electronic Health Record (EHR)-derived database. Real-world PFS (rwPFS) was estimated as the time from treatment line start to progression or death, where progression was abstracted from clinician notes and radiology/pathology reports by trained medical reviewers. Analyses examined rwPFS following the patient's first line containing ALK TKI. For patients who received crizotinib as their first TKI followed by a second ALK TKI, a similar analysis examined rwPFS following their second ALK TKI line. Data were censored at end of follow-up for patients without progression or death. The median and 95% confidence interval (CI) of rwPFS following first and second ALK TKI were obtained from Kaplan-Meier methods.

Results: Of 409 ALK TKI-treated patients with advanced ALK+ NSCLC, mean age was 60.4 years and 51.6% were female. Most patients (n = 379; 92.7%) received crizotinib as their first ALK TKI; of these, 180 (47.5%) were later treated with a second ALK TKI (e.g. ceritinib, alectinib). Median (95% CI) rwPFS was 7.5 (6.6-8.6) months following first ALK TKI; and 6.4 (5.2-8.2) months following second ALK TKI post-crizotinib (including 6.3 [4.3-8.4] months for ceritinib (n = 99) and 7.6 [5.2-13.6] months for alectinib (n = 64)).

Conclusions: In this real-world analysis of patients with advanced ALK+ NSCLC treated with earlier approved ALK TKIs, rwPFS remains short, indicating a clear need for more effective treatments of ALK+ NSCLC.

Editorial acknowledgement: Writer: Beth Nordstrom; company: Evidera.

Legal entity responsible for the study: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Funding: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Disclosure: M. Jahanzeb: Research grant: Lilly, Boehringer Ingelheim, Callisto; Research grant and consultant: Ipsen, Roche/Genentech, Pfizer. H.M. Lin: Employment, stock and other ownership: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. X. Pan, A. Desai: Employment: Takeda. B.L. Nordstrom: Employment: Evidera. All other authors have declared no conflicts of interest.

1399P Impact of lorlatinib on patient-reported outcomes (PROs) in patients (Pts) with advanced ALK+ or ROS1+ non-small cell lung cancer (NSCLC)

S. Peters[1], A.T. Shaw[2], B. Besse[3], E. Felip[4], B.J. Solomon[5], R.A. Soo[6], A. Bearz[7], S.M. Gadgeel[8], C-C. Lin[9], S. Kao[10], T. Seto[11], E.T. Masters[12], A. Abbattista[13], J.S. Clancy[14], H. Thurm[15], A. Reisman[16], D.R. Camidge[17]

[1]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Gustave Roussy Cancer Campus/Paris-Sud University, Villejuif/Orsay, France, [4]Vall d'Hebron Institute of Oncology, Barcelona, Spain, [5]Peter MacCallum Cancer Centre, Melbourne, Australia, [6]National University Cancer Institute, Singapore, [7]National Cancer Institute, Aviano, Italy, [8]Barbara Ann Karmanos Cancer Institute, University of Michigan, Detroit, MI, USA, [9]National Taiwan University Hospital, Taipei, Taiwan, [10]Chris O'Brien, Lifehouse, Camperdown, Australia, [11]National Kyushu Cancer Center, Tokyo, Japan, [12]Pfizer Oncology, New York, NY, USA, [13]Pfizer Oncology, Milan, Italy, [14]Pfizer Oncology, Cambridge, MA, USA, [15]Pfizer Oncology, La Jolla, CA, USA, [16]Pfizer Global Product Development, New York, NY, USA, [17]University of Colorado, Aurora, CO, USA

Background: Lorlatinib is a selective, potent, brain-penetrant, third-generation ALK/ROS1 tyrosine kinase inhibitor with robust clinical activity in pts with ALK-positive (ALK+) or ROS1-positive (ROS1+) advanced NSCLC. The phase 1/2 study (NCT01970865) assessed lorlatinib in pts with ALK+ or ROS1+ NSCLC based on prior treatment. Phase 2 efficacy/safety was previously reported. Here, we present PRO results.

Methods: In this ongoing open-label, multicenter study, pts received lorlatinib 100 mg once daily. Global quality of life (QoL), pt functioning and symptoms were assessed with the European Organisation for Research and Treatment of Cancer QoL Questionnaire Core 30 (QLQ-C30) and the Lung Cancer 13 module (QLQ-LC13) at baseline (BL) and on day 1 of each cycle. Higher scores indicated higher functioning/QoL or greater symptom severity. Change from BL (ΔBL) was summarized; a ≥ 10-point ΔBL (improved or worsened) was considered clinically meaningful. An average of mean ΔBL was calculated for each pt across cycles to determine the proportion of pts with a clinically meaningful change.

Results: Median treatment duration was 8.3 months. Interim PRO data were analyzed through cycle 24; the completion rate was ≥94%. Clinically meaningful improvements from BL were seen for global QoL; most pts had improved (43%) or stable (neither improved nor worsened) scores (40%). Clinically meaningful improvements occurred in functioning domains and symptoms; further details will be presented. The highest proportion of pts improved in emotional (38%), role (38%) and social (34%) functioning domains. Proportions of pts with improved/stable/worse cognitive functioning were 24%/51%/24%. Most pts had improved or stable symptom scores; the greatest proportions of pts improved for symptoms of fatigue (49%), insomnia (45%) and appetite loss (42%) on QLQ-C30 and cough (44%), pain in other parts (33%) and pain in chest (30%) on QLQ-LC13. The symptom with the greatest proportion of pts with clinically meaningful worsening was peripheral neuropathy (38%).

Conclusions: Lorlatinib showed favorable clinical benefit and improvements in global QoL, functioning and key NSCLC symptoms in pts with ALK+ or ROS1+ NSCLC.

Clinical trial identification: Clinical trial registration: NCT01970865.

Editorial acknowledgement: Editorial assistance was provided by Brian Szente, PhD, of inScience Communications, Springer Healthcare (New York, NY, USA) and funded by Pfizer.

Legal entity responsible for the study: Pfizer.

Funding: Pfizer.

Disclosure: S. Peters: Consulting or advisory role: Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Roche, AstraZeneca; Speakers' bureau: AstraZeneca, Roche, Bristol-Myers Squibb, MSD, Boehringer Ingelheim. A.T. Shaw: Speakers or advisory board: Pfizer, Novartis, Genentech, Roche, Ariad, Takeda, Ignyta, Blueprint Medicines, Loxo, Daiichi Sankyo, EMD Serono, Taiho Pharmaceutical, KSQ Therapeutics, Natera; Honoraria: Pfizer, Novartis, Roche/Genentech, Foundation Medicine, Takeda; Research funding: Pfizer, Novartis, Roche/Genentech. B. Besse: Travel, accommodations, expenses: Roche, Pfizer, Bristol-Myers Squibb/Medarex, Novartis, Pierre Fabre. Institutional: Research funding: AstraZeneca, Roche/Genentech, Pfizer, Boehringer Ingelheim, Lilly, Servier, Onxeo, Bristol-Myers Squibb, Ose Pharma, Inivata, Novartis. E. Felip: Consulting or advisory role: AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, GuardantHealth, MSD, Novartis, Pfizer, Roche, Takeda, Merck; Speakers' bureau: AstraZeneca, Boehringer Ingelheim, BMS, MSD, Novartis, Pfizer, Roche. B.J. Solomon: Honoraria: Bristol-Myers Squibb, AstraZeneca; Royalty, IP Rights/Patent Holder: Veristrat (Biodesix); Travel, accommodations, expenses: AstraZeneca, Roche, Merck, Bristol-Myers Squibb, Novartis; Institutional: Speakers or advisory board: AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Roche/Genentech, Novartis; Research funding: Pfizer. R.A. Soo: Consulting or advisory role: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech, Taiho Pharmaceutical; Honoraria: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech; Research funding: AstraZeneca. A. Bearz: Speakers' bureau: MSD, Roche, BMS, Pfizer, Takeda, Eli-Lilly, Novartis; Consultant: MSD, Roche, BMS, Pfizer, Takeda, Eli-Lilly, Novartis. S.M. Gadgeel: Consulting or advisory role: Pfizer, Genentech/Roche, Ariad, AstraZeneca, Bristol-Myers Squibb; Speakers' bureau: AstraZeneca; Travel, accommodations, expenses: Ariad/Takeda, Genentech/Roche; Institutional: Research funding: Pfizer, Clovis Oncology, Merck, Genentech/Roche, Incyte, Millennium, AstraZeneca/MedImmune, Bristol-Myers

Squibb, Halozyme, Acerta Pharma, Acea Biosciences, Janssen Oncology, Novartis, Five Prime Therapeutics, OncoMed. S. Kao: Honoraria: AstraZeneca, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb: Consulting or advisory role: Pfizer, AstraZeneca, Boehringer Ingelheim; Research funding: Pfizer. T. Seto: Honoraria: Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Kissei Pharmaceutical, MSD, Nippon Boehringer Ingelheim, Pfizer Japan, YakultHonsha, Bristol-Myers Squibb, Kyowa Hakko Kirin, Mochida Pharmaceutical, Nippon Kayaku, Ono Pharmaceutical, Roche Singapore, Sanofi, Showa Yakuhin Kako, Taiho Pharmaceutical, Takeda Pharmaceutical; Institutional: Research funding: Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Kissei Pharmaceutical, MSD, Nippon Boehringer Ingelheim, Pfizer Japan, YakultHonsha, Bayer Yakuhin, Eisai, Merck Serono, Novartis Pharma, Verastem. E.T. Masters, A. Abbattista, H. Thurm, A. Reisman: Employee and stock: Pfizer. J.S. Clancy: Employee: Pfizer. D.R. Camidge: Advisor/board: Roche, G1 Therapeutics, Mersana, Takeda, AstraZeneca, Genoptix, Ignyta, Daiichi Sankyo, Hansoh, Lycera, Bio-thera, Revolution Med; Research funding: Takeda. All other authors have declared no conflicts of interest.

1401P The efficacy and safety of crizotinib in patients with ROS1 positive advanced stage NSCLC: The real-world experience from Turkey

S. Kilickap[1], Ö.F. Ölmez[2], I. Cicin[3], U. Demirci[4], O. Alan[5], D. Cabuk[6], T. Şakalar[7], A.M. Tatlı[8], F. Başol Buğdaycı[9], Y. Eralp[10], M. Uysal[11], A. Demirkazık[12], B. Bilgin[13], B. Yıldız[14], M. Karaağaç[15], K. Okutur[16], A. Sakin[17]

[1]Medical Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Department of Medical Oncology, Medipol University, Istanbul, Turkey, [3]Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Turkey, [4]Department of Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Training and Research Hospital, Ankara, Turkey, [5]Medical Oncology, Marmara University Hospital, Istanbul, Turkey, [6]Department of Medical Oncology, Kocaeli University, Kocaeli, Turkey, [7]Medical Oncology, Erciyer University School of Medicine, Kayseri, Turkey, [8]Department of Medical Oncology, Akdeniz University Faculty of Medicine, Antalya, Turkey, [9]Department of Medical Oncology, Sanatoryum Chest Disease Hospital, Ankara, Turkey, [10]Department of Medical Oncology, Istanbul University Faculty of Medicine, Istanbul, Turkey, [11]Department of Medical Oncology, Afyon Kocatepe University Faculty of Medicine, Afyon, Turkey, [12]Department of Medical Oncology, Ankara University Faculty of Medicine, Ankara, Turkey, [13]Department of Medical Oncology, Yildirim Beyazit University Faculty of Medicine, Ankara, Turkey, [14]Department of Medical Oncology, Gulhane Education and Research Hospital, Ankara, Turkey, [15]Department of Medical Oncology, Meram University Faculty of Medicine, Konya, Turkey, [16]Department of Medical Oncology, MedicalPark Hospitals, Istanbul, Turkey, [17]Department of Medical Oncology, Okmeydani Education and Research Hospital, Istanbul, Turkey

Background: ROS1 mutation occurs in approximately 1-2% of patients with NSCLC. There are limited data on the efficacy of crizotinib therapy in the treatment of ROS1-positive advanced stage NSCLC. The survival results of two studies evaluating the efficacy of crizotinib in these patients are contradictory. In the study, we aimed to evaluate real life data of the patients with ROS1 positive advanced stage NSCLC treated with crizotinib in Turkey.

Methods: In this multicenter study, patients with ROS1-positive NSCLC treated with crizotinib were retrospectively analyzed. Clinical and demographic characteristics of the disease, response rates median PFS and side effects with crizotinib were evaluated in 42 patients.

Results: Twenty-two of the patients (52.4%) were female, and 23 (54.8%) were non-smoker. The median age at the time of diagnosis was 51 (20-80) years. The most common histology was adenocarcinoma (n ve %). At baseline, 12 (28.6%) patients had pleural effusion, 11 (26.2%) had brain metastasis, and 17 (40.5%) had bone metastasis. The baseline ECOG performance score was "0" in 28.6% and "1" in 64.3%. Crizotinib was used in 45.2% of patients at the first line, 42.9% at the second line, and 12.0% in the next steps. The most common side effect was fatigue (43%). In 4 patients vascular event developed (3 thromboemboli, 1 acute MI). Brain metastasis developed in 31% of the patients at the follow-up. The overall response rate with crizotinib was 59.5% with 9.5% complete remission and 50.0% partial remission. The disease control rate was 83.3%. The median PFS was 13.2 months and the 12-month PFS was 53%. Twelve-month OS was 62%, the median OS was 25 months. Two patients who developed progression were treated with lorlatinib and one patient was treated with ceritinib and and then alectinib. Overall survival in these patients were 24 months, 28 months and 13.7 months, respectively.

Conclusions: In 2 published studies, median PFS in patients with ROS1-positive NSCLC with treated crizotinib were reported as 9.1 and 19.2 months independently of the treatment step. In our study, the median PFS was 13.2 months in patients as a result of real-life data of patients in Turkey. The clinical features of the disease are compatible with the literature.

Legal entity responsible for the study: Turkish Oncology Group, Lung Cancer Subgrup.

Funding: Has not received any funding.

Disclosure: S. Kilickap: Pfizer. All other authors have declared no conflicts of interest.

1402P Docetaxel plus ramucirumab with primary prophylactic pegylated-granulocyte-colony stimulating factor for pretreated non-small cell lung cancer

D. Harada[1], A. Hata[2], C. Okuda[2], R. Kaji[2], Y. Masuda[3], Y. Takechi[4], T. Kozuki[1], N. Nogami[1], N. Katakami[2]

[1]Department of Thoracic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, [2]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [3]Department of Pharmacy, Kobe City Medical Center General Hospital, Kobe, Japan, [4]Department of Pharmacy, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

Background: A Japanese randomized phase II trial comparing docetaxel plus ramucirumab with docetaxel monotherapy (JVCG) showed that effectiveness of additional ramucirumab was comparable to that of a randomized phase III trial (REVEL). However, in the JVCG study, febrile neutropenia (FN) was confirmed in 34% of the patients in the combination arm. It was assumed that the high frequency of FN was related to the fact that preventive prophylactic pegylated (PEG)-granulocyte-colony stimulating factor (G-CSF) was administered to only 6% of the patients. The aim of our study was to evaluate the efficacy and safety of docetaxel plus ramucirumab with primary prophylactic PEG-G-CSF for Japanese pretreated non-small cell lung cancer (NSCLC).

Methods: We retrospectively reviewed medical records of pretreated NSCLC cases who had received docetaxel plus ramucirumab in our departments.

Results: Sixty-one pretreated NSCLC patients underwent docetaxel plus ramucirumab. Primary prophylactic PEG-G-CSF was performed in 52 (85%) patients (prophylactic group). No FN (0%) was confirmed in 52 prophylactic group patients, whereas FN was observed in 3 (33%) of 9 non-prophylactic group patients. Among prophylactic group, median lines of prior therapy was 2 (range, 1-9). Median cycles of docetaxel plus ramucirumab was 3 (range, 1-25) (9 and 3 cases moved to ramucirumab and docetaxel monotherapies, respectively). Response rate and disease control rate were 30.8% and 73.1%, respectively. Median progression-free survival was 4.5 (95% confidence interval [CI], 3.0-6.6) months. Median overall survival was 11.4 (95% CI, 8.0-13.9) months. Six (11.5%) patients had grade 3/4 neutropenia. Observed grade 3 (incidence $\geq$10%) adverse event (AE) was oral mucositis (13.5%). There were no grade 4/5 non-hematological AEs.

Conclusions: Our study demonstrated the efficacy and safety of docetaxel plus ramucirumab with PEG-G-CSF. Primary prophylactic PEG-G-CSF could markedly reduce incidence of FN in Japanese clinical practice.

Editorial acknowledgement: We thank Ayami Asakawa, Mizuho Awaki, Suemi Minamihara, Hiroko Ishikawa and Mamiya Atagi for their assistance, and Mr. David Martin for writing support.

Legal entity responsible for the study: Akito Hata.

Funding: Has not received any funding.

Disclosure: D. Harada: Lecture fees: Ono, Bristol-Myers Squibb, Yakult Honsha, Kyowa Hakko Kirin, AstraZeneca, Nippon Boehringer Ingelheim, Eli Lilly Japan. A. Hata: Lecture fees: Chugai, AstraZeneca, Boeringer Ingelheim, Eli Lilly. T. Kozuki: Honoraria: Chugai, AstraZeneca, Eli Lilly Japan, Boehringer Ingelheim, Ono, Bristol-Myers Squibb, Taiho, MSD, Pfizer, Kyowa Hakko Kirin; Research funding: Chugai, AstraZeneca, MSD, Eli Lilly Japan. N. Nogami: Honoraria: Astellas, AstraZeneca, Ono, Taiho, Chugai, Eli Lilly, Boehringer Ingelheim, Pfizer. N. Katakami: Grants: AstraZeneca, Eisai, Ono, Kyowa Kirin, Shionogi, Daiichi-Sankyo, Taiho, Chugai, Eli Lilly, Boeringer Ingelheim, Merck Serono; Payment for lectures: Dainippon Sumitomo, Chugai, Boeringer Ingelheim, AstraZeneca, Eli Lilly, Taiho, Janssen, Novartis, Pfizer, Ono, Daiichi-Sankyo. All other authors have declared no conflicts of interest.

1403P Open-label multicenter randomized phase II study of docetaxel plus bevacizumab or pemetrexed plus bevacizumab for elderly (≥75 years old) patients (pts) with previously untreated advanced non-squamous non-small cell lung cancer (NSCLC): TORG1323

T. Honda[1], T. Kouzuki[2], Y. Tsunezuka[3], N. Seki[1], T. Shibayama[4], T. Okimoto[5], H. Taniguchi[6], Y. Takeda[7], N. Hata[8], K. Sugimoto[9], N. Takahashi[10], K. Sakai[11], T. Nishimura[12], S. Ikeda[13], S. Watanabe[14], K. Mori[15], T. Shinkai[16]

[1]Department of Internal Medicine, Division of Medical Oncology, Teikyo University, Tokyo, Japan, [2]Department of Respiratory Medicine, Shikoku Cancer Center, Ehime, Japan, [3]Department of General Thoracic Surgery, Ishikawa Prefectural Central Hospital, Ishikawa, Japan, [4]Department of Respiratory Medicine, Okayama Medical Center, Okayama, Japan, [5]Department of Internal Medicine, Division of Medical Oncology & Respiratory Medicine, Shimane University Faculty of Medicine, Shimane, Japan, [6]Department of Respiratory Medicine, Toyama Prefectural Central Hospital, Toyama, Japan, [7]Respiratory Medicine, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan, [8]Department of Respiratory Medicine, Kawaguchi Municipal Medical Center, Saitama, Japan, [9]Department of Respiratory Medicine, Japanese Red Cross Kobe Hospital, Hyogo, Japan, [10]Department of Respiratory Medicine, Nihon University Itabashi Hospital, Tokyo, Japan, [11]Department of Pulmonary Medicine, Saitama Medical Center, Saitama, Japan, [12]Department of Respiratory Medicine, Kyoto Katsura Hospital, Kyoto, Japan, [13]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan, [14]Department of Respiratory Medicine, Niigata University Medical & Dental Hospital, Niigata, Japan, [15]Department of Respiratory Medicine, Jizankai Medical Foundation Tsuboi Cancer Center Hospital, Fukushima, Japan, [16]Department of Respiratory Medicine, Shonan East General Hospital, Kanagawa, Japan

Background: The addition of bevacizumab (B) to platinum doublets prolongs the survival for non-squamous (NSQ) NSCLC. The role of monotherapy with B is unclear for elderly NSQ NSCLC patients (pts). We presented the comparable efficacy data in a previous meeting. Here, we present the survival and quality of life analyses of TORG1323.

Methods: Pts were pathologically diagnosed untreated elderly (≥75 years old) NSQ NSCLC, who were stage IIIB, IV, or recurrent disease, and PS 0-1. EGFR mutation or ALKrearranged pts were allowed after receiving each tyrosine kinase inhibitor. Pts were randomized 1:1 to receiving either docetaxel (D) or pemetrexed (P) with B. The primary endpoint was progression-free survival (PFS) assessed by independent review committee. B was administered 15 mg/kg, D was 50 mg/m^2, or P was 500 mg/m^2 every 3 weeks until disease progression or unacceptable toxicity based on our previous studies. Selection design was adopted for this study. The planned sample size was 120 pts to yield 80% power to select an optimal regimen correctly and PB is chosen for the further evaluation if the point estimate of hazard ratio (HR) for PFS was ≤1.20.

Results: Enrollment was terminated early at the end of March 2017 because of slow accrual. A total of 103 pts (DB/PB= 51/52 pts) were enrolled and 99 pts (49/50 pts) comprise the full analysis set. Patient characteristics were well balanced between the two arms. Median age was 78 (range: 75-88) in DB and 79 (75-94) in PB. EGFR mutation+/ALK translocation+/wild type/unknown= 13/0/34/2 in DB and 13/2/33/2 in PB. A total of 77 events occurred at data cut-off, which corresponded to 77.7% power. The median PFS of DB and PB were 6.1 months (mo) and 4.6 mo (HR 1.03, 95%C.I. 0.66-1.61: p = 0.901). The median OS of DB and PB were 18.7 mo and 26.6 mo (HR 0.69, 95% C.I. 0.36-1.30; p = 0.2465). The mean change from baseline of Functional Assessment of Cancer Therapy - Lung (FACT-L) total was -8.4 in DB and -2.7 in PB (p = 0.0096).

Conclusions: PB results in less deterioration of QoL. The efficacy is comparable between the two arms for elderly (≥75 years old) advanced NSQ NSCLC.

Clinical trial identification: UMIN000012786 01-Jan-2014.

Legal entity responsible for the study: Thoracic Oncology Research Group.

Funding: Chugai Pharmacutical Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

1404P Safety of nintedanib plus docetaxel in advanced non-squamous NSCLC (nsNSCLC) patients: The preliminary results of the SENECA (second-line nintedanib in non-small cell lung cancer) trial

A.M. Morelli[1], M.R. Migliorino[2], A. Morabito[3], R. Chiari[4], F. Grossi[5], P. Bordi[6], F. Di Costanzo[7], A. Delmonte[8], G. Romano[9], A. Misino[10], V. Scotti[11], V. Gregorc[12], S. Pisconti[13], G.L. Ceresoli[14], A. Del Conte[15], I. Colantonio[16], L. Ciuffreda[17], E. Capelletto[1], I. Stura[18], S. Novello[1]

[1]Department of Oncology, University of Turin, AOU San Luigi, Orbassano, Italy, [2]UOSD Pneumologia Oncologica, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy, [3]Thoracic Medical Oncology, Istituto Nazionale Tumori, "Fondazione G. Pascale" - IRCCS, Naples, Italy, [4]Medical Oncology, Santa Maria della Misericordia Hospital, Perugia, Italy, [5]Lung Cancer Unit, Ospedale Policlinico San Martino, Genoa, Italy, [6]Medical Oncology Unit, University Hospital, Parma, Italy, [7]Medical Oncology, AOU Careggi, Florence, Italy, [8]Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) - IRCCS, Meldola, Italy, [9]UO Oncologia, Ospedale Vito Fazzi, Lecce, Italy, [10]Oncology Unit, Clinical Cancer Center "Giovanni Paolo II", Bari, Italy, [11]Radiation Oncology Unit, Oncology Department, Azienda Ospedaliero-Universitaria Careggi, Florence Italy, [12]Department of Oncology, IRCCS Ospedale San Raffaele, Milan, Italy, [13]S.C. Oncologia Medica, P.O.C.S.S. Annunziata - S.G. Moscati, ASL Taranto, Statte, Italy, [14]Medical Oncology, Humanitas Gavazzeni, Bergamo, Italy, [15]Oncology Unit, Centro di Riferimento Oncologico (CRO) - IRCCS, Pordenone, Italy, [16]Medical Oncology, St. Croce e Carle General Hospital, Cuneo, Italy, [17]S.C. Oncologia Medica I, A.O.U. Città della Salute e della Scienza di Torino, Presidio Molinette, Turin, Italy, [18]Department of Public Health and Paediatric Sciences, University of Turin, Turin, Italy

Background: The SENECA trial, a phase IIb, open label, multicentre study, aimed to investigate in the real life efficacy and safety of nintedanib plus docetaxel, used weekly (T1) or q3wks (T2), in pretreated nsNSCLC patients, stratified for relapse-timing (within or over 3 months from end of first-line therapy). Preliminary efficacy data have been previously presented: no difference in median Progression Free-Survival and a similar trend in Overall Survival between T1 and T2 were showed. Weekly docetaxel has better tolerability than q3wks administration: aim of this study is to evaluate two different docetaxel schedules combined with nintedanib, in order to potentially maximize their use.

Methods: Baseline characteristics have been already presented. Incidence and severity of treatment-related Adverse Events (AEs) were evaluated from beginning of treatment until 28 days after its completion, according to Common Terminology Criteria for Adverse Events (CTCAE) version 3, in 167 patients (receiving at least one dose of study drugs) enrolled in 18 Italian oncologic centres, between January 2016 and March 2018.

Results: Incidence of any grades AEs was numerically higher in T2 compared to T1 (484 vs 450 events, respectively); a complete overview of AEs (≥ 5% incidence in either group) is reassumed in Table1. Docetaxel was reduced in 14.4% patients, more frequently in T2 vs T1 (18.8% vs 9.7%). Nintedanib reduction was needed in 19.8% of patients, 23.2% in T1 and 15.3% in T2, mainly for diarrhea. Thirty-one (18.6%) patients permanently discontinued study drugs (11 in T1 vs 20 in T2) due to hypersensitivity reactions and pain.

Table: 1404P Main AEs observed in the SENECA trial according to docetaxel schedule and CTCAE grade

AEs	N = 167					
	T1 (N = 82)	T2 (N = 85)	p-value	T1 (N = 82)	T2 (N = 85)	p-value
	Any Grades			Grade ≥ 3		
Fatigue	44(53.6%)	56(65.9%)	0.10	5(6.1%)	10(11.7%)	0.20
Diarrhea	41(50%)	40(47%)	0.70	4(4.8%)	4(4.7%)	0.95
ALT elevation	24(29.3%)	17(20%)	0.16	4(4.8%)	5(5.9%)	0.77
Afebrile Neutropenia	11(13.4%)	45(52.9%)	<0.0001	3(3.6%)	17(20%)	<0.0001
Pain	19(23.2%)	21(24.7%)	0.81	3(3.6%)	2(2.3%)	0.62
Anemia	18(21.9%)	16(18.8%)	0.61	1(1.2%)	1(1.2%)	0.30
Nausea	17(20.7%)	14(16.5%)	0.47	3(3.6%)	3(3.5%)	0.96
Dyspnea	16(19.5%)	18(21.2%)	0.78	2(2.4%)	2(2.3%)	0.97
Fever	15(18.3%)	9(10.6%)	0.15	2(2.4%)	0(0%)	0.14
Cough	13(15.8%)	14(16.5%)	0.91	0(0%)	0(0%)	NE
Decreased Platelets	11(13.4%)	2(2.3%)	0.007	0(0%)	0(0%)	NE
Skin Toxicity	11(13.4%)	9(10.6%)	0.57	0(0%)	1(1.2%)	0.32
Oral Mucositis	10(12.2%)	19(22.3%)	0.08	3(3.6%)	1(1.2%)	0.29
GGT elevation	9(11%)	10(11.8%)	0.87	3(3.6%)	5(5.9%)	0.50
Vomiting	7(8.5%)	15(17.6%)	0.08	0(0%)	1(1.2%)	0.32
Decreased leukocytes	5(6.1%)	10(11.8%)	0.20	0(0%)	2(2.3%)	0.16
AST elevation	6(7.3%)	6(7%)	0.94	2(2.4%)	1(1.2%)	0.53
Dysgeusia	6(7.3%)	5(5.9%)	0.70	0(0%)	0(0%)	NE
Parestesie	4(4.9%)	1(1.2%)	0.38	7(8.5%)	0(0%)	0.97

ALT: alanine aminotrasferase; NE: not evaluable; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase.

Conclusions: Preliminary safety data of SENECA trial show statistically significant differences only in a few of the items explored (particularly afebrile neutropenia), but underline a clear trend of higher tolerability for weekly docetaxel combination treatment in second line nsNSCLC patients.

Clinical trial identification: EudraCT: 2014-005016-42.

Legal entity responsible for the study: Department of Oncology, University of Turin.

Funding: Department of Oncology- University of Turin.

Disclosure: A. Morabito: Honoraria: Roche, AstraZeneca, Boehringer Ingelheim, Pfizer, MSD, BMS. F. Grossi: Advisory boards and lectures: Boehringer Ingelheim, MSD, BMS, AstraZeneca; Lectures: Lilly, Celgene, Amgen, Roche. V. Scotti: Advisory boards and speaker's fee: BI S. Novello: Speakers' bureau: BI, AstraZeneca, Roche, MSD, BMS, Ely Lilly, Takeda, Pfizer. All other authors have declared no conflicts of interest.

1405P Circulating tumor DNA (ctDNA) in advanced non-small cell lung cancer (NSCLC) from HIV-infected patients is associated to shorter overall survival (OS): Results from phase II trial (IFCT-1001 CHIVA)

M. Wislez[1], H. Blons[2], C. Domblides[1], F. Barlesi[3], J. Mazieres[4], I. Monnet[5], L. Kiakouama Maleka[6], X. Quantin[7], L. Taillade[8], H. Lena[9], P. Fraisse[10], H. Janicot[11], C. Audigier Valette[12], E. Amour[13], A. Langlais1[3], N. Rabbe[14], J. Cadranel[1], P. Laurent puig[15], A. Lavolé[1]

[1]Pneumologie, APHP, CancerEst, Tenon University Hospital, Paris, France, [2]Biochimie, UF de Pharmacogénétique et Oncologie Moléculaire, APHP, Paris, France, [3]Service d'Oncologie Médicale, Aix-Marseille University - Faculté de Médecine Nord, Marseille, France, [4]Thoracic Oncology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [5]Pneumology, CH Intercommunal de Créteil, Créteil, France, [6]Pneumologie, Hôpital de la Croix-Rousse, Lyon, France, [7]Pneumologie, Hopital Arnaud de Villeneuve, Montpellier, France, [8]Oncologie Médicale, APHP, Pitie Salpetriere, Paris, France, [9]Pneumologie, CHU de Pontchaillou, Rennes, France, [10]Pneumologie, Hopital Civil, Strasbourg, France, [11]Pneumology, University Hospital Center of Clermont-Ferrand, Clermont-Ferrand, France, [12]Pneumologie, Hospital Sainte Musse, Toulon, France, [13]Clinical Research Unit, French Cooperative Thoracic Intergroup, Paris, France, [14]GRC n°04, Theranoscan, APHP, Tenon University Hospital, Paris, France, [15]Biochimie, UF de Pharmacogénétique et Oncologie Moléculaire, Paris Descartes University, Paris, France

Background: Lung cancer is one of the most common non-AIDS-defined malignancies. Its prognosis has been considered to be poorer in HIV-positive patients (pts) than is the general population. Circulating tumor DNA (ctDNA) has been shown to be a prognostic marker in HIV-undetermined pts. Our goal was to assess its prognosis value in HIV-positive pts.

Methods: 61 HIV-positive pts with advanced non-squamous NSCLC were included in IFCT phase II trial evaluating carboplatin AUC5 pemetrexed 500 mg/m^2 every 3 weeks, as first-line of treatment. Baseline blood samples were collected in all pts; ctDNA was assessed by ultra-deep targeted NGS using a dedicated variant caller algorithm.

Results: 55 (90%) samples were available. They were from 42 males (76.4%), 53 ± 7 years (mean ± SD), smokers (92.7%), stage III (9%) or IV (91%) and performance status (PS) 0-1 (83.6%). 18 pts were AIDS (32.7%) and 49 received HAART (89%). Mean (±SD) CD4 counts were 223/μL±222 and viral load of 39.5 [0-95499]. Disease control rate at 4 cycles was 32.7% (n = 18). PFS was 3.5 months (IC95% 2.6-4.7). OS was 8.8 months (IC95% 5.9-13.7). ctDNA was detected in 35 pts (64%) with 22 and 13 pts having high [2-49%] or low ctDNA [0.7-2%] loads, respectively. Among positive samples, 77% had a TP53 mutation and 43% had more than one alteration. Alterations in oncogene drivers were identified in KRAS, NRAS, EGFR, BRAF and MET and were mutually exclusive. ctDNA positivity was not related to clinical parameters. In multivariate analysis, AIDS status (HR 2.17 (1.09-4.32), p = 0.03) and positive ctDNA (HR 4.31 (2.06-8.99), <0.0001) were significantly associated to PFS and, PS 2 vs. 0-1 (HR 4.10 (1.62-10.36), p=.003) and positive ctDNA (HR 3.52 (1.72-7.19), p = 0.0006) to OS. Similar results were found when groups were analyzed according to ctDNA quantification, low versus high versus null.

Conclusions: ctDNA detection and quantification using ultra-deep targeted NGS is an independent prognostic factor of OS and PFS in advanced NSCLC from HIV-infected pts.

Clinical trial identification: NCT01296113.

Legal entity responsible for the study: IFCT (French Cooperative Thoracic Intergroup).

Funding: Lilly.

Disclosure: M. Wislez: Advisory boards: AstraZeneca, Roche, BMS, MSD, Novartis, Boehringer Ingelheim; Corporate-sponsored research: BMS, Boehringer Ingelheim; Travel: Roche, BMS, Novartis, Pfizer. C. Domblides: Speaker: AstraZeneca; Travel: Pierre Fabre, AstraZeneca, Pfizer, Amgen, MSD, Roche; Research funding: AstraZeneca. F. Barlesi: Consulting or advisory role: Roche/Genentech, Pfizer, Novartis, Pierre Fabre, Bristol-Myers Squibb, AstraZeneca/MedImmune, Boehringer Ingelheim, Lilly, Merck Serono, MSD Oncology, Takeda. Travel, accommodations, expenses: Roche/Genentech, Bristol-Myers Squibb, AstraZeneca/MedImmune; Honoraria: Genentech/Roche, Pfizer, Pierre Fabre, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, Novartis, Pierre Fabre, Merck Serono, MSD Oncology, Takeda. J. Mazieres: Advisory boards: AstraZeneca, Roche, BMS, MSD, Novartis, Pfizer; Research funding: AstraZeneca, Roche, BMS; Travel: Roche, BMS, Novartis, Pfizer. J. Cadranel: Principal investigator: AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, MSD, Novartis, Roche, Takeda; Consultancy: AstraZeneca, Boehringer Ingelheim, BMS, Lilly, Novartis, MSD, Pfizer, Roche; Speakers' bureau: AstraZeneca, BMS, MSD, Pfizer. All other authors have declared no conflicts of interest.

1406P Final results of the concordance analysis of PD-L1 immunohistochemistry (IHC) assays and polymerase chain reaction (PCR) in non-small lung cancer (NSCLC) patients

I. Tsimafeyeu[1], E.N. Imyanitov[2], L. Zavalishina[3], G. Raskin[4], P. Povilaitite[5], N. Savelov[6], E. Kharitonova[1], A. Rumyantsev[7], I. Pugach[1], Y. Andreeva[3], A. Petrov[5], G. Frank[3], S. Tjulandin[7]

[1]Russian Society of Clinical Oncology, Moscow, Russian Federation, [2]Laboratory of Molecular Oncology, N.N.Petrov Research Inst. of Oncology, Saint Petersburg, Russian Federation, [3]Pathology Department, Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation, [4]Pathology, A.M. Granov Russian Scientific Centre of Radiology and Surgical Technologies, Saint-Petersburg, Russian Federation, [5]Dept. of Pathology, Rostov Regional Bureau of Pathology, Rostov-on-Don, Russian Federation, [6]Lab. of Pathology, Moscow City Oncology Hospital No. 62, Moscow, Russian Federation, [7]Dept. of Clinical Pharmacology and Chemotherapy, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation

Background: The goal of the CLOVER study is to perform a pairwise comparison of 4 tests based on the same patient population: 3 validated PD-L1 IHC assays [Ventana SP142 (atezolizumab), Ventana SP263 (durvalumab), Dako 22C3 (pembrolizumab) and one PCR test.

Methods: 473 NSCLC samples (including 81 EGFR+, 36 ALK+, 131 squamous cell carcinoma) were stained with PD-L1 IHC assays. Four pathologists independently evaluated the percentages of tumor (TC) and tumor infiltrating immune cells (IC) staining positive at any intensity. PD-L1 transcripts were quantified by Taqman RT-PCR assay using SDHA as a gene-referee; dCT = 2 was chosen as a threshold between positive and negative RNA expression. The concordance analysis was performed to assess (1) correlation of IC and TC between different assays, (2) the predictive properties of one test of another. One test-specific cutoff rule for each assay was pre-specified as: for first-line TC or IC ≥ 5% for SP142, TC ≥ 25% for SP263, TC ≥ 50% for 22C3, and for second-line TC ≥ 50% or IC ≥ 10% for SP142, TC ≥ 25% for SP263, TC ≥ 1% for 22C3.

Results: Pearson Correlation Coefficients (PCC) for TC were: 0.71, 0.87 and 0.75 between SP142/22C3, SP263/22C3 and SP142/SP263, respectively. PCC for IC were: 0.45, 0.61 and 0.68 for the same pairs. Low correlation was observed between PCR test and any of the IHC assays for TC and IC. Table represents how well one assay can predictthe same outcome (positivity or negativity) of another assay using recommended individual cutoffs for each test. Among patients who were negative by PCR, 92%-99% of the patients were negative by any of the three IHC assays using corresponding recommended cutoff. Among patients who were positive by PCR, 9-45% of them were positive by IHC assays.

Table: 1406P Probability of negative test B, given negative test A

Test A	Test B					
	SP142		SP263		22C3	
	First-line	Second-line	First-line	Second-line	First-line	Second-line
SP142	-	-	92%	85%	97%	65%
SP263	91%	98%	-	-	99%	76%
22C3	88%	99%	91%	99%	-	-
Probability of Positive Test B, given Positive Test A						
SP142	-	-	65%	76%	48%	94%
SP263	68%	28%	-	-	57%	98%
22C3	82%	17%	93%	49%	-	-

Conclusions: PCR should not be recommended as a substitute for a PD-L1 IHC assay due to high probability of false positive prediction and low PCC. 22C3 could be considered as a substitute for SP263 in first-line.

Legal entity responsible for the study: Russian Society of Clinical Oncology.

Funding: AstraZeneca, BMS, MSD, Roche.

Disclosure: All authors have declared no conflicts of interest.

1407P Derived neutrophil-to lymphocyte ratio (dNLR) change between baseline and cycle 2 is correlated with benefit during immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (NSCLC) patients

L. Mezquita[1], K. Arbour[2], E. Auclin[3], D. Saravia[4], H. Rizvi[2], L. Hendriks[5], D. Planchard[6], W. Park[4], E. Nadal[7], J.C. Ruffinelli Rodriguez[8], S. Ponce[9], C. Audigier-Valette[10], A.P. Marilniello[11], G. Zalcman[12], M. Majem[13], G. Schiavone[14], A-M.C. Dingemans[15], G. Lopes[16], M.D. Hellmann[2], B. Besse[17]

[1]Medical Oncology Department, Gustave Roussy, Villejuif, France, [2]Medical Oncology Department, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3]Oncology, Hopital European George Pompidou, Paris, France, [4]Medical Oncology Department, Sylvester Comprehensive Cancer Center, Miami, FL, USA, [5]Pulmonary Diseases, Maastricht University Medical Center (MUMC), Maastricht, Netherlands, [6]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [7]Medical Oncology Department, Institut Catala de Oncologia, Barcelona, Spain, [8]Medical Oncology Department, Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain, [9]Oncología Médica, Hospital Universitario 12 de Octubre, Madrid, Spain, [10]Pneumology Department, Centre Hospitalier Sainte Musse, Toulon, France, [11]Department of Oncology, University of Turin, Turin, Italy, [12]Oncology, Hôpital Bichat, Paris, France, [13]Medical Oncology Services, Hospital De La Santa Creu I Sant Pau, Barcelona, Spain, [14]Medical Oncology Department, University of Turin, Turin, Italy, [15]Pulmonology, Maastricht University Medical Center (MUMC), Maastricht, Netherlands, [16]Clinical Medicine, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA, [17]Department of Cancer Medicine, Gustave Roussy Institut de Cancérologie, Villejuif, France

Background: Baseline dNLR is associated with ICI outcomes in advanced NSCLC; we previously reported that the early dNLR change during ICI was correlated to benefit in 292 advanced NSCLC patients. We aimed to confirm the impact of dNLR monitoring in a larger cohort.

Methods: 1225 patients with advanced NSCLC treated with ICI (PD1/PDL1 +/- CTLA4) from 10 European/US centers were identified between Nov. 2012 and Mar. 2018. dNLR at baseline and before cycle 2 were retrospectively collected. dNLR was defined as neutrophils/(leucocytes-neutrophils). dNLR monitoring, combining dNLR at baseline (B) et before cycle 2 (C2) stratified the 3 groups: good (if dNLR$\leq$3 remained low at B and C2), intermediate (if dNLR status increased $\leq$3 at B and >3 at C2 or decreased >3 at B and $\leq$3 at C2), poor (dNLR>3 at B and C2).

Results: 689 (56%) were males, 1058 (87%) smokers, 1066 (87%) with PS $\leq$ 1, with median age 65 years; 926 (76%) had nonsquamous; 108 were KRASm. PDL1 was known in 403/1225 (33%) and was $\geq$1% in 270 (67%). The median PFS and OS were 3.1m [95% CI 3-4] and 12m [10-13.7]. dNLR was >3 at B in 416 (34%) and before C2 in 417 pts (34%). At C2, the dNLR status changed in 267 pts, with 133 (11%) dNLR decreased and 134 (11%) dNLR increased. The median OS was 18.6m [16-21] for the good group when dNLR remained low (n = 675, 55%), 9.2m [8-13.9] for the intermediate when dNLR changed (n = 267, 22%) and 5m [4-6.3] for the poor group when dNLR remained high (dNLR>3, n = 283, 23%) (P < 0.0001). The median PFS was 5m [4-5.5] for the good group, 2.6m [2-4] for the intermediate and 2m [2-2.6] for the poor group (P < 0.0001). The poor group was associated with radiological disease progression (OR 2.22, CI 1.33-3.7, P = 0.002).

Conclusions: Baseline and 2nd cycle dNLR monitoring can early discriminate the benefit to ICI in advanced NSCLC patients on treatment. dNLR should be prospectively studied in clinical trials.

Legal entity responsible for the study: Benjamin Besse.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1408P Prognostic factors in non-small cell lung cancer (NSCLC) patients (pts) with brain metastases (BM) treated with immune checkpoint inhibitors (ICI)

L. Hendriks[1], C. Henon[1], E. Auclin[2], L. Mezquita[1], R. Ferrara[1], C. Audigier Valette[3], J. Mazieres[4], C. Lefebvre[4], S. Le Moulec[5], B. Duchemann[6], C. Le Pechoux[7], A. Botticella[7], S. Ammari[8], A. Gazzah[9], C. Caramella[8], J. Adam[10], D. Planchard[1], D. De Ruysscher[11], A-M.C. Dingemans[12], B. Besse[1]

[1]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [2]Oncology, Hopital European George Pompidou, Paris, France, [3]Pneumology, Hospital Sainte Musse, Toulon, France, [4]Thoracic Oncology, Hospital Larrey, Toulouse, France, [5]Medical Oncology, HIA Val de Grace, Paris, France, [6]Pulmonary Diseases, Hôpital Avicenne, Bobigny, France, [7]Radiation Oncology, Institut Gustave Roussy, Villejuif, France, [8]Radiology, Institut Gustave Roussy, Villejuif, France, [9]Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, [10]Pathology, Institut Gustave Roussy, Villejuif, France, [11]Radiation Oncology, Maastricht University Medical Centre (MUMC)-MAASTRO Clinic, Maastricht, Netherlands, [12]Pulmonology, Maastricht University Medical Center (MUMC), Maastricht, Netherlands

Background: Brain metastases (BM) are frequent in NSCLC. Unfortunately, pts with (untreated) BM are often excluded from ICI trials and prognostic factors in ICI treated BM pts are largely unknown.

Methods: Retrospective data collection of all consecutive advanced ICI treated NSCLC pts in 6 centers (5 French, 1 Dutch) (nov 2012 – March 2018). All BM pts were selected; (intracranial) overall response rate (investigator assessed), progression free survival (PFS), overall survival (OS) data were collected. Active BM: non-irradiated new and/or growing lesions on brain imaging < 6 weeks before ICI start.

Results: 241/945 (26%) pts had BM: 61% male, 76% WHO PS 0-1, median age 61 years, 75% nonsquamous, 4% driver mutation, 31% known PD-L1 (61% $\geq$1% expression). ICI treatment was median 2nd line (range 1-8), 95% had monotherapy ICI. Median time BM diagnosis till ICI start: 184 days. >5 BM: 30%, active BM: 40%, symptomatic: 14%, steroid use: 26%, known disease specific Graded Prognostic Assessment (ds-GPA) at start of ICI: 94% (36% 0-1, 58% 1.5-2.5, 6% 3), previous cranial irradiation (RT): 68% (56% stereotactic, 44% whole brain), median time RT to ICI start: 109 days. Median follow-up: 14 months. 78% had PD on ICI: 12% BM only, 28% extracranial, 50% both, 10% no imaging (clinical PD). At PD, 23% of BM only PD pts had extracranial response and 21% of extracranial only PD pts had cranial response. Median (95% CI) PFS and OS were 2 (1-2) and 9 (7-13) months, respectively. In multivariate analysis, > 2 metastatic organs and symptomatic BM at ICI start were associated with a worse PFS and OS; higher ds-GPA with superior PFS and OS (Table). In univariate analysis, active BM vs stable BM and brain RT vs no brain RT were not associated with outcome (HR PFS 0.98 (p = 0.66)/ HR OS 0.93 (p = 0.92) and HR PFS 0.82 (p = 0.19) / HR OS 0.82 (p = 0.27)).

Conclusions: Number of metastatic organs, symptomatic BM and ds-GPA are associated with outcome in BM pts treated with ICI.

Legal entity responsible for the study: Gustave Roussy.

Funding: L. Hendriks: Grant: DUERTECC/euronco.

Disclosure: L. Hendriks: Outside the current abstract: Research funding: Roche; Advisory board: Boehringer Ingelheim, BMS; Travel reimbursement: Roche, BMS. C. Le Pechoux: Outside the current abstract: Advisory board: Astrazeneca. A-M.C. Dingemans: Outside the current abstract: Advisory board: BMS, MSD, Roche. B. Besse: Outside the current abstract: Institutional grants for clinical and translational research: AstraZeneca, BMS, Boehringer Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Servier, Onxeo, OncoMed, Inivata, Ose Pharma, Loxo. All other authors have declared no conflicts of interest.

Table: 1407P

Multivariate analysis	Progression-free Survival (PFS)			Overall Survival (OS)		
	HR	95% CI	P value	HR	95% CI	P value
Age >65 years	0.98	0.79-1.21	0.847	1.15	0.89-1.47	0.292
Gender Male	0.92	0.72-1.18	0.525	1.05	0.79-1.41	0.712
Smoking Former/current smoker	0.56	0.38-0.84	0.005	0.49	0.49-1.23	0.294
Histology Squamous	1.25	0.98-1.60	0.20	1.33	0.99-1.78	0.16
N# line of ICI >2	0.88	0.70-1.09	0.232	0.93	0.72-1.20	0.581
N# metastatic sites >2	1.56	1.26-1.94	<0.0001	1.70	1.31-2.2	<0.0001
Performance status $\geq$2	1.73	.29-2.31	<0.0001	2.05	1.49-2.82	<0.0001
dNLR monitoring Intermediate Poor	1.24 1.62	0.94-1.62 1.22-2.13	0.003	1.23 2.34	0.89-1.70 1.72-3.18	<0.0001

Table: 1408P

Factor	PFS HR (95% CI)	p-value	OS HR (95% CI)	p-value
Smoking yes vs no	0.75 (0.38-1.51)	0.42	0.86 (0.38-1.94)	0.71
Histology squamous vs adeno	1.11 (0.71-1.73)	0.80	1.42 (0.83-2.43)	0.36
Nr of organs with metastases > 2 vs ≤ 2	1.66 (1.15-2.39)	0.007	1.58 (1.02-2.47)	0.04
Immuno line > 2 vs ≤ 2	0.89 (0.63-1.26)	0.52	1.06 (0.71-1.59)	0.78
Use of corticosteroids at ICI start yes vs no	2.16 (1.47-3.18)	<0.001	1.51 (0.95-2.38)	0.08
BM symptomatic at start IO yes vs no	1.38 (0.86-2.23)	0.19	1.71 (1.01-2.90)	0.046
Ds-GPA 1.5-2.5 vs 0-1 Ds-GPA 3 vs 0-1	0.61 (0.43-0.85) 0.77 (0.38-1.55)	0.01	0.44 (0.29-0.66) 0.50 (0.21-1.21)	0.0003

1409P Association of efficacy and immune-related adverse events (irAEs) in patients with NSCLC receiving immune-checkpoint inhibitors (ICIs)

M. Riudavets Melia[1], I. Gabriela Sullivan[1], A. Barba Joaquín[1], G. Anguera Palacios[1], L.P. del Carpio[1], C. Molto Valiente[1], S.D. Camacho Arellano[1], S. Moron Asensio[1], P. Gomila Pons[1], M. Andres Granyó[1], D. Castillo Villegas[2], C. Facundo Molas[3], E. Garcia Planella[4], C. González Blanco[5], A. Barnadas Molins[1], I. Gich Saladich[6], M. Majem Tarruella[1]

[1]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2]Pneumology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]Nephrology, Puigvert Foundation, Barcelona, Spain, [4]Gastroenterology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [5]Endocrinology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [6]Epidemiology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Background: ICIs are a standard treatment in advanced NSCLC. However, ICIs can induce irAEs that may interrupt treatment. Here we report the incidence of irAEs and its correlation with efficacy.

Methods: We retrospectively analyzed 101 patients (pts) with advanced NSCLC receiving ICIs in our institution from March 2014 to January 2018. IrAEs were graded following CTCAE v4.0. Kaplan Meier and log-rank tests were used to evaluate progression-free (PFS) and overall survival (OS). Analyses were performed using SPSS v24 package.

Results: Median age was 66.4 [37-85] years, 74.3% were male. 33 (32.7%) pts presented squamous and 68 (67.3%) non-squamous histology. Most frequent ICIs were nivolumab (50%), pembrolizumab (31%) and atezolizumab (16%), used as monotherapy (79.2%) or in combination with chemotherapy (20.8%). Median duration of treatment was 2.7 [0.6-26.2] months. 61 (60.4%) pts developed 106 irAEs, with a mean of 1.02 [0-4] irAEs/pts. Most frequent irAEs were rash (24.5%), pruritus (22.6%), diarrhea (21%), thyroid dysfuncion (10.5%), arthritis (8.5%), hepatitis (2.9%) and pneumonitis (2%). 8 (7.5%) patients experienced grade (G) 3-4 irAEs: 1 G3 pneumonitis, 4 G3 diarrhea, 1 G3 mucositis, 1 G3 nephritis and 1 G3 haemolytic anemia. There was one treatment-related death due to pneumonitis. 47 (46.5%) pts received systemic corticosteroids during immunotherapy, 29.8% for irAEs management. 11 (10.9%) pts discontinued treatment due to irAEs. At the time of data analysis, 86.8% of irAEs had improved. With a median follow-up of 8.9 [0.6-48.2] months, median OS was superior in pts experiencing irAEs: not reached (NR) vs 7.8 [95%CI, 5.2-10.5] months (p 0.001). Similarly, PFS was significantly longer: 6.2 [95%CI, 2.3-10.1] vs 2.7 [95%CI, 1.8-3.5] months ($p < 0.0001$). OS was higher in pts who didn't receive steroids during ICIs: NR vs 9.9 [95%CI, 6.8-13.0] months (p 0.024). No association was found between efficacy and the use of antibiotics in the 3 months before first ICIs injection or during treatment.

Conclusions: Development of irAEs was associated with efficacy of ICIs in pts with advanced NSCLC. A negative correlation between the use of systemic corticosteroids and outcomes was found.

Legal entity responsible for the study: Medical Oncology Department, Hospital de la Santa Creu i Sant Pau.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1410P Tumor mutation burden (TMB) estimation using small-sized targeted next-generation sequencing (NGS) to predict efficacy of immune checkpoint inhibitors (ICIs) for non-small cell lung cancer (NSCLC)

T. Ikeda[1], K. Ohashi[2], A. Sekine[3], Y. Ohe[4], T. Tsuda[5], Y. Kataoka[6], S. Hara[7], N. Okamoto[8], M. Kodani[9], S. Matsumoto[10], K. Goto[11]

[1]Second Department of Internal Medicine, Nagaski University Hospital, Nagasaki, Japan, [2]Internal medicine II, Okayama, Japan, [3]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan, [4]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan, [5]Department of Internal Medicine, Toyama Prefectural Central Hospital, Toyama, Japan, [6]Respiratory Mesicine, Hyogo Prefectural Amagasaki Hospital, Amagasaki, Japan, [7]Department of Respiratory Medicine, Itami City Hospital, Itami, Japan, [8]Department of Thoracic Malignancy, Osaka Habikino Medical Center, Habikino, Japan, [9]3rd Internal Medicine, Tottori University Hospital, Yonago, Japan, [10]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [11]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: TMB is promising as a biomarker for the treatment with ICIs. However, because it is difficult to apply whole exon-based TMB analysis into the current practice, clinically applicable simple methods for estimating TMB are needed. The aim of this study was to evaluate TMB based on a small-sized targeted NGS as a biomarker for ICIs.

Methods: Since March 2015 to April 2017, a total of 2243 NSCLC patients (pts) from 244 institutions were enrolled in our large-scale nationwide genome screening network (LC-SCRUM-Japan). Tumor samples were subjected to a 260 kb-sized NGS assay, Oncomine Comprehensive Assay (OCA) ver.1, targeting 143 cancer-related genes. TMB, number of somatic mutations/Mb, was assessed from the results of OCA ver.1 assay, and a cut-off point of TMB to predict response to ICIs was determined by ROC curve. Clinico-genomic database of LC-SCRUM-Japan was utilized for this analysis.

Results: 470 NSCLCs, consisting of 359 adenocarcinomas, 73 squamous cell carcinomas and 38 others, were evaluated in this study. The median number of mutations was 11.5/Mb (range, 0-130.8/Mb). We defined number of mutations ≧15.4/Mb as high TMB and <15.4/Mb as low TMB. High TMB was observed 34.3% (123/359) in adenocarcinoma and 41.1% (30/73) in squamous cell carcinoma. The response rate was higher in pts with high TMB than in those with low TMB (13.3% [23/173] vs. 5.7% [17/297], $p = 0.0059$). The durable clinical benefit (DCB; complete response, partial response or stable disease that lasted >6 months) rate also tended to be higher in pts with high TMB than in those with low TMB (17.3% [30/173] vs. 11.8% [35/297], $p = 0.0980$). The progression-free survival (PFS) was not significantly different between the high and low TMB pts (median PFS, 4.4 vs. 3.3 months, $p = 0.1401$).

Conclusions: TMB estimated by OCA ver.1 seemed to be correlated with response rate and DCB but not PFS in NSCLC pts treated with ICIs, suggesting a limitation of TMB estimation by this small-sized targeted NGS as a biomarker of ICIs. Optimal TMB estimation to predict the efficacy of ICIs are warranted.

Legal entity responsible for the study: National Cancer Center Hospital East.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1411P Identification of genomic markers of sensitivity and resistance to checkpoint inhibitors in non-small cell lung cancer in a real world clinico-genomic database

K. Murugesan, G. Li, G. Kaushik, G. Singal, V.A. Miller, G.M. Frampton, L.A. Albacker

Cancer Genomics, Foundation Medicine, Inc., Cambridge, MA, USA

Background: Treatment of non-small cell lung cancer (NSCLC) with checkpoint inhibitors (CI) that block the PD-L1 pathway has resulted in profound responses but only in a subset of patients. Our aim was to examine biomarkers associated with response and resistance to CI in advanced NSCLC to help inform patient stratification.

Methods: We examined 820 lung adenocarcinoma (LUAD) samples that had matched PD-L1 staining and received genomic profiling to measure tumor mutational burden (TMB) and genomic alterations in 315 genes (FM cohort). We also examined progression free survival (PFS) of 1310 CI treated patients in a HIPAA compliant, real world clinicogenomic database (CGDB). These patients received the FoundationOne assay as part of routine care and had electronic health record data available in the Flatiron Health Database (Singal, ASCO 2017).

Results: In the CGDB, we observed known associations between likelihood of PFS and TMB, loss of STK11. TMB correlated with median PFS in months (mPFS): TMB > 20 mutations per MB (N = 164) – 6 mo vs TMB < =20 (N = 1146) – 2.8 mo, P = 1e-07). Patients with STK11 loss had reduced mPFS (wt 3.1 mo vs mut 2.5 mo, P = 0.01). We analyzed PDL1 staining for driver alterations in LUADs in the FM cohort. EGFR mutant samples were enriched for PDL1 negative staining (FM cohort: P = 6.3e-5) and the EGFR cohort had reduced mPFS (CGDB: wt 3 mo vs mut 2.4 mo, P = 0.003). Samples with MET exon 14 skipping mutations were enriched for PDL1 high positive staining (FM: P = 2.3e-5), but the MET cohort had similar mPFS (CGDB: wt 3 mo vs mut 2.7 mo, P = 0.8). Samples with BRAF alterations trended towards both PDL1 high positive staining (FM: P = 0.06) and increased mPFS (CGDB: wt 2.9 mo vs mut 4.6 mo, P = 0.2).

Conclusions: We examined PFS of NSCLC patients on CI therapies in a clinicogenomic database and observed known associations with TMB, STK11 and EGFR alterations. We found that, at a population level, MET altered patients did not have enhanced mPFS despite increased PDL1 HP staining, suggesting dual or targeted therapies. Real-world datasets such as the CGDB hold promise in prioritizing therapies and identifying biomarkers of response and resistance.

Legal entity responsible for the study: Foundation Medicine Inc., Cambridge, Massachusetts, United States of America.

Funding: Foundation Medicine Inc., Cambridge, Massachusetts, United States of America.

Disclosure: K. Murugesan, G. Li, G. Kaushik, G. Singal, V.A. Miller, L.A. Albacker, G.M. Frampton: Employee: Foundation Medicine Inc.

1412P HLA-DrbB1 heterozygosis and early auto-antibody rise predict prolonged survival in metastatic NSCLC patients undergoing PD-1 blockade

P. Correale[1], R. Giannicola[1], C. Botta[2], P.S. Tagliaferri[2], P. Pastina[3], M. Monoriti[4], R. Saladino[4], A. Falzea[1], V. Barbieri[2], G. D'Arrigo[5], G. Tripepi[5], P. Tassone[2], L. Pirtoli[3]

[1]Onco-Hematology and Radiotherapy, Grande Ospedale Metropolitano, Reggio Calabria, Italy, [2]Magna Grecia University, Medical Oncology Unit, AUO Mater Domini, Catanzaro, Italy, [3]Radiotherapy Unit, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy, [4]Patologia Clinica, Grande Ospedale Metropolitano, Reggio Calabria, Italy, [5]CNR IFC, Reggio Calabria, Italy

Background: PD-1/PDL-1-blockade by nivolumab is a promising and efficacious treatment for mNSCLC patients. It acts by rescuing PD-1-inactivated tumor-infiltrating-lymphocytes, an event indispensable for a short-term antitumor response. Nevertheless, continuous immune-priming is needed to avoid clonal-T-cell exhaustion and to prolong patient survival. We have investigated, whether class-I/II HLA homo/heterozygosis, antigen cascade and cross-priming measured as auto-antibody (AAbs) rise may predict patient outcomes with nivolumab treatment.

Methods: This is a retrospective study including ninety-eight mNSCLC patients who received nivolumab (3mg/kg every 15 days) between September 2015 and March 2018 as a second line of treatment. Log-rank test and Mantel-Cox analysis were carried out to correlate PFS and OS with homo/heterozygosis HLA status, respectively, for locus A, B, C and DrB1 and baseline and post-treatment levels of AAbs [anti-nuclear antibodies (ANA), extractable nuclear antigen (ENA), anti-smooth cell antigen (ASMA), anti-neutrophil cytoplasmic antigens (ANCA)].

Results: A PFS and OS of 13.68 (95%CI:10.85 -16.5) and 16.41 (95%CI:13.48- 19.34) months, were, respectively, recorded. They were not correlated with histology, sex or previous radiotherapy. HLA-DrB1 heterozygosis showed a significant advantage in OS (HR = 0.18, 95%CI:0.036-0.902; p = 0.037). A prolonged survival was also found in patients who showed early rise (within thirty days) of one (score 1, HR = 0.235, 95% CI: 0.084-0.654. P = 0.018) or more AAbs (score 2, HR = 0.22, 95% CI: 0.081-0.624, P = 0.001). Finally, Cox analysis revealed a predictive role for treatment-related early increase in eosinophil cell counts (OS, HR: 0.68, 95% CI: 0.57-0.81, P = 0.031).

Conclusions: Heterozygosis in the HLA-DrB1 locus and early rise in ANA, ENA and/or ASMA is predictive of longer OS in nivolumab-treated mNSCLC patients. These data support the hypothesis that continuous and efficient tumor antigen-release and cross-priming during PD1/PDL-1 blockade is critical for long-term patient survival. These results offer a strong rationale to design future immunotherapy trials in NSCLC patients.

Legal entity responsible for the study: Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1413P Neutrophil-platelet score (NPS), a predictive systemic inflammation score for PD-1 immune checkpoint inhibitors (ICI) in pretreated advanced non-small cell lung cancer (NSCLC) patients

X. Mielgo Rubio[1], M. Sereno Moyano[2], L.E. Chara[3], R. López-Castro[4], J. Rubio-Martínez[5], A. Velastegui[6], C. Olier-Garate[1], S. Falagán[2], I. Gómez-Barreda[3], A. Riquelme[7], J. Silva-Ruiz[1], J. Moreno-Rubio[8], C. López[3], C. Bueno[7], A. Cardeña[9], E. Pérez-Fernández[10], M.P. Martí-Castelló[11], M.J. Sotelo-Lezama[7]

[1]Oncology Unit, Hospital Universitario Fundación Alcorcón, Alcorcón, Spain, [2]Medical Oncology, Hospital Infanta Sofia, Ss De Los Reyes, Spain, [3]Medical Oncology, Hospital Universitario Guadalajara, Guadalajara, Spain, [4]Medical Oncology, Hospital Universitario Clínico de Valladolid, Valladolid, Spain, [5]Medical Oncology, Hospital Universitario Móstoles, Móstoles, Spain, [6]Medical Oncology, Hospital Universitario Rey Juan Carlos, Móstoles, Spain, [7]Medical Oncology, Hospital Infanta Cristina, Parla, Spain, [8]Medical Oncology, Hospital Infanta Sofia, Madrid, Spain, [9]Oncology, Hospital Universitario Fundación Alcorcón, Madrid, Spain, [10]Research Unit, Statistical Support, Hospital Universitario Fundación Alcorcón, Alcorcón, Spain, [11]Medicine, Universidad Rey Juan Carlos, Alcorcón, Spain

Background: Systemic inflammation response can be characterized by changes of peripheral blood cell amounts. Several blood cell-based scores have been found to have prognostic value in some tumors treated with ICI. Neutrophil-platelet score (NPS) is a systemic inflammation-based score characterizing 3 prognostic groups: good (0), neutrophils < =7500 and platelets < =400000; intermediate (1), neutrophils >7500 or platelets >400000; poor (2), neutrophils >7500 and platelets >400000). It has never been evaluated as prognostic biomarker in NSCLC patients treated with ICI.

Methods: This is a multicenter retrospective study with the aim to evaluate prognostic value of NPS in patients with pretreated advanced NSCLC treated with PD-1 ICI between March 2015 and April 2018. Clinical data were contributed by 7 medical centers in Spain. Primary endpoint was association of NPS with overall survival (OS).

Results: 168 patients were included. Median age 65 years (39-85). 134(79,8%) were male and 121(72%) were PS > =1. Predominant histologies were adenocarcinoma (50%) and squamous-cell carcinoma (42,9%). 92,3% received nivolumab and 7,7% pembrolizumab. 2,3% had EGFR mutations, and 0,6% ALK rearrangement. PD-L1 IHC was available in 25% (<1%: 36,6%; 1-49%: 39%; > =50%: 24,4%). Median number of prior lines was 1 (1-5). Median number of cycles 11 (1-68). Median follow-up time 6,3m. Response rate (RR) was 30,4% and disease control rate (DCR) 52%. Median PFS and OS were 5,6 months (m) (3,9-7,3) and 11,4 m (9,4-13,5). According to NPS, median OS for good, intermediate, and poor prognostic groups was 11,9m (9,4-14,4), 6,8m (3,3-10,2), and 3m (1,4-4,6), respectively (p = 0,003). Higher NPS was associated with poor OS: NPS1 HR 1,73 (95%CI,1,13-2,65),p=0,01; NPS2 HR 2,89 (95%CI,1,31-6,39), p = 0,009). No significant association between NPS and PFS was found. NPS was associated with DCR, NPS2 had more patients with progression disease as best response to ICI than NPS1 and 0 (86 vs 57 vs 42%, p = 0,039).

Conclusions: NPS predicted OS and DCR in pretreated advanced NSCLC patients who received treatment with PD-1 ICI nivolumab or pembrolizumab. These results need to be validated in prospective studies.

Legal entity responsible for the study: Xabier Mielgo Rubio.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1414P Prediction of PD-1 immunotherapy (IO) response for KRAS mutated non-small cell lung cancer (NSCLC) based on co-mutations using a computational biological model

H. Wakelee[1], J. Aredo[2], S. Vali[3], N.K. Singh[4], S.V. Vasista[4], U. Mitra[4], T. Abbasi[3], S.K. Padda[5]

[1]Medicine/Oncology, Stanford Advanced Medicine Center, Stanford, CA, USA, [2]School of Medicine, Stanford University, Stanford, CA, USA, [3]Research, Cellworks Group, San Jose, CA, USA, [4]Research, Cellworks Research India Pvt. Ltd, Bangalore, India, [5]Medicine/Oncology, Stanford University, Stanford, CA, USA

Background: KRAS mutated NSCLC is a heterogeneous disease due to the impact of co-mutations (co-mut). In preclinical models, KRASco-mut differentially activate downstream pathways and affect the tumor immune microenvironment in diverse ways. Data suggest KRASco-mut may affect sensitivity to PD-1 axis IO.

Methods: Genomic information of 2974 NSCLC patients was input into computational biological model (CBM) software (Cellworks Group, San Jose, CA). Computational protein network maps of disease characteristics were generated for each patient. CBM was used to predict sensitivity to PD-1 axis IO in KRASco-mut subsets including: KRAS/TP53, KRAS/CDKN2A, KRAS/STK11, KRAS/KEAP1, KRAS/STK11/KEAP1, KRAS/PIK3CA, and KRAS without co-mut. The 3 key metrics used to predict sensitivity included PD-L1 expression; Dendritic Cell Infiltration Index (9 chemokine markers); and Immunosuppressive Biomarker Expression (14 markers). Correlation of CBM prediction of IO sensitivity was examined in a clinical cohort of 36 KRASmutated NSCLC patients with available overall survival (OS) data from Stanford University treated with PD-1 axis IO during their treatment course.

Results: In the overall cohort, withregards to prediction of sensitivity to PD-1 axis IO, CBM predicted the majority of patients with KRAS/KEAP1and KRAS/STK11/KEAP1 to not benefit from IO, whereas CBM predicted the majority of patients with KRAS/TP53, KRAS/PI3KCA, and KRAS without co-mut to benefit. No definitive predictions could be made for KRAS/STK11and KRAS/CDKN2A. In the clinical cohort of 36 patients treated with PD-1 axis IO during their treatment course, CBM was able to assess 27 of these patients, identifying patients with OS > 12 months, with 82.8% positive predictive value, 42.9% negative predictive value, and 75% concordance.

Conclusions: CBM predicted certain subsets of KRASmutated NSCLC based on co-mut are more likely to be sensitive to PD-1 axis IO. In a small clinical cohort of KRASmutated NSCLC treated with PD-1 axis IO, in light of existing biomarkers, CBM identified patients with improved prognosis with good positive predictive value.

Legal entity responsible for the study: Cellworks Group.

Funding: Cellworks Group.

Disclosure: S. Vali, T. Abbasi: Employee and stockholder: Cellworks Group. N.K. Singh, S.V. Vasista, U. Mitra: Employee: Cellworks Research India Pvt. Ltd. All other authors have declared no conflicts of interest.

1415P Association between early immune-related adverse events and clinical outcomes in patients with advanced non-small cell lung cancer treated with pembrolizumab as first-line therapy: A retrospective multicenter cohort study

K. Hosoya[1], D. Fujimoto[1], M. Tamiya[2], A. Tamiya[3], H. Suzuki[4], K. Hirano[5], T. Yokoyama[6], M. Morita[7], Y. Fukuda[8], M. Kanazu[9], T. Makio[10]

[1]Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan, [2]Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan, [3]Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan, [4]Thoracic Oncology, Osaka Habikino Medical Center, Osaka, Japan, [5]Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan, [6]Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan, [7]Respiratory Medicine, Kobe City Medical Center West Hospital, Kobe, Japan, [8]Respiratory Medicine, Himeji Medical Center, Himeji, Japan, [9]Thoracic Oncology, National Hospital Organization Toneyama National Hospital, Toyonaka, Japan, [10]Respiratory Medicine, Itami City Hospital, Itami, Japan

Background: Previous studies have shown that early immune-related adverse events (irAEs) are associated with better outcomes in patients with advanced non-small cell lung cancer (NSCLC) who received nivolumab, and the associations differ among various types of early irAEs. However, these previous studies included patients regardless of their PD-L1 status and lines of therapy.

Methods: We retrospectively analyzed patients with advanced NSCLC and PD-L1 TPS of ≥ 50% who received pembrolizumab as the first line therapy at 10 institutions between February 2017 and January 2018. Patients were excluded if they were treated with systemic glucocorticoids or other immunosuppressive agents. Early irAEs were defined as irAEs that occurred within 3 weeks after commencing pembrolizumab therapy.

Results: In total, 145 patients were included; their median age was 71 (range: 39-87) years. Of the 145 patients, 122 (84%) were men, 119 (82%) had PS 0-1, and 5 (3%) had EGFR-mutations or ALK-rearrangements. In all patients, the objective response and disease control rates were 55% and 77%, respectively. Common early irAEs included rash, pyrexia, and interstitial lung disease. The objective response and disease control rates were significantly higher in patients with early irAEs than in those without (79% versus 46% and 95% versus 71% [both $p < 0.01$]), respectively. Similarly, the median PFS was significantly longer in patients with early irAEs than those without (not reached versus 7.0 months, $p = 0.04$). When we analyzed the association between types of early irAEs and clinical outcomes, rash and/or pyrexia was strongly associated with longer PFS than those without rash or pyrexia (not reached vs. 6.9 months, $p = 0.01$). The follow-up is ongoing.

Conclusions: In patients with advanced NSCLC and PD-L1 TPS of ≥ 50% who received first-line pembrolizumab, early irAEs were associated with better clinical outcomes. Moreover, early development of rash and pyrexia was strongly associated with better clinical outcomes.

Clinical trial identification: UMIN000032470.

Legal entity responsible for the study: Hanshin Oncology clinical Problem Evaluation group (HOPE).

Funding: Has not received any funding.

Disclosure: D. Fujimoto, M. Tamiya, A. Tamiya, K. Hirano: Speaking fees: MSD, Taiho. T. Yokoyama: Speaking fees: Taiho. M. Kanazu: Speaking fees: MSD. All other authors have declared no conflicts of interest.

1416P Immunosenescence (iSenescence) correlates with disease progression in advanced non-small cell lung cancer (aNSCLC) patients treated with PD-(L)1 inhibitors (IO)

R. Ferrara[1], M. Naigeon[1], E. Auclin[2], B. Duchemann[1], L. Cassard[1], J. Medhi[1], L. Boselli[1], J. Grivel[1], A. Desnoyer[1], L. Mezquita[3], F. Aboubakar[3], L. Hendriks[3], D. Planchard[3], C. Caramella[4], J. Remon[3], M. Ngocamus[5], C. Nicotra[5], B. Besse[3], N. Chaput[1]

[1]Laboratory of Immune Oncology, Institut Gustave Roussy, Villejuif, France, [2]Oncology, Hopital European George Pompidou, Paris, France, [3]Department of Medical Oncology, Gustave Roussy Institute, Villejuif, France, [4]Radiology, Institut Gustave Roussy, Villejuif, France, [5]Drug Development Department, Institut Gustave Roussy, Villejuif, France

Background: iSenescence is a progressive remodeling of immune functions with a multifactorial etiology (i.e. aging, chronic inflammation, cancer). Although the absence of CD28 and the expression of CD57 and Killer-cell lectin-like receptor G1 (KLRG1) on peripheral T-lymphocytes are potential hallmarks of iSenescence, the characterization of such phenotype in IO-treated aNSCLC patients and the correlation with clinical characteristics and benefit from immunotherapy are currently unknown.

Methods: A senescent immune phenotype (SIP) defined as a percentage of circulating $CD8^+CD28^-CD57^+KLRG1^+$ T-lymphocytes was assessed by flow cytometry (FC) on fresh blood from aNSCLC patients treated with IO in a single institution (03/2017–04/2018). A log-rank maximization method was used to identify a SIP cut-off level and dichotomize patients accordingly. The objective was to correlate SIP with clinical characteristics and RECIST response by univariate logistic regression analysis.

Results: 39 aNSCLC patients were evaluable for SIP before IO: 38% ≥ 65 years, 87% non-squamous, 38% KRAS mutated, 54% with PD-L1 expression ≥1%, 13% chemotherapy naïve. Among 30 patients evaluable for IO response, 53% had progression (PD), 27% stability (SD), 20% partial response (PR). Median PFS was 1.9 months (95% CI 1.5; 2.5). OS was not calculated due to the short follow-up [6 months (95% CI 4-11)]. SIP (% $CD28^-CD57^+KLRG1^+$) median value on circulating $CD8^+$ lymphocytes was 15.26% (min 1.87%, max 56.28%). Overall, 13 (33%) of 39 patients had >22.25% $CD8^+$ lymphocytes with a $CD28^-CD57^+KLRG1^+$ phenotype, being classified as SIP^+. SIP status did not significantly correlate with age, IO-baseline patients' characteristics or previous chemotherapy exposure. Among patients evaluable for IO response, only 1 (10%) of 10 SIP^+ experienced disease control (PR/SD), compared to 13 (65%) of 20 SIP^- patients; similarly, PD rate was significantly higher in SIP^+ compared to SIP^- patients (90% vs 35%, $p = 0.007$).

Conclusions: iSenescence, monitored by FC measurement of 3 surface molecules on circulating $CD8^+$ lymphocytes, is observed in 33% of aNSCLC patients, is independent of age and correlates with lower disease control rate upon IO.

Legal entity responsible for the study: Institut Gustave Roussy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1417P Preliminary results of PRINCiPe (predictors of resistance to immunotherapy with nivolumab [NIV]) study in advanced pretreated non-small cell lung cancer (APNSCLC), investigating the role of an immune genomic signature (IGS) including JAK2, JAK3, PIAS4, PTPN2, STAT3, IFNAR2 alterations

S. Pilotto[1], G. Grizzi[1], I. Sperduti[2], M. Simbolo[3], C. Vicentini[3], A. Caliò[3], M. Caccese[1], A. Mafficini[3], L. Carbognin[1], V. Corbo[3], A. Gkountakos[3], A. Santo[1], M. Infante[4], M. Brunelli[3], A. Scarpa[5], G. Tortora[1], E. Bria[6]

[1]Medical Oncology, University of Verona, AOUI Verona, Verona, Italy, [2]Biostatistics, Regina Elena National Cancer Institute, Rome, Italy, [3]Department of Diagnostics and Public Health, Section of Anatomical Pathology, University and Hospital Trust of Verona, Verona, Italy, [4]Thoracic Surgery, AOUI Verona, Verona, Italy, [5]ARC-Net Research Centre and Department of Diagnostics and Public Health, AOU Verona, Verona, Italy, [6]UOC Oncologia Medica, Università Cattolica del Sacro Cuore - Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Background: Although immunotherapy impressively improved the outcome of APNSCLC, many patients (pts) rapidly progress. The mechanism of resistance may be influenced by genomic abnormalities in immune-escape/editing genes.

Methods: FFPE-tumor blocks of APNSCLC pts undergone NIV were retrospectively sequenced for Somatic Mutations/Copy Number Variations (SM/CNV) (Ampliseq 17-genes customized panel: APLNR, B2M, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IRF9, JAK1, JAK2, JAK3, PIAS4, PTPN2, SOCS1, STAT1, STAT2, STAT3, TYK2). End-points of PRINCiPe study: overall-, progression-free-survival (OS/PFS) and objective response rate (ORR).

Results: 24 APNSCLC pts were gathered (median age 69.5 yrs, median number of previous lines 3 [2-5], 2nd line NIV [70.8%], male/female 79.2/20.8%, squamous/non-squamous 41.7/58.3%, EGFR mutant 5 [20.8%], median follow-up 6.8 months [range 1-23], deaths 14 [58.3%]). JAK3/JAK2 (6/3 pts, 25/12.5%) CNV, and IFNAR2/STAT3 SM (2 pts, 8.3%) were the most frequent abnormalities. Pts (12) with JAK3, PIAS4, PTPN2, STAT3, IFNAR2 SM and/or JAK2/3 CNV (IGS+) had a significantly lower OS/PFS than those without (IGS-). At multivariate analysis, IGS+ was independently associated with shorter OS (HR 4.90, 95% CI 1.40-16.5, $p = 0.01$) and PFS (HR 6.10, 95% CI 2.0-18.7, $p = 0.001$); the (previous) surgery was significantly associated

with longer PFS (HR 4.20, 95% CI 1.1-11.4, p = 0.03). IGS+ pts were significantly more associated with the presence of liver metastases (p = 0.04). A trend towards lower activity of NIV in EGFR+ pts was found.

Table: 1417P

	IGS+	IGS-	p-value
ORR (%, 95% CI)	-	16.6% (2-31)	0.09
Median OS (months, 95% CI)	4 (1-8)	13 (n.e.)	0.046
Median PFS (months, 95% CI)	3 (2-3.5)	6 (5-9)	0.002

Conclusions: The derived IGS appears to identify APNSCLC pts with a lower chance to benefit from NIV, supporting intrinsic resistance. Given the small sample, a prospective larger and external validation is ongoing.

Legal entity responsible for the study: Emilio Bria.

Funding: University of Verona.

Disclosure: All authors have declared no conflicts of interest.

1418P The need of re-biopsy: Increase in PD-L1 expression from initial stage to recurrence of non-small cell lung cancer

M. Lacour[1], S.Y. Lee[2], U. Rulle[3], A. Soltermann[3], E.J. Rushing[4], D. Soldini[3], S. Hiltbrunner[2], W. Weder[1], A. Curioni-Fontecedro[2]

[1]Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland, [2]Medical Oncology / Haematology, University Hospital Zurich, Zurich, Switzerland, [3]Surgical Pathology, University Hospital Zurich, Zurich, Switzerland, [4]Neuropathology, University Hospital Zurich, Zurich, Switzerland

Background: Non-small cell lung cancer (NSCLC) has the highest mortality rate of all cancers worldwide. Developments in oncological therapy have led to new therapeutic guidelines including immunotherapy such as PD-1/ PD-L1 inhibitors. However, PD-L1 expression in tumor cells might be a dynamic process explaining variability in PD-L1 expression. To test the hypothesis of PD-L1 conversion in patients presenting with NSCLC we evaluated PD-L1 expression in initial tumor samples as well as at recurrence.

Methods: We retrospectively examined PD-L1 expression in resected specimens of patients with NSCLC as well as in biopsies at recurrence by immunohistochemistry (IHC). Patients presenting NSCLC recurrence after adjuvant chemotherapy and with no adjuvant chemotherapy were included. IHC score was defined as the proportion of tumor cells with stained cell membrane. Migration of IHC group was considered as a significant change in PD-L1. Four IHC score groups were defined: TC0 <1%, TC1 ≥1 <5%, TC2 ≥5 <50% and TC3 ≥50%

Results: In total, 36 patients were included. All patients presented adenocarcinoma. 20 patients (56%) underwent adjuvant chemotherapy after surgical resection and 16 patients (44%) had no adjuvant chemotherapy. Initial PD-L1 expression was present in 10 out of 36 patients corresponding to 28%. Out of 20 patients receiving adjuvant chemotherapy 7 patients (35%) showed significant upregulation in PD-L1 expression at recurrence. In comparison to patients with no adjuvant therapy, where only 2 out of 16 (12.5%) showed significant change in PD-L1 expression. Furthermore, 6 out of 36 patients (17%) were PD-L1 negative and had become positive at NSCLC recurrence.

Conclusions: Progress in immunotherapy has led to new therapeutic guidelines. We demonstrated that chemotherapy might increase PD-L1 expression in NSCLC specimens. These findings suggest that chemotherapy in combination with immunotherapy might constitute a new therapeutic strategy for locally advanced NSCLC. Furthermore, in about 17% of our patients, the initial tumor sample proved PD-L1 negative, but a significant change in PD-L1 expression at tumor recurrence was demonstrated. This might suggest the use of PD-L1 inhibitors in first line therapy, even if PD-L1 expression is not present at time of diagnosis.

Legal entity responsible for the study: Alessandra Curioni-Fontecedro.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1419P Basal lymphopenia as a potential predictor of benefit from immunotherapy in metastatic non-small cell lung cancer

G. Galli[1], M. Poggi[1], G. Fucà[1], G. Lo Russo[1], C. Proto[1], D. Signorelli[1], M. Vitali[1], M. Ganzinelli[1], N. Zilembo[1], F. de Braud[1], M.C. Garassino[2], M. Imbimbo[1]

[1]Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [2]Thoracic Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

Background: Immunotherapy (IO) is an established treatment (tx) option for metastatic non-small cell lung cancer (mNSCLC). Nonetheless, as only a minority of pts shows tumor response, research is focusing on identification of predictive factors to improve pts' selection. The potential role of blood cell count alterations has been proposed, but evidence is contradictory. We aimed at studying the role of lymphopenia in a cohort of mNSCLC pts treated with IO.

Methods: We retrospectively collected data about all mNSCLC pts treated with IO at Istituto Nazionale dei Tumori, Milan, Italy, from 04/2013 to 01/2018. Basal lymphopenia (Lp) was defined as a lymphocyte count (LC)≤900/mL at the first administration of IO and was considered as a categorical variable. Survival was estimated with Kaplan-Meier method; log-rank test was used to compare curves. Multivariate analyses were performed with Cox proportional model.

Results: We identified 150 pts, with a median age of 66.5 years. IO was an antiPD1 in 64.0% of cases, an antiPDL1 in 31.3% of cases, and a combination antiPDL1/CTLA4 in 4.7% of cases. IO was administered as a first line tx in 23 pts, as a second line tx in 66 cases, as a more advanced line of tx in 61 cases. Median progression free survival (PFS) and overall survival (OS) of the global population were 3.2 and 11.2 months (mos), respectively. Though non-statistically significant, there was a tendency towards a lower response rate (RR) for cases with basal Lp (10.0% vs 25.0%, p.0881); disease control rate (DCR) for the same group was significantly worse (30.0% vs 58.4%, p.0074) than for cases without Lp. Pts with Lp also showed shorter PFS and OS than cases with normal LC (PFS 1.9 vs 3.0 mos, p.0010; OS 4.5 vs 13.5 mos, p<.0001). The impact of LC on OS retained significance after correction for the effects of performance status, which was the only other variable influencing this endpoint.

Conclusions: The presence of Lp at the beginning of IO was related to inferior disease control and shorter survival in the analyzed cohort. Given the limitations of a retrospective study, these results need confirmation in larger case series. Nonetheless, the suggestion that Lp may predict poor benefit from IO in mNSCLC warrants further investigation.

Legal entity responsible for the study: Istituto Nazionale dei Tumori.

Funding: Has not received any funding.

Disclosure: G. Lo Russo: Honoraria: Eli Lilly, BMS, AstraZeneca. C. Proto: Honoraria: BMS, MSD, Eli Lilly. D. Signorelli: Honoraria: AstraZeneca, Boehringer Ingelheim, BMS. M.C. Garassino: Honoraria: Boehringer Ingelheim, AstraZeneca, Roche. M. Imbimbo: Honoraria: BMS. All other authors have declared no conflicts of interest.

1420P Soluble immune biomarkers to anti-PD1 treatment in non-small cell lung cancer (NSCLC)

J. Garde-Noguera[1], E. Jantus-Lewintre[2], B. Honrubia Peris[3], S. Gallach Garcia[4], F. Zhang[5], J. García Sánchez[3], S. Calabuig Fariñas[6], A. Blasco Cordellat[7], N. Piera Molons[3], J. Vidal-Martinez[1], J. Murado-Pardo[1], L.D. Condori Farfan[8], R. Gisbert-Criado[1], E. Escorihuela[9], C. Camps[10]

[1]Medical Oncology, Hospital Arnau de Vilanova, Valencia, Spain, [2]Laboratorio de Oncología Molecular, Fundación para la Investigación, Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain, [3]Oncology, Hospital Arnau de Vilanova, Valencia, Spain, [4]Molecular Oncology Laboratory, Fundación de Investigación Hospital General Universitario de Valencia - CIBERONC, Valencia, Spain, [5]Molecular Oncology, Fundación de Investigación Hospital General Universitario de Valencia, Valencia, Spain, [6]Medical Oncology Service, Molecular Oncology Lab., Fundación Investigación Hospital General Universitario Valencia, Valencia, Spain, [7]Medical Oncology, Hospital General Universitario Valencia, Valencia, Spain, [8] Medical Oncology, Hospital General Universitario Valencia, Valencia, Spain, [9]Laboratorio de Oncología Molecular, Fundación para la Investigación, Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain, Departament de Biotecnologia, Universitat Politécnica de València, Valencia, Spain, [10]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain

Background: Anti-PD1 antibodies has become the standard second line treatment for advanced Non-Small-Cell Lung Cancer (NSCLC). The efficacy of these treatments seems to be higher in tumors expressing PDL1. However, the difficulty to achieve tumour samples for the analysis of PDL1 is a barrier for precise oncology. The aim of this study was to evaluate the utility of circulating biomarkers such as sPDL1, sPDL2, sCD80 and sHVEM as predictors of response to PD1 blockers in NSCLC.

Methods: Blood samples were collected before treatment from 34 NSCLC pts who received anti-PD1 therapy (second line). Plasma levels of four immune-markers were measured through ELISA and Multiplex bead-based assays. When needed, continuous variables were categorized using the median or quartiles as a cut-off. Non parametric test were used for correlations between analytical variables and clinical-pathological parameters, response rate. For survival analysis (progression free- PFS or overall survival - OS) Kaplan Meier curves and long-rank test were performed.

Results: Median age of the pts included in the study was 64y, 73% were males and 67% adenocarcinomas. Median plasma levels of PDL1, PDL2, CD80 and HVEM were 1.31, 1.12, 0.197 and 0.451 ng/ml, respectively. No relevant association between clinic-pathological parameters and the plasma markers analyzed were found. Interestingly, response rate in patients with sPDL1 in the first quartile (Q1) was 11%, whereas for those in the Q2 and Q3 were 44% and 40%, respectively and the percentage raises to 50% in the Q4. Patients with higher plasma levels of CD80 had a significant increase in PFS compared to those with sCD80 below the median (14.50 vs 1.70 months, p = 0.026, respectively).

Conclusions: In conclusion, circulating immune markers can be reliable detected in plasma of advanced NSCLC pts. In pts treated with anti-PD1 antibodies, sPDL1 and sCD80 seem to be related to the degree of response or PFS. Further investigations to assess the role of these biomarkers in the context of immunotherapy are needed.

Legal entity responsible for the study: Comité Etico de Investigacion de Hospital Arnau de Vilanova de Valencia, Spain.

Funding: grant PI15-00753 from Instituto de Salud Carlos III and Arnal Planelles Foundation.

Disclosure: All authors have declared no conflicts of interest.

1421P Clinical characterization of rare EGFR mutations in non-small cell lung cancer and in silico prediction of drug sensitivity

S. Ikemura[1], H. Yasuda[2], S. Matsumoto[3], M. Kamada[4], T. Betsuyaku[2], Y. Okuno[4], K. Goto[5], K. Tsuchihara[6], K. Soejima[7]

[1]Cancer Center, Keio University School of Medicine, Tokyo, Japan, [2]Department of Pulmonary Medicine, Keio University School of Medicine, Tokyo, Japan, [3]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [4]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [5]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [6]Division of Translational Genomics, Group of Translational Research, National Cancer Center Hospital, Tokyo, Japan, [7]Clinical and Translational Research Center, Translational Research Division, Keio University Hospital, Tokyo, Japan

Background: Recent genome scale characterization of cancers identified overwhelming numbers of novel, rare and uncharacterized somatic mutations, variance of unknown significance (VUS), in non-small cell lung cancer (NSCLC). In order to make these VUS data clinically useful, further functional and biological characterization of each mutation is mandatory. In addition, development of novel strategies to overcome mutation diversity of lung cancer is needed.

Methods: Using the large-scale prospective cohort data of the LC-SCRUM-Japan, nationwide lung cancer clinical and the genomic characterization network in Japan, we characterized the frequency and distribution of rare EGFR mutations in NSCLC and the clinical course of the patients harboring these mutations. In addition, to perform functional and biological characterization of each mutation, we created a Ba/F3 EGFR minor mutation library. Furthermore, the in silico sensitivity prediction model has been developed to demonstrate binding affinity of protein and drug compound and applied to EGFR tyrosine kinase inhibitor with mutated EGFR.

Results: Of the 2164 NSCLC patients examined by LC-SCRUM-Japan, 113 (5.2%) harbored rare EGFR mutations. We found the diverse distribution of EGFR mutations throughout the gene, the most frequent group included EGFR exon 20 insertion mutations (52 cases). We clarified the sensitivity profile of the VUS to EGFR tyrosine kinase inhibitors. Binding affinities calculated by the in silico sensitivity prediction model showed statistically significant correlation (R2: 0.7425, $p < 0.05$) with the experimentally observed IC50 values.

Conclusions: These data may help in choosing or predicting the appropriate inhibitor for lung cancer with VUS in EGFR, thereby contributing to the further development of precision medicine. Here, we clarified the diversity of VUS in EGFR and provide novel insights, via supercomputer utilized drug sensitivity prediction, in the cancer field.

Legal entity responsible for the study: Keio University School of Medicine.

Funding: Grants-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Disclosure: All authors have declared no conflicts of interest.

1422P Evolution and clinical impact of EGFR mutations in circulating free DNA in the BELIEF trial

A. Curioni[1], E. Felip[2], U. Dafni[3], M-A. Molina[4], O. Gautschi[5], S. Peters[6], B. Massutí[7], R. Palmero[8], S. Ponce[9], E. Carcereny[10], M. Früh[11], M. Pless[12], S. Popat[13], S. Cuffe[14], N. Karachaliou[15], R. Kammler[16], M. Kassapian[17], H. Roschitzki-Voser[16], R.A. Stahel[1], R. Rosell[15]

[1]Department of Haematology and Oncology, Division of Oncology, University Hospital Zurich, Zurich, Switzerland, [2]Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [3]National and Kapodistrian University of Athens and, Frontier Science Foundation-Hellas, Athens, Attica, Greece, [4]Pangaea Biotech S.L., Quirón Dexeus University Hospital, Barcelona, Spain, [5]Medical Oncology, Cantonal Hospital Lucerne, Lucern, Switzerland, [6]Département d'Oncologie, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, [7]ISABIAL Oncologia Médica, Hospital Universitario Alicante, Alicante, Spain, [8]Catalan Institute of Oncology, Hospital Duran i Reynals, L'Hospitalet de Llobregat, Llobregat, Spain, [9]Oncología Médica, Hospital Universitario 12 de Octubre, Madrid, Spain, [10]Hospital Germans Trias i Pujol, Catalan Institute of Oncology, Badalona, Spain, [11]Swiss Group for Clinical Cancer Research (SAKK) and Department of Oncology / Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland, [12]Medical Oncology, Kantonsspital Winterthur, Winterthur, Switzerland, [13]Medical Oncology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [14]Cancer Trials Ireland and Medical Oncology, St James's Hospital, Dublin, Ireland, [15]Institute of Oncology Rosell, University Hospital Sagrat Cor, Barcelona, Spain, [16]European Thoracic Oncology Platform (ETOP), Bern, Switzerland, [17]National and Kapodistrian University of Athens, Frontier Science Foundation-Hellas, Athens, Greece

Background: BELIEF, a single-arm, phase 2 trial, showed a median (med) progression-free survival (PFS) of 13.2 months (m) with erlotinib and bevacizumab in patients (pts) with advanced EGFR mutated NSCLC (Rosell et al 2017). We prospectively and longitudinally examined the evolution of sensitizing EGFR and p.T790M mutations, in circulating free DNA (cfDNA).

Methods: Blood samples were collected at baseline (BaS), at time of response (6w) and at progression (PD) and sent to a central laboratory. cfDNA was purified, and EGFR mutations were analyzed with real-time PCR assay. The fully validated assay is highly specific (>99%) and sensitive (76%) for EGFR sensitizing mutations.

Results: As of 12 March 2018, at a med follow-up of 47m (IQR: 42, 59), 2 pts (2%) are still on full protocol treatment, while 95 PFS events (87%) and 70 deaths (64%) have occurred. The med PFS is 13.2m (95% CI: 10.3, 15.5), the med overall survival (OS) is 30.2m (95% CI: 23.1, 39.6) and the 2-year OS is 58.4% (95% CI: 48.2-67.2%). cfDNA are available at BaS for 91 pts, at 6w for 72 pts and at PD for 58 pts. EGFR mutations identified in blood were also originally found in tissue. 69 pts had cfDNA assessment both at BaS and 6w. Med PFS was 19.1m for 24 pts without EGFR mutations in cfDNA at BaS and at 6w, versus 12.6m for 43 pts with EGFR mutations detected in cfDNA at BaS, but not at 6w ($p = 0.019$). 46 pts had the 3-pronged assessments (BaS, 6w, PD). The med PFS for the BaS negative group that remained negative at PD was 17.4m (12 pts), while for the BaS positive group that converted to negative at 6w and remained negative at PD was 13.1m (7pts; $p = 0.72$). For those BaS positive who converted to negative at 6w, but later became positive again at PD, the med PFS was 10.6m ($p = 0.20$). At PD, 41% of pts harbored T790M. For pts with BaS EGFR mutations, the med PFS was 13.4m (16 pts) in those without T790M, and 9m (17 pts) for the T790M mutated at PD ($p = 0.14$).

Conclusions: These data suggest the absence of sensitizing EGFR mutations in cfDNA at BaS confers significantly better PFS than in pts with EGFR mutant cfDNA. A trend of shorter PFS is seen in the subgroup of pts with BaS EGFR mutant cfDNA, from whom, at PD, EGFR mutations were again detected. EGFR mutant cfDNA could be an indicator for co-occurring oncogenic events and the use of cfDNA exome platforms should be encouraged.

Clinical trial identification: NCT01562028.

Legal entity responsible for the study: European Thoracic Oncology Platform (ETOP)

Funding: Hoffmann-La Roche.

Disclosure: A. Curioni: Research support: Novartis; Honoraria: MSD, BMS, Boehringer Ingelheim, Roche, Pfizer, Novartis, AstraZeneca. E. Felip: Advisory board and speaker's bureau: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celegene, Eli Lilly, Guardant Health, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Abbvie, Merck. B. Massutí: Consulting or advisory role: Roche, Boehringer Ingelheim, BMS, MSD, AstraZeneca; Speaker's bureau: Roche, Amgen, Merck Serono, Pfizer, AstraZeneca, Boehringer Ingelheim; Travel grants: MSD, Janssen, Roche. M. Früh: Research support: BMS, AstraZeneca; Honoraria to institution for advisory: MSD, Roche, AstraZeneca, BMS, Boehringer Ingelheim. M. Pless: Advisory board role: Roche. S. Popat: Honoraria: Boehringer Ingelheim, AstraZeneca, Roche, Takeda, Chugai Pharma; Consulting or advisory role: Boehringer Ingelheim, Roche, Novartis, Pfizer, AstraZeneca, BMS, MSD, Guardant Health, Abbvie; Travel grants: Boehring Ingelheim, BMS, MSD; Research funding to institution: Boehringer Ingelheim, Epizyme, BMS, Clovis Oncology, Roche, Lilly, Takeda. S. Cuffe: Sponsorship of travel, registration, accommodation for attendances at conferences: ASCO, WCLC from Pfizer, BMS, MSD, Amgen, Roche, Ipsen. R.A. Stahel: Consulting or advisory role: Roche; Speaker's bureach: Roche. All other authors have declared no conflicts of interest.

1423P Pre-treatment EGFR-T790M subclones in lung adenocarcinoma harboring activating mutation of EGFR: A positive prognostic factor for survival?

I. Prediletto[1], E. Vasile[1], R. Bruno[2], E. Macerola[2], G. Pasquini[1], G. Fontanini[2], A. Falcone[1]

[1]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, [2]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy

Background: In lung adenocarcinoma, activating mutation of EGFR (aEGFR) and EGFR-T790M can coexist. T790M confers resistance to 1st and 2nd generation TKIs, the standard 1st line treatment. T790M may also be observed at diagnosis (preT790M+) in 0,5-3% cases using standard techniques and up to 30% with highly sensitive ones. FDA and EMA approved osimertinib, a 3rd generation TKI overcoming T790M resistance, for 2nd-line in patients T790M+. Recently FDA approved it for 1st-line of aEGFR+ metastatic disease. Current guidelines make no distinction in aEGFR patients with or without preT790M+. In the osimertinib era it becomes important to detect properly T790M at diagnosis and to define the best strategy for preT790M+. The aim of this study was to find differences in terms of survival and response rate between preT790M+ and wild-type for T790M (WT), detecting T790M with a highly sensitive technique.

Methods: We selected aEGFR+ lung adenocarcinoma who received 1st or 2nd generation TKI in 1st line treatment in our Institution. We reanalyzed the tumor samples of the diagnosis with RainDrop Digital PCR. For statistical analysis we used Kaplan-Meyer method and log-rank test.

Results: We analyzed tumor samples of 28 subjects. At diagnosis, all were wild-type for T790M with standard techniques. With RainDrop Digital PCR, preT790M+ were 28,6% ($n = 8$). In $\geq 2^{nd}$ lines 50% of preT790M+ and 30% of WT received osimertinib,

according to T790M detection after progression. 1-yr and 2-yr survival were, respectively, 100% and 89% for preT790M+; 68% and 60% for WT. Median OS (mOS) of preT790M+ was not reached at the end of followup and 32.7 months for WT ($p = 0.098$). There were no differences in mOS stratifying by osimertinib use the study population ($p = 0.792$) and preT790M+ subgroup ($p = 1.000$). RR was 87,5% for preT790M+, 60% for WT ($p = 0.241$). Median PFS was 10,4 months for preT790M+, 13.3 months for WT ($p = 0.721$).

Conclusions: Our data, with the limits of the small sample size, show that the coexistence at diagnosis of aEGFR and T790M is not negligible. PreT790M+ tumors could represent a more indolent disease. Further studies are needed to define the optimal timing for osimertinib in these patients.

Legal entity responsible for the study: University of Pisa, Italy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1424P The plasma ctDNA monitoring during epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment in patients with EGFR mutant non-small cell lung cancer (JP-CLEAR trial)

K. Usui[1], T. Yokoyama[2], A. Kisohara[3], Y. Mori[4], Y. Takeda[5], H. Ishida[6], N. Kusano[7], K. Kishi[8], U. Katsushima[9], T. Kuwako[10], H. Aono[11], Y. Shikama[12], K. Minato[13], H. Matsushima[14], K. Uemura[15], Y. Ohashi[16], H. Kunitoh[17]

[1]Division of Respirology, NTT Medical Center Tokyo, Tokyo, Japan, [2]Department of Respiratory Medicine, Kyorin University Hospital, Tokyo, Japan, [3]Division of Respirology, Kasukabe Medical Center, Saitama, Japan, [4]Division of Respiratory Medicine, Iwate Prefectural Central Hospital, Iwate, Japan, [5]Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan, [6]Division of Medical Oncology, Showa University School of Medicine, Tokyo, Japan, [7]Department of Respiratory Medicine, Fujisawa City Hospital, Kanagawa, Japan, [8]Department of Respiratory Medicine, Toranomon Hospital, Tokyo, Japan, [9]Department of Medical Oncology, Kansai Electric Power Hospital, Osaka, Japan, [10]Department of Respiratory Medicine, National Hospital Organization Shibukawa Medical Center, Gunma, Japan, [11]Respiratory Medicine, Mitsui Memorial Hospital, Tokyo, Japan, [12]Department of Respiratory Medicine, Showa University Fujigaoka Hospital, Kanagawa, Japan, [13]Department of Respiratory Medicine, Gunma Prefectural Cancer Center, Gunma, Japan, [14]Department of Respiratory Medicine, Japanase Red Cross Saitama Hospital, Saitama, Japan, [15]Division of Biostatistics and Bioinformatics, Interfacluty Initiative in Information Studies, The University of Tokyo, Tokyo, Japan, [16]Department of Integraded Science and Technology, Chuo University, Tokyo, Japan, [17]Department of Medical Oncology, Japanese Red Cross Medical Center, Tokyo, Japan

Background: Approximately 60% of EGFR mutant non-small cell lung cancer (NSCLC) patients treated with first/second generation EGFR-TKIs will acquire resistance by the T790M mutation. Since osimertinib, a third generation EGFR-TKI, is active for NSCLC with T790M, re-biopsy to examine the T790M status at the disease progression is necessary to administer osimertinib adequately. T790M monitoring in patients receiving EGFR-TKIs by plasma ctDNA could give valuable clinical information.

Methods: Patients with advanced or post-operative recurrent NSCLC with the sensitive EGFR mutations who receive the first EGFR-TKI treatment are eligible. Plasma samples at the baseline and the several timings of the disease are analyzed for EGFR mutation status using Cobas EGFR Mutation Test®.

Results: Between September 2016 and March 2017, 122 patients at 15 institutions in Japan were enrolled. Total 1291 plasma samples from 121 patients were analyzed for EGFR mutation status at March 2018. At the baseline, the sensitive EGFR mutation (Ex19 del 14, L858R 15) was detected in 29 (23.9%) of 121 patients and the resistant EGFR mutation T790M was detected in 3 (2.5%) patients. During the follow up period, 63 (52.1%) patients experienced disease progression and 62 (51.2%) stopped the first EGFR-TKI treatment. Twenty-one (17.5%) patients showed T790M in plasma ctDNA. Median time from the first EGFR-TKI treatment to the detection of T790M in plasma ctDNA was 441 days. Although 30 patients received re-biopsy to examine the EGFR mutation status at the disease progression, T790M was detected in only eight (22.2%) of the 36 re-biopsied materials. Seven (87.5%) of the eight patients who showed T790M in the re-biopsied materials received osimertinib, whereas 12 (57.1%) of the 21 patients with T790M detection in plasma received osimertinib, 4 (19.0%) continued the first EGFR-TKI, and 4 (19.0%) received platinum-based chemotherapy.

Conclusions: Although ctDNA monitoring during the EGFR-TKI treatment is useful, further investigation is necessary to elucidate the efficacy of osimertinib treatment based on the T790M detection in plasma ctDNA.

Clinical trial identification: UMIN000023248.

Legal entity responsible for the study: CSPOR.

Funding: CSPOR, AstraZeneca

Disclosure: Y. Takeda: Grant/research funding: Taiho, Chugai, Kyowa Hakko Kirin, Boehringer Ingelheim. K. Uemura: Advisory: Ono, Zeria. Y. Ohashi: Executive compensation: Statcom; Honorarium for lecture: Sanofi, Eisai; Consultation: Chugai, Taiho, Kowa; Compensation for IDMC: Shionogi; Travel expense: Yakult, Takeda; Honorarium: Public Health Research Foundation, Daiichi-Sankyo. H. Kunitoh: Honorarium: AstraZeneca. All other authors have declared no conflicts of interest.

1425P ABCB1 genetic polymorphism and pharmacokinetic analysis of low dose erlotinib in frail patients with EGFR mutation (mt)-positive, non-small cell lung cancer: TORG1425

S. Miyamoto[1], T. Tokkito[2], A. Bessho[3], N. Fukamatsu[3], H. Kunitoh[1], M. Ishii[4], H. Tanaka[5], H. Aono[6], T. Fukui[7], K. Kusaka[8], Y. Hosomi[9], A. Hamada[10], K. Yamada[2], H. Okamoto[11]

[1]Medical Oncology, Japanese Red Cross Medical Center, Tokyo, Japan, [2]Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan, [3]Respiratory Medicine, Japanese Red Cross Okayama Hospital, Okayama, Japan, [4]Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Yokohama, Japan, [5]Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan, [6]Respiratory Medicine, Mitsui Memorial Hospital, Tokyo, Japan, [7]Respiratory Medicine, Kitasato University School of Medicine, Sagamihara, Japan, [8]Respiratory Medicine, National Hospital Organization Tokyo National Hospital, Kiyose, Japan, [9]Department of Thoracic Oncology & Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [10]Molecular Pharmacology, National Cancer Center Research Institute, Tokyo, Japan, [11]Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Yokohama, Kanagawa, Japan

Background: We conducted a trial evaluating the efficacy of low-dose erlotinib (ERL) in frail patients with EGFR-mt non-small cell lung cancer (NSCLC). The primary endpoint was met, with the objective response rate (ORR) of 60% (2018 ASCO Abstr. 9063). Previously, it has been reported that ABCB1 genetic polymorphisms affect pharmacokinetics (PK) of ERL and associated adverse events. We investigated ERL plasma concentration and efficacy, as well as the effects of ABCB1 genetic polymorphisms in the patients who participated in this trial.

Methods: Frail patients with EGFR-mt NSCLC who had not undergone chemotherapy were enrolled and administered 50 mg of ERL. Blood samples were collected prior to treatment for ABCB1 genetic polymorphism testing and at 15 days ($\pm$7 days) after initiating ERL administration to measure steady-state trough values. The samples were analyzed at the central laboratory. Plasma concentration was measured with a high-performance liquid chromatograph-tandem mass spectrometery and ABCB1 gene polymorphism analysis using the i-densy™ genetic testing platform.

Results: Of the patients who participated in the trial between December 2014 and April 2017 ($n = 80$), ERL plasma concentration could be measured in 48 patients (males/females 17/31; median age 80 (range 49-90); PS 0-1/2/3-4 35/7/6) and genetic analysis in 45 patients. The ORR for low-dose ERL in the 48 patients was 62.5% (CR/PR/SD/PD/NE 1/29/12/3/3), and the median plasma concentration was 685 ng/ml (range 153-1950). ABCB genetic polymorphism analysis results were: C3435T; TT/non-TT 7/38, G2677T/A; TT/non-TT 7/38, C1236T; TT/non-TT 17/28, with all-TT/others: 5/40. The plasma ERL concentrations did not differ according to response: median plasma concentrations (ng/ml) of CR+PR/SD/PD cases were 701/737/590, $p = 0.435$. Genetic polymorphisms were not correlated with ERL PK, nor were they associated with diarrhea ($p = 0.202$) or rash ($p = 0.29$) by Mann-Whitney tests.

Conclusions: In this trial, no clear correlation was observed between ERL PK and efficacy. In frail patients, low-dose ERL administration of 50 mg is effective and safe, regardless of ABCB genetic polymorphisms.

Clinical trial identification: UMIN000015949, release date: 2014/12/15

Legal entity responsible for the study: NPO Thoracic Oncology Research Group.

Funding: Has not received any funding.

Disclosure: T. Tokkito: Chugai Pharmaceutical (Research funding), AstraZeneca (research funding), MSD (research funding). A. Bessho: Chugai Pharmaceutical Co. (honoraria). H. Tanaka: AstraZeneca (research funding, honoraria), Ono Pharmaceutical (research funding, honoraria), Chugai Pharma (research funding, honoraria), Boehringer Ingelheim (honoraria), MSD (research funding, honoraria), Lilly (research funding, honoraria), Taiho Pharmaceutical (research funding, honoraria), Bristol-Myers Squibb Japan (research funding, honoraria), Pfizer (research funding, honoraria), Novartis (honoraria), Takeda (research funding), Astellas Pharma (research funding), Merck Serono (research funding). T. Fukui: AstraZeneca K.K. (honoraria), Boehringer-Ingelheim Japan Inc. (honoraria), Chugai Pharmaceutical Co. Ltd. (honoraria), Novartis Pharma K.K. (honoraria), Ono Pharmaceutical Co. Ltd. (honoraria), Pfizer Japan Inc. (honoraria), Taiho Pharmaceutical Co. Ltd. (honoraria) Y. Hosomi: AstraZeneca (honoraria), Taiho Pharmaceutical (honoraria), Lilly Japan (honoraria), Chugai Pharma Ono Pharmaceutical (honoraria), Bristol-Myers Squibb Japan (honoraria), MSD (honoraria). K. Yamada: Pfizer Japan (honoraria), Chugai Pharmaceutical (honoraria), Eli Lilly Japan (honoraria), AstraZeneca (honoraria), Ono (honoraria). H. Okamoto: Takeda (research funding), MSD (research funding), Ono (research funding), Astrazeneca (research funding), Merck (research funding), Chugai (research funding), Taiho (research funding), Bristol (research funding), Eli Lilly (research funding), Daiich Sankyo (research funding). All other authors have declared no conflicts of interest.

1426P Longitudinal plasma monitoring of subjects treated with EGFR-TKIs allows better understanding of evolution of acquired resistance and can inform optimal treatment strategies

J. Palma[1], P. Vitazka[2], N. Tikoo[3], A. Balasubramanyam[3], L. Xi[4], S. Yaung[4], E. Kwok[5], A. Lovejoy[6], D. Klass[6], M. Heibeck[7], K. Probst[8], A. Rehfeldt[8], E. Meldgaard[9], A. Madsen[10], M. Clement[10], B. Sorensen[10], P. Meldgaard[9]

[1]Medical Scientific Affairs, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [2]Clinical Science, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [3]Biometrics, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [4]Bioinformatics, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [5]Clinical Operations, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [6]Development, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, [7]Biometrics, Roche Sequencing Solutions, Inc., Potsdam, Germany, [8]Clinical Operations, Roche Sequencing Solutions, Inc., Potsdam, Germany, [9]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, [10]Clinical-Biochemistry, Aarhus University Hospital, Aarhus, Denmark

Background: Targeted therapy (EGFR tyrosine kinase inhibitors, EGFR-TKIs) has been proven effective in NSCLC patients with activating EGFR mutations. Despite the initial response, most patients progress. Several acquired-resistance mutations have been described, including the EGFR T790M mutation. Here we use longitudinal plasma monitoring to identify different mechanisms of acquired resistance to EGFR-TKIs and demonstrate that tumor heterogeneity and clonal evolution may play a role in the outcome of subjects treated with osimertinib.

Methods: Tumor and plasma were collected from 13 subjects with metastatic lung adenocarcinoma treated with erlotinib followed by osimertinib, upon the development of resistance (T790M positive). Overall, 10 FFPE tumor and 115 longitudinally collected plasma specimens were analyzed with either the FDA-approved cobas® EGFR Mutation Test v2 or a 197-gene NGS assay (AVENIO ctDNA Surveillance Kit and AVENIO Tumor Tissue Surveillance Kit prototype, Research Use Only). Detected EGFR and non-EGFR mutations were correlated with disease control (evaluated by RECIST1.1).

Results: The concordance of EGFR mutations (L858R, T790M, Ex19Del) detected by cobas® and AVENIO assay in pre-osimertinib plasma samples was 92.31% (n = 12/13). The AVENIO assay detected additional mutations in ~6 non-EGFR genes. Some of these mutations were already present in pre-erlotinib plasma samples. Not all mutations showed directional change in allelic fraction (AF) after treatment with osimertinib, i.e. some subjects had a complete loss of T790M mutation, whereas other mutations remained unchanged or their AF increased, suggesting clonal heterogeneity. In general, subjects with more than 5 non-EGFR mutations (median count = 5) had a significantly lower median overall survival (OS) benefit of 30.5 months (n = 13, log-rank p-value=0.0048, HR = 12, 95% CI (1.5, 104)).

Conclusions: Longitudinal ctDNA monitoring of subjects treated with EGFR-TKIs with a multi-gene NGS panel enables identification of different resistance mechanisms and can potentially guide a selection of optimal treatment combination and sequencing strategies.

Legal entity responsible for the study: Roche.

Funding: Roche.

Disclosure: J. Palma, N. Tikoo: Employment and stocks: Roche. P. Vitazka, A. Balasubramanyam, L. Xi, S. Yaung, E. Kwok, M. Heibeck, K. Probst, A. Rehfeldt, A. Lovejoy: Employment: Roche. D. Klass: Employment: Roche Sequencing Solutions; Royalties for ctDNA detection: IP; Former shareholder: CAPP Medical. B. Sorensen, P. Meldgaard: Research support and advisory board: Roche. All other authors have declared no conflicts of interest.

1427P Applicability of lung-molGPA index in non-small cell lung cancer patients with various gene alterations and brain metastases

K. Chen[1], Y. Fan[2], Z. Huang[2], Y. Xu[3], X. Yu[1], H. Wang[1]

[1]Chemotherapy Department, Zhejiang Cancer Hospital, Hangzhou, China, [2]Key laboratory on Diagnosis and Treatment Technology on Thoracic Cancer, Zhejiang Cancer Hospital, Hangzhou, China, [3]Key Laboratory on Diagnosis and Treatment Technology on Thoracic Cancer, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China

Background: The Lung-molGPA index is based on the original Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) by incorporating recently reported gene alteration data for non-small cell lung cancer (NSCLC) patients with brain metastases (BM). However, the prognostic prediction value of DS-GPA and Lung-molGPA models remains undetermined, especially in patients with different molecule types.

Methods: A total of 1184 NSCLC patients with BM analyses for clinical factors and outcomes were identified at Zhejiang Cancer Hospital, China. All prognostic factors were weighted for significance by hazard ratios. The applicability of DS-GPA and Lung-molGPA were reappraised in NSCLC patients with BM and various genetic profiles. Additionally, a modified Lung-molGPA, was newly developed for mutant NSCLC patients.

Results: The NSCLC patients in the present study had a median survival of 14.0 months from the time of BM diagnosis. Both DS-GPA and Lung-molGPA models could predict the outcomes ($P < 0.001$), while Lung-molGPA model appeared to exhibit better accurate prediction. Furthermore, Lung-molGPA scores exhibited a discrimination capability in patients with gene variations (3.5-4.0 vs 2.5-3.0 vs 1.5-2.0 vs 0-1.0=62.0 vs 32.0 vs 17.7 vs 3.2 months, $P < 0.001$). However, no significant difference was reached in wild-type patients ($P = 0.133$). Regarding the oncogene-positive NSCLC patients with BM, a modified Lung-molGPA index had been established derived from the prognostic factors with the C-index of 0.73 (95% CI: 0.73-0.80) to accurately calculate the survival probability ($P < 0.001$).

Conclusions: In an era of precision medicine, the Lung-molGPA could precisely predict the prognosis of mutant NSCLC patients with BM, while not working in wild-type patients.

Legal entity responsible for the study: Yun Fan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1428P Testing for and frequency of molecular alterations in patients with advanced NSCLC in Germany. Results from the prospective German registry CRISP (AIO-TRK-0315)

F. Griesinger[1], W.E.E. Eberhardt[2], A. Nusch[3], M. Reiser[4], C. Bernhardt[5], N. Marschner[6], M. Jaenicke[7], A. Fleitz[8], L. Spring[7], J. Sahlmann[9], A. Karatas[10], A. Hipper[10], W. Weichert[11], A. Rittmeyer[12], H. Bischoff[13], C. Waller[14], M. Thomas[15]

[1]Klinik für Hämatologie und Onkologie, Pius Hospital, Oldenburg, Germany, [2]Department of Medical Oncology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany, [3]Onkologie, Onkologische Praxis Velbert, Velbert, Germany, [4]Onkologie, PIOH (Köln Zentrum) - Praxis Internistischer Onkologie und Hämatologie, Cologne, Germany, [5]Onkologie, Gemeinschaftspraxis für Hämatologie und Onkologie, Dortmund, Germany, [6]Medical Oncology, Praxis für Interdisziplinaere Onkologie, Freiburg, Germany, [7]Clinical Epidemiology, IOMEDICO, Freiburg, Germany, [8]Clinical Epidemiology, IOMEDICO AG, Freiburg, Germany, [9]Datamanagement, Statistics and Medical Informatics, IOMEDICO, Freiburg, Germany, [10]AIO Studien gGmbH, AIO Studien gGmbH, Berlin, Germany, [11]Institute of Pathology, Technical University of Munich, Munich, Germany, [12]LKI Lungenfachklinik Immenhausen, LKI Lungenfachklinik Immenhausen, Immenhausen, Germany, [13]Thoraxonkologie, Thoraxklinik Heidelberg, Heidelberg, Germany, [14]Hematology, Oncology and Stem Cell Transplantation, Universitätsklinikum Freiburg Klinik für Innere Medizin Hämatologie, Onkologie und Stammzelltransplantation, Freiburg, Germany, [15]Thoraxonkologie, Thoraxklinik, Heidelberg, Germany

Background: Several therapies targeting molecular alterations in subgroups of NSCLC patients (pts) have been approved and require pts to be tested for these targets. Thorough knowledge of the diagnostic and therapeutic algorithm in routine practice is crucial to evaluate and improve the quality of care.

Methods: The prospective, national clinical research platform CRISP recruits pts in currently 149 representative cancer centres in all therapeutic sectors in Germany. Up to 8000 pts will be recruited and followed until death or up to a maximum of 3 years, respectively. Data from 823 pts recruited by 89 centers by June 30th, 2017 was analysed regarding molecular testing. An update with data cut June 30th, 2018 including at least 2.000 pts by 130 centres will be presented at the conference.

Results: Median age was 67 years and 61% of pts were male. 12% of pts were never smokers. 79% of pts had non-squamous carcinoma (nsqc), 21% squamous carcinoma (sqc). Overall 84% (nsqc 92%, sqc 52%) of pts were tested with at least one test method at the start of treatment. Median turn around time was 2 weeks for next generation sequencing (NGS), 10 days for FISH and one week for other sequencing and IHC. In pts with nsqc (n = 653) 32% of pts were tested by NGS, 45% by other sequencing and 49% by IHC and 38% by FISH. Molecular test rates for EGFR, ALK , and ROS-1 were 73%, 70%, and 53% respectively. In pts with sqc (n = 170) 12% of pts were tested by NGS, 11% by other sequencing, 34% by IHC and 10% by FISH. Molecular test rates for EGFR, ALK, and ROS-1 were 23%, 21%, and 15%, respectively. Test rates for PD-L1 increased from 23% in 2016 to 48% in the first half of 2017. For pts with nsqc for whom test results were available at time of analysis, an EGFR alteration was detected in 15% (n = 71), an ALK alteration in 8% (n = 37), and a ROS-1 alteration in 3% (n = 10) of pts. 24% (n = 65) of pts for whom PD-L1 tumour proportion score (TPS) results were available had a TPS ≥50%.

Conclusions: CRISP presents current real life data on molecular testing from all treatment sectors in Germany. Pts are frequently tested for molecular alterations. NGS is used in one third of nsqc pts. Reasons for testing / non-testing and changes over time will be discussed based on the 2018 data cut.

Clinical trial identification: NCT02622581.

Legal entity responsible for the study: AIO-Studien-gGmbH.

Funding: CRISP is supported by AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Celgene GmbH, Lilly Deutschland GmbH, MSD SHARP & DOHME GmbH, Novartis Pharma GmbH, Pfizer Pharma GmbH, Roche Pharma AG and Takeda Pharma Vertrieb GmbH & Co.KG.

Disclosure: All authors have declared no conflicts of interest.

1429P Molecular landscape of osimertinib resistance revealed by targeted panel sequencing and patient-derived cancer models in non-small cell lung cancer patients

M.H. Hong[1], M.H. Kim[1], S-Y. Kim[2], S.G. Heo[3], H-N. Kang[3], C-W. Park[3], J.C. Barrett[4], D. Stetson[4], J. Chmielecki[4], A. Markovets[5], H.R. Kim[1], B.C. Cho[1]

[1]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Institute for Cancer Research, JE-UK Institute for Cancer Research, Gumi-City, Republic of Korea, [3]Institute for Cancer Research, JE-UK Institute for Cancer Research, Gumi-city, Republic of Korea, [4]Translational Science, AstraZeneca, Waltham, MA, USA, [5]BioScience, AstraZeneca, Waltham, MA, USA

Background: Recent studies demonstrated profound clinical activity of osimertinib in epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) patients. However, the emergence of resistance limits the clinical benefit inevitably, demanding dissection of its underlying mechanisms. Here, we provide the molecular landscape of osimertinib resistance investigated by clinical sample sequencing and patient-derived cancer models.

Methods: The paired tumor tissue (n = 10) and plasma samples (n = 8) were collected from 12 EGFR-mutant NSCLC patients before and after osimertinib treatment in the ASTRIS trial (NCT02474355). The tissue and plasma DNAs were analyzed by targeted next-generation sequencing (NGS) of 112 cancer-related genes (AZ100 panel). The patient-derived cancer cell lines (PDC) and tumor xenografts (PDTX) were established from osimertinib-treated patients. Osimertinib resistant cell line (PC9-GR/AR) was also established by chronic drug administration. The preclinical resistance models were investigated by whole-exome sequencing (WES) and RNA-seq.

Results: The paired baseline and progression sample analysis identified the emergence of acquired mutations, EGFR C797S (n = 1), KRAS G12D (n = 1), and PIK3CA E545K mutations (n = 2), in the progression samples. One of these progression tissue samples with an acquired PIK3CA mutation also lost EGFR. A preexisting KRAS G12D mutation and PTEN loss were also identified in two patients who showed primary resistance to osimertinib. The WES of osimertinib-resistant PDC revealed amplification of GLI1, CDK4, and CCND1. The osimertinib-resistant PDTXs harboring PIK3CA H1047R mutation and MET amplification were established, and PI3K inhibitors and MET inhibitors will be tested. The RNA-seq analysis showed upregulation of epithelial-mesenchymal transition signatures in PC9-GR/AR cells compared to PC9-GR cells that are potentially related to epigenetic resistance mechanisms.

Conclusions: Our multi-layered molecular analysis of osimertinib-resistant patients' clinical samples and patient-derived cancer models demonstrates a diverse spectrum of osimertinib resistance mechanisms.

Legal entity responsible for the study: Byoung Chul Cho.

Funding: AstraZeneca.

Disclosure: J.C. Barrett, D. Stetson, J. Chmielecki, A. Markovets: Employee: AstraZeneca. All other authors have declared no conflicts of interest.

1430P Cell-free circulating tumour DNA (ctDNA) in the management of patients with non-biopsiable advanced non-small cell lung cancer (NSCLC)

M. Kushnir[1], H. Winter[1], C. Murias[1], P. Bains[1], C.Z. Abbosh[2], D. Papadatos-Pastos[3], T. Newsome-Davis[4], T. Ahmed[3], C. Swanton[5], M.D. Forster[6], D. Moore[7], P. Bennett[8], I. Faull[9], R.B. Lanman[10], H-T. Arkenau[11]

[1]Early Phase Trials, Sarah Cannon Research Institute, London, UK, [2]Oncology, St. James's University Hospital Leeds, Leeds, UK, [3]Medical Oncology, University College Hospital, London, UK, [4]Medical Oncology, Chelsea and Westminster, London, UK, [5]Translational Cancer Therapeutics, The Francis Crick Institute, London, UK, [6]Medical Oncology, University College London Cancer Institute, London, UK, [7]Medical Oncology, University College London Cancer Institute, London, UK, [8]Genomics, Sarah Cannon Molecular Diagnostics, London, UK, [9]Business Development & Medical Affairs, Guardant Health, Barcelona, Spain, [10]Medical Affairs, Guardant Health, Redwood City, CA, USA, [11]SCRI, Sarah Cannon Research Institute SCRI UK, London, UK

Background: Genomic profiling of cell-free ctDNA is a non-invasive method to guide personalised medicine. We assessed the utility of ctDNA in routine clinical practice where tumor biopsy were impossible to obtain, tissue insufficient or clinically contraindicated.

Methods: A 73-gene panel using ctDNA NGS (Guardant360®) was offered to consecutive stage 4 NSCLC patients - results were discussed in our Genomics Review Board to assess potential actionable alterations and enrolment into clinical trials.

Results: 50 pts (37F:13M; median 64 yrs) participated. ctDNA was obtained in 6 treatment (Tx) naïve patients (pts), in 22pts post 1st-line, in 7pts post 2nd-line, in 5 pts post 3rd-line and in 5 pts with > 4 Tx – in 5 pts prior Tx was unknown. EGFR status at Dx was known in 40 (23mt/17wt) and unknown in 10 pts. Of the pts with known EGFRmt, 6 pts progressed on gefitinib, 7 pts on afatinib, 8 pts on erlotinib, and 2 pts did not receive prior anti-EGFR Tx. ctDNA testing confirmed EGFRmt in 14 pts. In 9 pts with previously Bx-proven EGFRmt ctDNA did not detect an EGFRmt - the lag time between Bx and ctDNA was a median of 18 months (range 1-94 months). New EGFRmt were found in 3 pts with unknown EGFR status allowing access to anti-EGFR Tx. Acquired T790M were found in 4 pts progressing on prior anti-EGFR Tx, those pts received osimertinib. In 1 pt with ctDNA T790M+, a concomitant solid Bx was T790M-. Other alterations were, TP53 (n = 23), KRAS (n = 7), ERBB2 (n = 1), NTRK1 (n = 2), NF1 (n = 12), MET (n = 7), BRAF (n = 5), PIK3CA (n = 5), ALK (n = 2), BRCA1 (n = 1), BRCA2 (n = 2), PDGFRA (n = 3), AR (n = 4), TERT (n = 3), CDK4 (n = 3), CDK6 (n = 3), FGFR2 (n = 2), STK11 (n = 2), KIT (n = 2), SMAD4 (n = 3), CDH1 (n = 1), NOTCH1 (n = 2), RB1 (n = 3), TSC1 (n = 1), ERBB1(n = 1), MTOR (n = 3), MYC (n = 3), ARAF (n = 1), GNAS (n = 1), AKT1(n = 1), CDKN2A (n = 2), ARID1A (n = 2), CTNNB1 (n = 1), CCNE1 (n = 1). Critical review in the GRB meeting was fundamental in interpreting the genetic alterations of significance.

Conclusions: We confirm the feasibility and clinical utility of ctDNA testing in NSCLC patients where tumor biopsies were insufficient, impossible or contraindicated and identified 7 pts (14%) who based on their ctDNA results received 1st/2nd-line anti-EGFR treatment, several more were recommended for clinical trials.

Legal entity responsible for the study: Sarah Cannon Research Institute.

Funding: Has not received any funding.

Disclosure: P. Bennett: Employee: Sarah Cannon Molecular Diagnostics. I. Faull, R.B. Lanman: Employee: Guardant. All other authors have declared no conflicts of interest.

1431P TP53 mutations impair overall survival of TKI-treated patients with oncogene-driven NSCLC

P. Christopoulos[1], M. Kirchner[2], F. Bozorgmehr[1], V. Endris[2], M. Elsayed[1], N. Magios[1], A-L. Volckmar[2], R. Penzel[2], F.J.F. Herth[3], C.P. Heussel[4], H. Winter[5], T. Muley[6], M. Meister[6], J.R. Fischer[7], S. Rieken[8], F. Lasitschka[2], H. Bischoff[1], P. Schirmacher[2], M. Thomas[1], A. Stenzinger[2]

[1]Department of Oncology, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [2]Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany, [3]Department of Pulmology, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [4]Diagnostic and Interventional Radiology with Nuclear Medicine, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [5]Department of Thoracic Surgery, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [6]Translational Research Unit, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [7]Department of Oncology, Lungenklinik Loewenstein, Loewenstein, Germany, [8]Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany

Background: Tyrosine kinase inhibitors (TKI) have considerably improved survival of patients with oncogene-driven non-small cell lung cancer (NSCLC). However, prognosis varies widely, and identification of molecular factors with a critical role for adverse outcome could facilitate further advances in management.

Methods: We retrospectively studied the clinical course of patients with metastatic epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-driven NSCLC and known baseline TP53 status that received TKI at our institutions. Overall survival (OS) from the start of treatment for metastatic disease was analyzed according to Kaplan-Meier or by Cox regression.

Results: A total of n = 149 $EGFR^+$ and n = 76 ALK^+ patients were included with a median age of 62 years (interquartile range [IQR] 19), a median ECOG performance status of 0.5 (IQR 1) and a predominance of female (136/225=60%) never-/light-smokers (median number of pack-years 9, IQR 16). Median OS was 36 months for $EGFR^+$ and 44 months for ALK^+ NSCLC patients. TP53 mutations were present at diagnosis in 34% (51/149) of $EGFR^+$ and 19% (15/76) of ALK^+ patients, and they were associated with inferior OS in both $EGFR^+$ (24 vs. 40 months in median, $p = 0.027$) and ALK^+ NSCLC (24 vs. 53 months, $p = 0.001$). Their adverse effect was comparable to that of a worse initial clinical condition as reflected by an ECOG performance status of 1 compared to 0 (HR = 1.8 for ECOG vs. 1.8 for TP53 mutations in $EGFR^+$ patients, and HR = 4.1 for ECOG vs. 3.7 for TP53 mutations in ALK^+ patients, all $p < 0.05$ in bivariable analyses), and it was independent from that of the oncogene variant in both patient groups (HR = 1.9 for other EGFR alterations vs. exon 19 indels, and HR = 1.8 for TP53 mutations vs. wild-type in $EGFR^+$ patients; HR = 2.3 for EML4-ALK V3 vs. V1/V2, and HR = 4.7 for TP53 mutations vs. wild-type in ALK^+ patients, all $p < 0.05$ in bivariable analyses).

Conclusions: TP53 mutations impair overall survival of TKI-treated patients with EGFR- and ALK-driven NCSLC independent of baseline clinical status and oncogene variant. Their detection could assist selection of cases for more aggressive management. Preclinical exploration of their role in acquired TKI resistance could guide novel therapeutic strategies.

Legal entity responsible for the study: Department of Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital, and Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany.

Funding: German Center for Lung Research (DZL) and German Cancer Consortium (DKTK).

Disclosure: F. Bozorgmehr: Research funding: BMS; Honorarium: MSD, Novartis. V. Endris: Advisory board and lecture fees: AstraZeneca, ThermoFisher. F.J.F. Herth: Advisory board fees and honoraria: Lilly, Roche, AstraZeneca, Novartis, Boehringer Ingelheim, Chiesi, Teva, Pulmonx BTG, Olympus; Research funding: Lilly, Roche, AstraZeneca, Novartis, Boehringer Ingelheim, Chiesi, Teva. C.P. Heussel: Consultation, lecture and other fees: Novartis, Basilea, Bayer, Grifols, Boehringer Ingelheim, Pierre Fabre, Covidien, Siemens, Chiesi, Intermune, MEDA Pharma, Bracco, Pfizer, MSD, Roche, Lilly, AstraZeneca, Schering-Plough, Essex, Gilead,

MeVis, Fresenius, Astellas; Stocks ownership: GSK. T. Muley: Research funding, Patents: Roche. J.R. Fischer: Advisory board honoraria: Boehringer Ingelheim, Roche, Celgene, AstraZeneca. F. Lasitschka: Advisory Board honoraria: BMS, MSD, Roche; Speaker's honorary: Novartis; Travel grants: BMS. P. Schirmacher: Advisory board honoraria: Pfizer, Roche, Novartis, AstraZeneca; Speaker's honoraria, Research funding: Roche, AstraZeneca, Novartis. M. Thomas: Advisory board honoraria: Novartis, Lilly, BMS, MSD, Roche, Celgene, Takeda, AbbVie, Boehringer Ingelheim; Speaker's honoraria: Lilly, MSD, Takeda; Research funding: AstraZeneca, BMS, Celgene, Novartis, Roche; Travel grants: BMS, MSD, Novartis, Boehringer Ingelheim. A. Stenzinger: Advisory board honoraria: BMS, AstraZeneca, ThermoFisher, BMS; Speaker's honoraria: BMS, Illumina, AstraZeneca, Novartis, ThermoFisher; Travel grants: Illumina, AstraZeneca, ThermoFisher; Research funding: Chugai. All other authors have declared no conflicts of interest.

1432P Hybrid capture NGS reliably detects a spectrum of clinically significant genetic aberrations in both, primary diagnostics and the relapse scenario

S. Schatz[1], M. Falk[2], R. Menon[3], L.C. Heukamp[3], J. Roeper[4], F. Griesinger[5], M. Tiemann[1]
[1]Hematopathology Hamburg, Hamburg, Germany, [2]Hematopathology Hamburg, Hamburg, Germany, [3]NEO New Oncology, Cologne, Germany, [4]Pius Hospital Oldenburg, University of Oldenburg, Oldenburg, Germany, [5]Pius Hospital Oldenburg, Oldenburg, Germany

Background: The purpose of this study was to analyze the frequency and type of genetic alterations in tyrosine kinase inhibitor (TKI)-naïve vs. TKI-treated NSCLC patients. We report a spectrum of resistance mechanisms upon TKI treatment in liquid biopsies using a comprehensive hybrid capture NGS test (HC-NGS).

Methods: We retrospectively collected mutational data of 200 solid NSCLC biopsies of treatment-naïve patients that were routinely tested for clinically relevant mutations by HC-NGS at our institution. In addition, we analyzed mutational data from 367 liquid biopsies of NSCLC patients whose disease progressed under treatment. Solid tumor biopsies and liquid biopsies were tested using a 39-gene HC-NGS panel including 39 clinically relevant genes (NEOselect, LOD 3.0%; NEOliquid, LOD 0.1%; NEO New Oncology GmbH, Cologne).

Results: Primary HC-NGS diagnostics in TKI -aïve patients revealed 12% (24/200) TKI-sensitive EGFR mutations, 5.0% (10/200) Alk/ROS/RET translocations, 0.5% (1/200) BRAF V600E, and in one patient a MET Exon 14 skipping mutation (0.5%, 1/200). Further, a variety of clinically relevant mutations were detected, among others, prognostically relevant TP53 mutations at a frequency of 52.0% (104/200). In addition, we tested 367 liquid biopsies from relapse patients. 30.9% (113/367) pts had an activating EGFR mutation and therefore presumably received EGFR TKI treatment. Of the 113 pts, 39.8% (45/113) developed a T790M resistance mutation and 1.8% (2/113) an additional MET amplification.

Conclusions: HC-NGS allows for comprehensive analysis of somatic tumor aberrations in the primary diagnostic setting as well as in the relapse scenario. Mechanisms of primary oncogenic activation as well as mechanisms of resistance are heterogeneous and include point mutations, translocations and gene amplifications. Therefore, HC-NGS should be used for diagnosis in both, the primary and the relapse setting.

Legal entity responsible for the study: Hematopathology Hamburg.

Funding: Has not received any funding.

Disclosure: L.C. Heukamp: Affiliations: Hematopathology Hamburg, NEO New Oncology. M. Tiemann: Anstellungsverhaltnis oder Führungsposition: CEO Institut für Heamatopathologie Hamburg Beratungs- bzw. Gutachtertätigkeit; Advisory boards: Novartis, Boehringer, Roche, AstraZeneca; Honorare erhalten von: Vortragshonorare: Novartis, Boehringer, Roche, AstraZeneca. All other authors have declared no conflicts of interest.

1433P Prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in advanced non-small cell lung cancer

K. Adamowicz[1], A. Romanowska[2], R.E. Zaucha[3]
[1]Regional Oncology Centre, Gdansk, Poland, [2]Clinical Oncology and Radiotherapy, University Clinical Center, Gdansk, Poland, [3]Radiotherapy and Clinical Oncology, Medical University of Gdansk, Gdansk, Poland

Background: Metastatic non-small cell lung cancer (NSCLC) represents one of the biggest therapeutic challenges. Palliative chemotherapy (CT) is the first-choice treatment in patients without targetable mutations. Unfortunately, reliable markers predicting response to CT have not been found yet. Most of NSCLC cases arise and develop in a background of smoking-related chronic inflammation. Since neutrophils are the most prevalent immune cell type in NSCLC microenvironment we hypothesized that the revelator of the inflammatory process such as the neutrophil to lymphocyte ratio (NLR) could have a prognostic or predictive value.

Methods: To evaluate the predictive and prognostic value of pretreatment NLR in NSCLC we analyzed data of the group of consecutive patients treated systemically for NSCLC at two institutions between January 2011 and December 2014. NLR was retrospectively calculated from the peripheral blood counts collected before therapy. Multivariate Cox logistic regression was used to assess the relationship between NLR and treatment results after adjusting for age, gender, ECOG, and cigarette smoking. Based on available data we chose NLR=3 as the cut-off level discriminating high (NLR >3) and low values.

Results: In the whole cohort ($N = 204$) with 184 patients (90%) being current or former smokers, 131 (64%) were male, 188 (92%) had a performance status (PS) 0 to 1, 93 patients (46%) had squamous cell cancer, 85 (42%) adenocarcinoma, and 26 (12%) other subtypes. Median age at diagnosis was 65 years (range 41 to 71.7 years). Platinum-based CT was administered in 92% of patients: cisplatin in 155 (76%), and carboplatin in 33 (16%) patients. NLR ranged from 2.04 to 4.62 (median = 3.02). Study groups created according to the NLR value were well balanced. There were 54 objective responses (26,5%) including 2 complete remissions. NLR was a significant and independent factor predicting response to treatment (OR 0.048; 95% CI 0.015-0.152; $p < 0.001$). Median overall survival in all patients was 12 months: 9.6 vs 13.2 months, respectively in NLR>3 vs ≤ 3 ($p < 0.001$).

Conclusions: NLR>3 was correlated with worse outcomes, therefore might be useful for identifying patients unlikely to benefit from CT.

Legal entity responsible for the study: Renata Zaucha.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1434P A phase II study of nedaplatin and nab-paclitaxel for patients with previously untreated advanced squamous cell lung cancer (KRSG1302)

T. Sugiyama[1], T. Kasai[1], N. Koyama[2], K. Kobayashi[3], E. Hoshi[4], M. Nakayama[5], K. Mori[6]
[1]Department of Medical Oncology, Tochigi Cancer Center, Utsunomiya, Japan, [2]Department of Clinical Oncology, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan, [3]Respiratory Medicine, Saitama Medical University Internatl Medical Centre, Saitama, Japan, [4]Thorcic Surgery, Saitama Cardiovascular and Respiratory Center, Kumagaya, Japan, [5]Thorcic Surgery, Saitama Medical Center, Kawagoe, Japan, [6]Respiratory Medicine, Tsuboi Cancer Center Hospital, Koriyama, Japan

Background: Nedaplatin (N) and nab-paclitaxel (nab-P) are efficacious in the treatment of non-small cell lung cancer (NSCLC), especially squamous cell lung cancer. Although a combination of N and nab-P was expected in the treatment of squamous cell lung cancer, there was no sufficient data.

Methods: The eligibility criteria were no prior chemotherapy; stage IIIB or stage IV squamous cell lung cancer; a performance status (PS) of 0–1; $75 >$ age > 20 years; and adequate hematologic, hepatic, and renal function. Patients (pts) received escalating doses of nab-P under a fixed dose of N (100 mg/m^2, day 1) every 3 weeks in the phase I part. The initial dose of nab-P was 100 mg/m^2 of day 1, 8 (level 1), and that of the next dose was 100 mg/m^2 of day 1, 8, 15 (level 2). In the phase II part, pts received the recommended dose (RD) of N/nab-P. The primary endpoint was tumor response, which was measured using Response Evaluation Criteria in Solid Tumors 1.1.

Results: Five pts were enrolled in the phase I part. Three pts of level 1 have experienced no dose-limiting toxicities (DLTs). Two pts of level 2 have experienced DLTs, which were febrile neutropenia and the down of PS, respectively. Therefore, level 1 was determined to RD. 23 pts were enrolled in phase II part. Three pts in level 1 and 23 pts in phase II were evaluable, together. Partial response, stable disease, and progressive disease were noted in 21, 0, and 2 pts, respectively, yielding a response rate of 91.3% (95%confidence interval [CI]: 72.0–98.9). The median progression-free survival was 223 days (95%CI: 144–330), and the median survival time was 358 days (95%CI: 255–950). The grade 3 and 4 toxicities observed during all cycles were neutropenia (5 and 9 pts), anemia (6 and 2 pts), thrombocytopenia (5 and 3 pts). Grade 3 febrile neutropenia, pneumonia, and acute coronary syndrome were observed in 1, 2, and 1 pts, respectively. However, there was no treatment related death.

Conclusions: A combination of N (100 mg/m^2, day 1) and nab-P (100 mg/m^2, day 1, 8) every 3 weeks was the recommended dose. N/nab-P in this recommended dose appears to be efficacious and torerable in patients with untreated advanced squamous cell lung cancer.

Legal entity responsible for the study: Kanto Respiratory Disease Study Group (KRSG)/JAPAN.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1435P Bevacizumab as first-line treatment in advanced non-squamous non-small cell lung cancer (NSCLC) in patients aged over 65 years in France: Final results of the AVANTAGE study

F. Lionel[1], D. Perol[2], P-J. Souquet[3], H. Le Caer[4], E. Dansin[5], C. Audigier Valette[6], J-L. Mouysset[7], M.L. Uffredi[8], M. Ionescu-Goga[9], K. Veerabudun[10], Y. Lelarge[11], E. Fabre-Guillevin[12]

[1]Service de Pneumologie et Cancérologie Thoracique, L'Hopital Nord Ouest, Villefranche Sur Saone, France, [2]Centre Léon Bérard, Lyon, France, [3]Service de Pneumologie et Cancérologie Thoracique, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [4]Pneumologie, Centre Hospitalier, Saint Brieuc, France, [5]Service de Pneumologie, Centre Oscar Lambret, Lille, France, [6]Service de Pneumologie, Hospital Sainte Musse, Toulon, France, [7]Medical Oncology, Clinique Rambot-Provençale, Aix-en-Provence, France, [8]Medical, Roche S.A.S., Boulogne-Billancourt, France, [9]Pharmaco-Vigilance, Roche S.A.S., Boulaogne-Billancourt, France, [10]Statistics, Aixial, Boulogne-Billancourt, France, [11]Operation Clinique, Hays, Paris, France, [12]Service de Pneumologie, La Défense, France

Background: NSCLC is frequent in elderly patients (pts), however there is limited information on the treatment of this population. This study describes the first-line treatment with bevacizumab (bev) of NSCLC elderly pts in real life in France.

Methods: AVANTAGE is a non-interventional, prospective, multicenter French study conducted in pts with advanced NSCLC starting first-line chemotherapy (CT) with bev. It includes 2 cohorts, pts aged 65-70 (C1), or $\geq$ 70 (C2) . Data were collected at inclusion and every 3 months subsequently for 18 months. The primary objective was to describe CT used with bev in first-line in routine clinical practice.

Results: A total of 249 pts were eligible (277 included) in 68 centers: 108 (43%) in C1 & 141 (57%) in C2. They were predominantly men (75%), ECOG PS 0-1 (85%) PS 2 (15%), G8 questionnaire score >14 (35%), stage IV (96%), Charlson comorbidity index unadjusted $\leq$2 (63%), and brain metastases identified in 18% of pts overall, 20% of pts in C2. Platinum-based doublet CT and pemetrexed (pem) was the most used combination with bev in 186 (75%) pts overall: - 81% of pts in C1 (62% cisplatin-pem and 18% carboplatin-pem) - 70% of pts in C2 (26% cisplatin-pem and 44% carboplatin-pem). The initial dose of bev with CT was 7.5 mg/kg/3 weeks in 70% of pts. Overall, maintenance treatment was administered to 61% pts, including 53% with bev (24% in monotherapy and 29% with pem). Maintenance was 64% in C1and 62% in C2. Median PFS was 7.1 months, and median OS was 12.3 months (14.9 months in C1, 11.3 months in C2). Overall, 92% of pts presented at least 1 AE. Pts with grade $\geq$ 3 AEs related to bev were 12% in C1 and 24% in C2. In the safety population (260), 148 pts died during the study. 3 pts (all in C2) died due to SAEs related to treatment (intestinal perforation; febrile neutropenia/septic shock/ thrombocytopenia; unknown cause).

Conclusions: AVANTAGE is the 1st prospective cohort conducted in routine clinical practice in France in elderly pts eligible for 1st-line CT with bev. The most frequently used treatment was the combination of platinum-pem doublet (75% of pts). Bev effectiveness as 1st line treatment in NSCLC was consistent with the efficacy observed in clinical trials in the elderly as was the safety profile.

Clinical trial identification: Clincial Trial Gov: NCT01893268.

Editorial acknowledgement: Dr Samia Rahal from ELTIUM (French medical writting company).

Legal entity responsible for the study: Roche S.A.S.

Funding: Roche S.A.S.

Disclosure: F. Lionel, D. Perol, H. Le Caer, P-J. Souquet: Payment for advisory: Roche. E. Dansin: Payment for advisory: Roche, Lilly, MSD. C. Audigier Valette: Payment for advisory: Roche, Pfizer, Boehringer Ingelheim, Lilly, AstraZeneca, Amgen, Bristol-Myers Squibb, Symex, MSD, Clovis Oncology, Novartis. J.-L. Mouysset, E. Fabre-Guillevin: Payment as study's investigator: Roche. M.L. Uffredi, M. Ionescu-Goga: Employee: Roche. K. Veerabudun, Y. Lelarge: Business partner employee: Roche.

1436P Randomized phase II study comparing cisplatin + pemetrexed + bevacizumab with carboplatin + paclitaxel + bevacizumab in treatment-naïve advanced non-squamous non-small cell lung cancer (CLEAR study)

R. Koyama[1], H. Udagawa[2], E. Sugiyama[3], K. Komuta[4], M. Mori[5], T. Yokoyama[6], T. Sasaki[7], H. Saito[8], H. Ishida[9], H. Nakagawa[10], A. Sekine[11], A. Tamura[12], M. Shingyoji[13], K. Mizuno[14], A. Nakamura[15], A. Kinoshita[16], T. Yamanaka[17], K. Goto[2]

[1]Department of Respiratory Medicine, Juntendo University Faculty of Medicine, Tokyo, Japan, [2]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [3]Division of Cancer Immunology, National Cancer Center, Kashiwa, Japan, [4]Department of Respiratory Medicine, Osaka Police Hospital, Osaka, Japan, [5]Department of Thoracic Oncology, National Hospital Organization Toneyama National Hospital, Toyonaka, Japan, [6]Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan, [7]Respiratory Center, Asahikawa Medical University, Asahikawa, Japan, [8]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan, [9]Division of Medical Oncology, Showa University School of Medicine, Tokyo, Japan, [10]Department of Respiratory Medicine, National Hospital Organization Hirosaki Hospital, Hirosaki, Japan, [11]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan, [12]Center for Pulmonary Diseases, National Hospital Organization Tokyo National Hospital, Tokyo, Japan, [13]Division of Respirology, Chiba Cancer Center, Chiba, Japan, [14]Department of Pulmonary Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan, [15]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan, [16]Department of Respiratory Medicine, Nagasaki Prefecture Shimabara Hospital, Shimabara, Japan, [17]Department of Biostatistics, Yokohama City University Hospital, Yokohama, Japan

Background: Bevacizumab (Bev) combined with platinum-based chemotherapy is a standard treatment for advanced non-squamous non-small-cell lung cancer (non-Sq NSCLC). Cisplatin + pemetrexed (CisPem) is suggested as the most promising chemotherapy regimen combined with Bev. However, no study has been conducted to evaluate the efficacy and safety of CisPemBev compared with carboplatin + paclitaxel + bevacizumab (CarPacBev) for advanced non-Sq NSCLC.

Methods: Treatment-naïve patients with advanced or recurrent EGFR/ALK-negative non-Sq NSCLC from 55 sites across Japan were randomly assigned in a 2:1 ratio to either CisPemBev (4 cycles of Cis [75 mg/m^2] + Pem [500 mg/m^2] + Bev [15 mg/kg] q3wk, followed by maintenance Pem + Bev q3wk until progression) or CarPacBev (4 cycles of Car [AUC 6] + Pac [200 mg/m^2] + Bev q3wk, followed by maintenance Bev q3wk until progression). The primary endpoint was progression-free survival (PFS) by central review. The secondary endpoints were overall survival (OS), overall response rate (ORR) and safety profile. The target numbers of patients and events were determined to be 210 and 170, respectively, to observe a point estimate of HR for PFS (CisPemBev/CarPacBev) <0.83 with a high probability (80%) when the true HR was 0.72. The data were cutoff in July, 2017. OS data were updated for this presentation in April, 2018.

Results: Between May 2014 and May 2016, 199 patients were randomly assigned to receive CisPemBev (N = 132) or CarPacBev (N = 67). In the primary analysis, PFS events occurred in 171 patients. The HR for PFS by central review (CisPemBev/CarPacBev) was 0.825 (95% CI 0.600-1.134, median PFS, 7.6 vs 7.0 months), and the ORR was 57% for CisPemBev and 55% for CarPacBev. OS events occurred in 119 patients. The median survival follow-up duration was 28.3 months. The median OS was 23.4 months for CisPemBev and 21.6 months for CarPacBev (HR 0.845, 95% CI 0.583-1.242).

Conclusions: PFS was prolonged with CisPemBev compared with CarPacBev. However, there was no difference in OS between two arms. CisPem is the most effective chemotherapy regimen combined with Bev for advanced non-Sq NSCLC.

Legal entity responsible for the study: National Cancer Center Hospital East.

Funding: Chugai Pharmaceutical.

Disclosure: H. Udagawa: Honoraria: Chugai Pharmaceutical. M. Mori: Honorarium for speech: AstraZeneca, Boehringer Ingelheim, Chugai, Eli Lilly, MSD, Ono Pharmaceutical, Shionogi; Research fund: Chugai. T. Yokoyama: Personal fees: Chugai Pharmaceutical, Eli Lilly Japan, outside the submitted work. T. Sasaki: Research grant: Boehringer Ingelheim and Pfizer. A. Sekine: Lecture fees: Boehringer Ingelheim, Chugai Pharmaceutical, AstraZeneca; Institutional financial support for contracted research: Boehringer Ingelheim. K. Goto: Honoraria: Chugai, Lilly Japan; Reserch grants: Chugai and Lilly Japan. All other authors have declared no conflicts of interest.

1437P Phase I dose expansion data for M6620 (formerly VX-970), a first-in-class ATR inhibitor, combined with gemcitabine (Gem) in patients (pts) with advanced non-small cell lung cancer (NSCLC)

R. Plummer[1], N. Cook[2], T. Arkenau[3], J. Melear[4], C. Redfern[5], A.I. Spira[6], K. Chung[7], T. Haddad[8], S.S. Ramalingam[9], R. Wesolowski[10], E. Dean[11], T. Goddemeier[12], M. Falk[13], G. Shapiro[14]

[1]Northern Centre for Cancer Care, Freeman Hospital, Newcastle Upon Tyne, UK, [2]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [3]Medical Oncology, Sarah Cannon Research Institute, London, UK, [4]Medical Oncology, Texas Oncology, Midtown, Austin, TX, USA, [5]Clinical Oncology Research, Sharp Memorial Hospital, San Diego, CA, USA, [6]Virginia Cancer Specialists, Fairfax, VA, USA, [7]Hematology/Oncology, Greenville Health System, Greenville, SC, USA, [8]Mayo Clinic, Rochester, MN, USA, [9]Department of Hematology and Medical Oncology, Emory University Winship Cancer Institute, Atlanta, GA, USA, [10]Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA, [11]Medical Oncology, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK, [12]Biostatistics, Merck KGaA, Darmstadt, Germany, [13]Global Research & Development, Merck Germany, Darmstadt, Germany, [14]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Ataxia telangiectasia and Rad3-related protein (ATR) is an essential DNA damage response regulator, and is required for proliferating cell survival. DNA-damaging agents often induce replicative stress leading to activation and reliance on ATR; inhibition of ATR signalling is an attractive strategy to sensitize tumors to DNA-damaging chemotherapy. M6620 is a potent, selective inhibitor of ATR with preclinical anticancer activity in combination with DNA-damaging chemotherapy. Here, we report dose expansion cohort data for a phase I trial of M6620 plus Gem in pts with advanced NSCLC (NCT02157792).

Methods: Eligible pts had measurable (RECIST 1.1) advanced NSCLC with up to 2 lines of prior therapy, with one including a platinum analog. Of 40 pts planned for enrollment, ≥20 had to have a TP53 mutation (TP53+), ≤10 ATM loss of expression (ATM–) (both alterations associated with ATR inhibitor sensitivity in preclinical studies), and ≈10 neither TP53+ nor ATM–; status was determined from fresh or archival tissue. Pts received Gem 1000 mg/m^2 on days 1 + 8 and M6620 210 mg/m^2 on days 2 + 9 of each 21-day cycle. Pharmacokinetics was assessed on day 2 of cycle 1. Primary endpoints were safety and overall response rate (ORR).

Results: The safety set included 33 pts who received combination therapy (median age, 62.0 years [range 36–76]; TP53+, 19; WHO PS 0/1, 9/23). 31/33 pts had a treatment-emergent adverse event (TEAE), with 19 (57.6%) having grade ≥3 TEAEs: fatigue (n = 6), neutropenia (4), anemia (3), thrombocytopenia (3), malaise (2), vomiting (2), ALT increase (2), AST increase (2), pneumonia (2), sepsis (2) (grade ≥3 TEAES occurring in ≥ 2 pts). Of the 24 treated pts with baseline and on-treatment assessments, 3 pts had a partial response (PR; ORR 12.5%) and 18 pts (75%) had stable disease (SD). Four pts had PR or SD ≥ 6 months (clinical benefit rate 16.7%). Updated efficacy and PK data will be presented from an upcoming analysis.

Conclusions: The ATR inhibitor M6620 combined with Gem showed signs of activity in advanced NSCLC; tolerability was acceptable.

Clinical trial identification: NCT02157792.

Editorial acknowledgement: Medical writing assistance (funded by Merck KGaA, Darmstadt, Germany) was provided by Martin Quinn, PhD of Bioscript Science (Macclesfield, UK).

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: R. Plummer: Clinical trial costs to institution to conduct the trial; Personal honoraria: Vertext Pharmaceuticals for advisory board. C. Redfern: Stock holdings: Pfizer. A.I. Spira: Research funding (to institution): Merck for study. T. Haddad: Research funding (institution): Takeda Oncology; Consulting: TerSera Therapeutics (fee donated to institution). S.S. Ramalingam: Consultant: Amgen, Abbvie, AstraZeneca, BMS, Lilly, Genentech/Roche, Loxo, Nektar and Merck. E. Dean: Commercial income to institution for the conduct on the study; Employment and owns stock: AstraZeneca. T. Goddemeier, M. Falk: Employee: Merck KGaA. G. Shapiro: Research funding: Merck/EMD Serono, Lilly, Pfizer; Advisory Board: Roche, Merck/EMD Serono, Lilly, Pfizer, G1 Therapeutics. All other authors have declared no conflicts of interest.

1438P A multicenter single-arm phase II study of nab-paclitaxel/carboplatin for non-small cell lung cancer patients with interstitial lung disease

Y. Usui[1], H. Kenmotsu[2], K. Mori[3], A. Ono[2], K. Yoh[4], T. Baba[5], Y. Fujiwara[6], O. Yamaguchi[7], R. Ko[8], H. Okamoto[9], N. Yamamoto[10], T. Ninomiya[11], T. Ogura[5], T. Kato[12]

[1]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [2]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [3]Clinical Trial Coordination Office Biostatistician, Shizuoka Cancer Center Hospital, Nagaizumi, Japan, [4]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [5]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan, [6]Developmental Therapeutics, National Cancer Center Hospital, Tokyo, Japan, [7]Department of Respiratory Medicine, Saitama Medical University International Medical Center, Saitama, Japan, [8]Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan, [9]Department of Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Yokohama, Japan, [10]Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan, [11]Department of Respiratory Medicine and Allergy, Okayama University, Okayama, Japan, [12]Division of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan

Background: The prognosis of non-small cell lung cancer (NSCLC) patients with interstitial lung disease (ILD) has been reported to be poor, and 10-20% of those receiving chemotherapy experienced exacerbation of ILD induced by chemotherapy. To evaluate the safety and efficacy of nab-paclitaxel (nab-P)/ carboplatin (C) for NSCLC patients with ILD, this multicenter phase II study was conducted.

Methods: Chemotherapy-naive patients with pathologically confirmed advanced NSCLC and ILD received 4 cycles of nab-P (100 mg/m^2, d1, 8, 15) + C (AUC=6 d1) every 3 weeks. ILDs were diagnosed based on the fibrosing ILD criteria and categorized to three patterns by investigators; usual interstitial pneumonia (UIP), possible UIP, inconsistent UIP. Primary endpoint was exacerbation-free rate (EFR) of ILD at 28 days after protocol treatment. Secondary endpoints were response rate, progression-free survival (PFS), overall survival (OS), EFR of ILD, toxicities.

Results: From 06/2014 to 12/2016, 94 patients were enrolled in this study, and 92 patients received protocol treatment. Median age was 70 years, 89% were male, 45/55% were PS 0/1, and 58% had non-squamous histology. In the primary analysis, EFR of ILD at 28 days after protocol treatment was 95.7% (88/92, 90%CI; 90.3-98.6). In the subgroup of patients with UIP pattern, EFR of ILD at 28 days was 94% (47/50). Response rate was 51% (90%CI; 40-62). At the time of data cutoff, median PFS was 6.1 months, and median OS was 15.1 months. The most common grade 3 or 4 adverse events were neutropenia (75%), leukopenia (53%), anemia (48%), thrombocytopenia (20%), hyponatremia (17%), febrile neutropenia (9%) and infection (7%). Two treatment-related deaths (one each of pulmonary infection and ILD exacerbation) were observed.

Conclusions: This study demonstrated that nab-P/C was well tolerated in NSCLC patients with ILD in terms of safety including risk of exacerbation of ILD, even if of UIP pattern. Although this study was a single arm, nab-P/C might be more effective compared with other regimens of previous reports.

Legal entity responsible for the study: Kanagawa Cardiovascular and Respiratory Center.

Funding: Japanese Ministry of Health, Labor and Welfare.

Disclosure: H. Kenmotsu: Grants and Honoraria: AstraZeneca K.K., Chugai Pharmaceutical Co, Ltd., Boeringer Ingelheim, Ono Pharmaceutical Co, Ltd., Bristol-Myers K.K, Eli Lilly K.K, Kyowa Hakko Kirin Co., Ltd., MSD K.K., Novartis Pharma K.K. K. Yoh: Research funding and honoraria: Taiho Pharmaceutical. T. Baba: Honoraria: Ono Pharmaceutical Co, Ltd, Bristol Myers Squibb K.K., AstraZeneca K.K., Toray Industries, INC, Daiichi Sankyo, Inc.; Speakers' bureau: AstraZeneca K.K., Boston Scientific Japan Co.,Ltd., Nippon Boehringer Ingelheim Co., Shionogi & Co., Ltd., Astellas Pharma Inc, Amco Inc., Asahi Kasei Pharma Corporation; Research funding: Taiho Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Savara Inc., Hisamitsu Pharmaceutical Co., Inc., AstraZeneca K.K. Y. Fujiwara: Grants: AbbVie, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Incyte, Merck Serono, Novartis grants; Personal fees: AstraZeneca, MSD, BMS, personal fees from Taiho, Ono, outside the submitted work. O. Yamaguchi: Honoraria: Bristol-Myers Squibb, Ono Pharmaceutical, AstraZeneca. H. Okamoto: Takeda, MSD, Ono, AstraZeneca, Merck, Chugai, Taiho, Bristol, Eli Lilly, Daiichi Sankyo. N. Yamamoto: Membership of advisory board: AstraZeneca, Boehringer-Ingelheim, Chugai, Eli Lilly, MSD, Takeda; Corporate-sponsored research: MSD, Eli Lilly, Chugai; Honoraria: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eli Lilly, MSD,

Novartis, Ono Pharmaceutcial Ltd., Pfizer, Takeda. T. Ninomiya: Honoraria: Chugai Pharmaceutical Co., Nippon Boehringer Ingerheim Co. T. Ogura: Advisory board: Nippon Boehringer Ingelheim Co., Shionogi & Co., Ltd; Speakers' bureau: Nippon Boehringer Ingelheim Co., Shionogi & Co., Ltd., Astellas Pharma Inc.; Research funding: Taiho Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co, Savara Inc, Hisamitsu Pharmaceutical Co., Inc., AstraZeneca K.K. T. Kato: Honoraria and Research grant: Bristol Myers Squibb and Taiho. All other authors have declared no conflicts of interest.

1439P HALO 107-201: A phase Ib, open-label, multicenter study of pegvorhyaluronidase alfa (PEGPH20) + docetaxel in patients (pts) with recurrent locally advanced or metastatic non-small cell lung cancer (NSCLC)

M. Baumgart[1], M. Muhsin[2], W. Wu[2], N. Gabrail[3]

[1]Department of Medicine, University of Rochester Medical Center, Rochester, NY, USA, [2]Clinical Development, Halozyme Therapeutics, Inc., San Diego, CA, USA, [3]Cancer and Research Facility, Gabrail Cancer Center, Canton, OH, USA

Background: Hyaluronan (HA) accumulation in solid tumors impedes drug access. PEGPH20 degrades tumor HA and may increase access and efficacy of therapies to the tumor. This study (NCT02346370) assessed PEGPH20 + docetaxel safety and tolerability in pts with Stage IIIB/IV squamous and nonsquamous NSCLC who have failed 1 platinum-based chemotherapy regimen and ≤3 systemic anticancer regimens.

Methods: This study was planned as dose escalation (standard 3 + 3 design) and dose expansion (in HAhigh patients). During dose escalation, eligible pts received PEGPH20 (1.6, 3.0 and 2.2 μg/kg) as an IV infusion on D1 and docetaxel 75 mg/m^2 IV on D2 of each 21-day cycle. Pts continued study treatment until disease progression or unacceptable toxicity in longterm follow-up. Primary objectives were PEGPH20 + docetaxel safety and tolerability and determination of the RP2D of PEGPH20. Secondary objectives included PEGPH20 + docetaxel efficacy and pharmacokinetics.

Results: The study discontinued early due to treatment landscape changes, including the introduction of immune checkpoint inhibitors and in standard of care for NSCLC, ie docetaxel became later-line therapy. Thus, R2PD was not determined but the highest tolerated dose was 2.2 μg/kg. Prior to discontinuation, 15 pts were treated (1.6 μg/kg n = 7; 3.0 μg/kg n = 4; 2.2 μg/kg n = 4). Most were female (66.7%) and had adenocarcinoma (66.7%); mean age was 62.6 years. ECOG PS was 0 or 1 in 46.7% and 53.3% of pts, respectively. Safety findings are summarized in the table. All TEs and all but one MSE reported were considered related to PEGPH20.

Conclusions: PEGPH20 + docetaxel safety and tolerability were acceptable. Given the observed rates of TEs and MSEs, more effective methods for management of these AEs with this drug combination should be explored in future studies.

Clinical trial identification: NCT02346370.

Editorial acknowledgement: Medical writing assistance provided by Deborah Cantu at Paragon, Knutsford, UK.

Legal entity responsible for the study: Halozyme Therapeutics, Inc.

Funding: Halozyme Therapeutics, Inc.

Disclosure: M. Baumgart, N. Gabrail: Investigator on clinical trials: Halozyme Therapeutics, Inc. M. Muhsin, W. Wu: Employee: Halozyme Therapeutics, Inc.

1440P Randomised phase II trial of oral vinorelbine (OV) and cisplatin (P) followed by maintenance with OV versus gemcitabine (GEM) and P followed by maintenance with GEM as first-line chemotherapy in advanced non-small cell lung cancer (NSCLC) patients (pts) with squamous (sq) histological type

F. Grossi[1], P. Jaskiewicz[2], E. Pichon[3], G. Czyzewicz[4], D.M. Kowalski[5], L. Ciuffreda[6], R. Garcia Gomez[7], S. Caruso[8], J. Bosch Barrera[9], C. Ta Thanh Minh[10], S. Gautier[11], H. Hervieu[12], S. Henriet[10], G.. De Castro Jr[13]

[1]Oncology, IRCCS AOU San Martino – IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [2]Oncology, The Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland, [3]CHRU Bretonneau, Tours, France, [4]Szpital Specjalistyczny im. Jana Pawla II, Krakow, Poland, [5]Oncology Department, The Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland, [6]Oncology Department, AOU S. Giovanni Battista – Molinette, Turin, Italy, [7]Oncology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain, [8]VAR, CH de la Dracénie-Draguignan, Draguignan, France, [9]Oncology Department, Hospital Universitari Josep Trueta, Girona, Spain, [10]Medical Affairs Oncology, Pierre Fabre Oncologie France, Boulogne-Billancourt, France, [11]Biometry Department, IRPF, Pierre Fabre, Toulouse, France, [12]Pierre Fabre, Boulogne-Billancourt, France, [13]Clinical Oncology, ICESP - Instituto do Câncer do Estado de São Paulo, Sao Paulo, Brazil

Background: The doublets OV+P and GEM+P are among standard treatment options in NSCLC. The study aims to assess efficacy, safety of OV+P (Arm A) and GEM+P (Arm B), followed by maintenance with OV or GEM respectively.

Methods: Pts were randomised to receive (every 3-week cycles): OV at 80 mg/m^2 D1 and D8 (60 mg/m^2 Cycle 1) + P 80 mg/m^2 D1 or GEM 1250 mg/m^2 (D1 and D8) + P 75 mg/m^2 D1. After 4 cycles of combination, pts without progressive disease received single agent OV or GEM respectively as maintenance until progression or unacceptable toxicity. Primary endpoint: Disease Control Rate (DCR) on study treatment period (combination, maintenance). Secondary endpoints: safety, efficacy, quality of life.

Results: 113 pts were included between 2013-2015 in intent-to-treat population (ITT). Baseline: 57 pts (Arm A)/ 56 pts (Arm B), median age of 61 and 64.5 years, stage IV 96.5% and 91.1% respectively. In Arm A/ B, 57 pts and 56 were treated in combination period; in maintenance, 29 and 28 pts were treated with OV or Gem. Final results (ITT) for study treatment period in Arm A/ B: DCR 73.7% [95%, CI (62.4; 100.0)] and 75% [95%, CI (63.7; 100.0)]. Median duration of treatment 12.1 and 13.2 weeks; objective response 24.6% [14.1; 37.8] and 30.4% [18.8; 44.1]; median [95% CI] duration of disease control in months (mo) 4.8 [4.1-5.7] and 5.2 [4.3-6.6]; median PFS: 4.2 (2.8-4.9) and 4.3 (3.1-5.5) mo; median survival: 10.2 (6.9-12.9) and 8.4 (5.3-11.9) mo. Total of any grades (Gr) of related adverse events (r-AEs) arm A/ B respectively: 87.7% and 92.9%. Any grade of related infections: 1.8% vs 8.9%.Gr 3-4 of selected r-AEs: nausea/ vomiting 1.8%/3.5% vs 8.9%/ 5.4%, peripheral neuropathy 0% vs1.8%, renal failure

Table: 1439P

	PEGPH20 1.6 μg/kg + docetaxel (n = 7)	PEGPH20 3.0 μg/kg + docetaxel (n = 4)	PEGPH20 2.2 μg/kg + docetaxel (n = 4)	Total (N = 15)
AE category				
Any AE, n (%)	7 (100)	4 (100)	4 (100)	15 (100)
Any Grade ≥3 AE, n (%)	5 (71.4)	4 (100)	3 (75.0)	12 (80.0)
Serious AEs (SAEs), n (%)[†]	3 (42.9)	3 (75.0)	1 (25.0)	7 (46.7)
AEs leading to discontinuation, n (%)	1 (14.3)	1 (25.0)	2 (50.0)	4 (26.7)
AEs with outcome of death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
AEs (≥50% of the total population), n (%)				
Fatigue	6 (85.7)	3 (75.0)	4 (100)	13 (86.7)
Muscle spasms	4 (57.1)	2 (50.0)	3 (75.0)	9 (60.0)
Myalgia	4 (57.1)[‡]	3 (75.0)	1 (25.0)	8 (53.3)
Thromboembolic events (TEs), n (%)[§]	0 (0)	1 (25.0)[¶]	3 (75.0)	4 (26.7)
Musculoskeletal events (MSEs), n (%)	6 (85.7)[‡]	4 (100)	4 (100)	14 (93.3)

[†]With the exception of two Grade 4 SAEs (gastroenteritis/Escherichia coli sepsis), and one Grade 2 SAE, most SAEs were Grade 3;
[‡]One event of Grade 2 myalgia was also considered a SAE;
[§]All thromboembolic events were considered related to PEGPH20;
[¶]One event of Grade 3 deep vein thrombosis was also considered to be a SAE

1.8% vs 3.6%, septic shock 0 vs 1.8%. Grade 1-2 related alopecia (8.8% vs 21.4%). One toxic death in each arm. Biological toxicities of gr 3-4 neutropenia 43.9%/37.5%, anaemia 17.5%/10.7%, thrombocytopenia 1.8%/10.7%. Full results to be presented at the meeting.

Conclusions: This study confirms efficacy, safety of OV+P in sq NSCLC with a trend for a better median survival for OV+P.

Clinical trial identification: EUDRACT NUMBER: 2012-003531-40.

Legal entity responsible for the study: Pierre Fabre Médicament.

Funding: Pierre Fabre Médicament.

Disclosure: F. Grossi: Consulting, advisory role: Pierre Fabre, BMS, MSD, Roche. E. Pichon: Consulting, advisory role: BMS, AstraZeneca; Travel/accomodation, expenses: Astrazeneca, BMS. G. Czyzewicz: Honoraria: Roche, BMS, AstraZeneca; Consulting, advisory board: AstraZeneca, BMS, MSD, Roche; Research funding: BMS, Roche, AstraZeneca, Pierre Fabre Medicament; Expert testimony, Astrazeneca; Travel/accomodation: AstraZeneca, Roche, Pfizer. J. Bosch Barrera: Consulting, advisory boards: Pierre Fabre, BMS, Roche, AstraZeneca, Boehringer Ingelheim. C. Ta Thanh Minh: Employment pharmaceutical industry (PFM); Other ownership interest; Research project (PFM); Travel/accommodation. S. Gautier, H. Hervieu, S. Henriet: Employment, stocker/other ownership, research funding: Pierre Fabre. G. De Castro Jr.: Consulting or advisory role: Teva, Pfizer, Bayer, Roche, MSD; Speakers' bureau: AstraZeneca, Bayer, Novartis, Roche, MSD, BMS, Merck; Travels expenses: MSD, Novartis, Pfizer, AstraZeneca, Roche; Boehringer Ingelheim; Honoraria: AstraZeneca, Pfizer, MSD. All other authors have declared no conflicts of interest.

1441P Phase III study comparing bevacizumab plus erlotinib (BE) to erlotinib (E) in patients (pts) with untreated NSCLC harboring EGFR mutations: NEJ026

Y. Kawashima1, T. Fukuhara[2], N. Furuya[3], H. Saito[4], K. Watanabe[2], S. Iwasawa[5], Y. Tsunezuka[6], O. Yamaguchi[7], M. Okada[8], K. Yoshimori[9], I. Nakachi[10], A. Gemma[11], K. Azuma[12], K. Hagiwara[13], T. Nukiwa[14], S. Morita[15], K. Kobayashi[16], M. Maemondo[17]

[1]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan, [2]Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan, [3]Division of Respiratory Medicine, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, [4]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan, [5]Respirology, Chiba University Graduate School of Medicine, Chiba, Japan, [6]Department of General Thoracic Surgery, Ishikawa Prefectural Central Hospital, Kanazawa, Japan, [7]Department of Respiratory Medicine, Saitama Medical University International Medical Center, Saitama, Japan, [8]Surgical Oncology, Hiroshima University, Hiroshima, Japan, [9]Department of Pulmonary Medicine, Clinical Cancer Center Fukujuji Hospital, Kiyose, Japan, [10]Pulmonary Division, Internal Medicine, Saiseikai Utsunomiya Hospital, Utsunomiya, Japan, [11]Division of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan, [12]Respirology, Neurology, and Rheumatology, Kurume University School of Medicine, Fukuoka, Japan, [13]Division of Pulmonary Medicine, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan, [14]Professor Emeritus, Tohoku University, Sendai, Japan, [15]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [16]Department of Respiratory Medicine, Saitama Medical University International Medical Centre, Saitama, Japan, [17]Division of Respiratory Medicine, Allergy, and Rheumatology. Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan

Background: Combinations of EGFR-TKIs and VEGF inhibitors are one of the candidates for next strategy for EGFR-mutated lung cancer. We conducted a phase III study comparing BE to E in pts with untreated non-small-cell lung cancer (NSCLC). This study includes the pts with central nervous system (CNS) metastases (mets).

Methods: Chemotherapy-naïve pts with advanced non-squamous NSCLC harboring EGFR-mutation were randomly assigned to receive either combination with erlotinib (150 mg daily) plus bevacizumab (15 mg/kg iv q3w) or erlotinib (150 mg daily). Pts with asymptomatic stable CNS mets that did not require corticosteroids were allowed to enroll. The primary endpoint was PFS. Secondary endpoints were OS, RR, safety, and QoL. This study was planned to enroll 214 pts in total.

Results: Between Jun 3, 2015, and Aug 31, 2016, 228 pts with EGFR mutations were enrolled. There were one cessation prior to the study treatment and one withdrawal of consent; the remaining 226 pts were assigned to BE (n = 112) and E (n = 114). Pts were followed up for a median of 12.4 months. The interim analysis showed that the study met its primary endpoint. At data cutoff (Sept 21, 2017), median PFS was 16.9 months (95% CI 14.2-21.0) in BE and 13.3 months (11.1-15.3) in E ($p = 0.0157$) (HR 0.605, 95% CI 0.417-0.877). The number of pts with CNS mets at the enrollment was 72 (32.1%). In pts without CNS mets, median PFS was 18.0 months (95% CI 15.4- not reached) in BE and 15.1 months (11.1-16.1) in E ($p = 0.0141$). In pts with CNS mets, median PFS was 12.7 months (95% CI 9.8- 18.1) in BE and 11.2months (8.8-14.7) in E ($p = 0.413$). Although some toxicities such as hemorrhage, proteinuria, and hypertension significantly increased in BE compared to in E, there was no significant difference among other toxicities between BE and E. Five cases had low-grade pneumonitis in E but no pneumonitis in BE. There was no treatment-related death.

Conclusions: In this study, BE as a combination of EGFR-TKIs and VEGF inhibitors achieved durable response, especially absence of CNS mets. BE is a promising regimen for EGFR-mutated NSCLC.

Clinical trial identification: UMIN000017069.

Legal entity responsible for the study: North East Japan Study Group (NEJSG).

Funding: Chugai Pharmaceutical.

Disclosure: T. Fukuhara: Research funding: AstraZeneca, MSD, Ono, Bristol-Myers, Chugai, Novartis. S. Iwasawa: Speakers' bureau: Ono Pharmaceutical Co., Ltd, AstraZeneca K.K.; Research funding to institution: Teijin Pharma Limited, Ono Pharmaceutical Co., Ltd. O. Yamaguchi: Consulting or advisory role: AstraZeneca; Speakers' bureau: AstraZeneca, Bristol-Myers Squibb, Ono Pharmaceutical, Boehringer Ingelheim Japan. M. Okada, A. Gemma: Speakers' bureau, research funding: Chugai Company. K. Hagiwara: Honoraria: AstraZeneca, Ono Pharmaceutical; Patents, royalties, intellectual property: LSI Medience. T. Nukiwa: Consulting or advisory role: Asahi Kasei, Nippon Boehringer Ingelheim. S. Morita: Honoraria: Chugai. K. Kobayashi: Consulting or advisory role: AstraZeneca; Speakers bureau: Chugai, AstraZeneca, Ono, Eli Lilly. M. Maemondo: Research funding, lecture fee: Chugai Pharmaceutical. All other authors have declared no conflicts of interest.

1442P Afatinib versus erlotinib as second-line treatment of patients (pts) with advanced lung squamous cell carcinoma (SCC): Final analysis of the global phase III LUX-Lung 8 (LL8) trial

G.D. Goss[1], M. Cobo[2], S. Lu[3], K. Syrigos[4], K.H. Lee[5], E. Göker[6], V. Georgoulias[7], W. Li[8], D. Isla[9], A. Morabito[10], Y.J. Min[11], A. Ardizzoni[12], A. Cseh[13], S. Bender[14], E. Felip[15]

[1]Medical Oncology, University of Ottawa, Ottawa, ON, Canada, [2]Medical Oncology, Hospital Carlos Haya, Malaga, Spain, [3]Medical Oncology, Shanghai Chest Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China, [4]3rd Department of Medicine, Athens School of Medicine, Athens, Greece, [5]Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Republic of Korea, [6]Medical Oncology, Ege University Faculty of Medicine, Izmir, Turkey, [7]Department of Medical Oncology, University Hospital of Heraklion, Crete, Greece, [8]Medical Oncology, The First Hospital of Jilin University, Changchun, China, [9]Medical Oncology, Hospital Lozano Blesa, Zaragoza, Spain, [10]Thoracic Department, Istituto Nazionale Tumori, IRCCS - Fondazione G.Pascale, Naples, Italy, [11]Department of Medicine, Uslan University Hospital, Uslan, Republic of Korea, [12]Hematology-Oncology, Policlinico S.Orsola, Bologna, Italy, [13]Medical Oncology, Boehringer Ingelheim RCV GmbH & Co. KG, Vienna, Austria, [14]Medical Oncology, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA, [15]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Primary LL8 data showed significantly improved PFS and OS with afatinib compared with erlotinib as second-line treatment in pts with lung SCC, leading to the approval of afatinib in this setting. As previously reported (data cut-off: Apr 2015), PFS (2.6 vs 1.9 months; HR 0.81 [95% CI 0.69–0.96]; $p = 0.01$), objective response rate (ORR; 5.5 vs 2.8%; $p = 0.06$) and disease control rate (DCR; 50.5 vs 39.5%; $p = 0.002$) were higher with afatinib vs erlotinib. PFS and OS benefits on afatinib appeared even greater for pts with ErbB mutation-positive tumours vs ErbB wild-type tumours. Here we present the final analysis of OS and safety data. Other efficacy endpoints were not updated; as of Apr 2015, only 9 (1%) pts remained on treatment, so minimal changes would be expected.

Methods: This open-label, multicentre, Phase III trial enrolled pts with stage IIIB/IV lung SCC who had progressed on $\geq$ 4 cycles of platinum-based chemotherapy. Pts were randomised 1:1 to receive afatinib (40 mg/day) or erlotinib (150 mg/day) until progression. Primary endpoint was PFS by independent radiological review. The key secondary endpoint was OS; other endpoints included ORR, DCR and safety.

Results: 795 patients were included (398 on afatinib; 397 on erlotinib). Baseline characteristics were well balanced between arms. Updated OS (data cut-off: Mar 2018) was significantly longer for afatinib than erlotinib (7.8 vs 6.8 months; HR 0.84 [95% CI 0.73–0.97]; $p = 0.019$). Overall AE profile was comparable between arms: 57.4% of afatinib and 57.5% of erlotinib pts reported AEs $\geq$grade 3 (G3); serious AEs were reported for 44.4% and 44.3% of pts, respectively. A higher incidence of drug-related $\geq$G3 diarrhoea (10.5 vs 2.5%) and G3 stomatitis (4.1 vs 0%) was reported on afatinib, and a higher incidence of G3 rash/acne was reported on erlotinib (5.9 vs 10.4%). AEs leading to treatment discontinuation were comparable across arms (20.4 vs 16.7%). Updated data on pts with long-term disease control (treatment $\geq$1 year) will be presented.

Conclusions: Results are consistent with those previously reported for LL8. Updated OS was significantly greater for afatinib than erlotinib. The AE profile was comparable across arms and manageable.

Clinical trial identification: NCT01523587.

Editorial acknowledgement: Christina Jennings of GeoMed, an Ashfield company, part of UDG Healthcare plc.

Legal entity responsible for the study: Boehringer Ingelheim.

Funding: Boehringer Ingelheim.

Disclosure: G.D. Goss: Speaker bureau: AstraZeneca, BMS, Pfizer, Celgene. A. Morabito: Honoraria: Roche, AstraZeneca, Boehringer, Pfizer, BMS, MSD. A. Ardizzoni: Membership on an advisory board or board of directors: MSD Corporate-sponsored research: BMS, Celgene. A. Cseh: Employment: Boehringer Ingelheim RCV GmbH & Co. KG. S. Bender: Employment: Boehringer Ingelheim Pharmaceuticals, Inc. E. Felip: Advisory Board: Eli Lilly, Pfizer, Roche, MSD, Boehringer Ingelheim; Lecture Fees: AstraZeneca, BMS, Novartis. All other authors have declared no conflicts of interest.

1443P Real world data of osimertinib in patients with central nervous system (CNS) metastasis in ASTRIS Korean subset

J.H. Kang[1], B.C. Cho[2], D-W. Kim[3], K. Park[4], J-S. Lee[5], S.S. Yoo[6], S.Y. Lee[7], C.H. Kim[8], S.H. Jang[9], Y-C. Kim[10], H-K. Yoon[11], S-W. Kim[12]

[1]Medical Oncology, Seoul St. Mary's Hospital, of the Catholic University, Seoul, Republic of Korea, [2]Medical Oncology, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea, [3]101, Daehak-Ro, Jongno-Gu, Seoul National University Hospital, Seoul, Republic of Korea, [4]Division of Heamatology/Oncology, Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [5]Oncology, Seoul National University Bundang Hospital, Gyeonggi-Do, Republic of Korea, [6]Department of Internal Medicine, Kyungpook National University Hospital, Daegyu, Republic of Korea, [7]Department of Internal Medicine, Korea University Guro Hospital, Seoul, Republic of Korea, [8]Department of Internal Medicine, Korea Cancer Center Hospital, Seoul, Republic of Korea, [9]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Gyeonggi-Do, Republic of Korea, [10]Lung Cancer Clinic, Chonnam National University Hwasun Hospital, Jeollanam-Do, Republic of Korea, [11]Department of Internal Medicine, The Catholic University of Korea, Yeouido St. Mary's hospital, Seoul, Republic of Korea, [12]Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: More than 40% of non-small cell lung cancer (NSCLC) patients develop CNS metastasis in their lifetime. Clinical studies have shown superior efficacy of osimertinib in CNS compared to platinum chemotherapy. Treatment efficacy in patients with or without CNS metastasis were observed within the second interim analysis of ASTRIS (NCT02474355). Data cut-off (DCO) was 20 October 2017.

Methods: In ASTRIS, advanced NSCLC patients with locally confirmed T790M mutation, prior EGFR-TKI therapy were enrolled. Patients with stable CNS metastases were allowed. The primary endpoint was overall survival (OS); other endpoints included investigator-assessed response rate (RR), progression-free survival (PFS), time to treatment discontinuation (TTD) and safety. These endpoints were also analyzed according to presence of CNS metastasis.

Results: In 466 Korean patients, CNS metastasis was evaluated in 310 patients and was present in 211 (68.1%) patients (CNS-met) and not present in 99 (31.9%) patients (CNS-no). 155 patients were not evaluated for CNS metastasis (CNS-ne). At DCO, 236 patients (50.6%) were ongoing and median duration of exposure was 11.2 (0–19) months. In patients evaluable for response, defined as at least one dose of osimertinib and one response assessment, RR was 71.0% (320/451; 95% CI, 66.5–75.1): Patients with (N = 211), without (N = 99), and not-evaluated CNS metastasis (N = 155) had RR of 68% (134/197), 79.6% (78/98), and 69.7% (108/155), respectively. Median PFS was 12.4 months (95% CI, 11.1-13.6); 10.8 months in CNS-met, 11.0 months in CNS-no, and 15.1 months in CNS-ne. Median TTD was 16.5 months (95% CI, 14.1-NC); 11.2 months in CNS-met, 14.7 months in CNS-no, and NC (95% CI, 15.5-NC) in CNS-ne. OS was not reached (data maturity: 19.7%). Serious adverse events (AE) regardless of causality were reported in 116 patients (24.9%) and AEs leading to death in 13 patients (2.8%). ILD/pneumonitis-like events were reported in 8 patients (1.7%), and QTc prolongation in 7 patients (1.5%).

Conclusions: In the ASTRIS Korean subset, patients with or without CNS metastasis had comparable efficacy outcomes. These data continue to support osimertinib's clinical benefit on EGFRm T790M NSCLC patients with CNS metastasis.

Clinical trial identification: NCT02474355.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.

1444P A randomized phase II trial of erlotinib or erlotinib and bevacizumab in patients with advanced EGFR mutant non-small cell lung cancer (NSCLC)

T.E. Stinchcombe[1], P.A. Janne[2], X. Wang[3], E.M. Bertino[4], J.M. Weiss[5], L. Bazhenova[6], L. Gu[3], C.J. Lau[2], C.P. Paweletz[2], A.J. Jaslowski[7], G.J. Gerstner[8], M.Q. Baggstrom[9], S.L. Graziano[10], J. BeardenIII,[11], E.E. Vokes[12]

[1]Medical Oncology, Duke Cancer Center, Durham, NC, USA, [2]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [3]Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, USA, [4]Medical Oncology, The Ohio State University James Cancer Hospital, Columbus, OH, USA, [5]Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]Medicine, Moores UCSD Cancer Center, La Jolla, CA, USA, [7]Medical Oncology, St. Mary's Hospital, Green Bay, WI, USA, [8]Medical Oncology, Illinois CancerCare, P.C., Peoria, IL, USA, [9]Medical Oncology, Washington University School of Medicine, St. Louis, MO, USA, [10]Medical Oncology, SUNY Upstate Medical University, Syracuse, NY, USA, [11]Medical Oncology, Palmetto Hematology Oncology Associates, Spartanburg, SC, USA, [12]Medical Oncology, The University of Chicago Medical Centre, Chicago, IL, USA

Background: A retrospective subset analysis from a phase 3 trial, and preclinical data supported prospective study of elrotinib and bevacizumab in patients (pts) with EGFR mutant NSCLC.

Methods: Pts were required to have an EGFR exon 19 deletion or exon 21 L858R mutation based on local testing. Pts were assigned to erlotinib 150 mg daily (E) or erlotinib 150 mg daily and bevacizumab 15 mg/kg IV every 3 weeks (EB). The primary objective was progression-free survival (PFS); secondary objectives were objective response rate (ORR), and overall survival (OS). cfDNA samples were collected at baseline, at time of imaging, and disease progression. The study was designed to detect a hazard ratio (HR) of 0.667 in favor of EB, with a power of 81% at one-sided significance level of 0.20; under exponential hazards. HR corresponds to an improvement in median PFS from 10 to 15 months.

Results: From 11/2012 to 8/2016 88 pts were enrolled. The median age was 63 years (range 31 to 84), the majority were women (70%), had a history of never smoking (55%), performance status (PS) of 1 (51%), and EGFR exon 19 deletion (67%). With a median follow-up of 23 months, 69 PFS events have been observed. A statistically significant difference in PFS in pts assigned to EB compared to E was not observed (HR of 0.87, 95 CI: 0.54-1.43; p = 0.59; median PFS 17.9 and 13.5 months, respectively). The ORR in the EB and E arms were 83% vs 81% (p = 1.0). 33 OS events have been observed. The OS analysis of pts assigned to EB compared to E revealed a HR of 1.54, 95% CI: 0.74-3.19, p = 0.25; median OS 29.9 months and not evaluable, respectively. Grade $\geq$ 3 adverse events (rate $\geq$ 10%) in the EB and E arms were: rash (26% and 18%), diarrhea (9% and 13%), hypertension (40% and 22%), and proteinuria (12% and 0%). In EB and E arms 23 and 21 pts received subsequent therapies; in the EB and E arms osimertinib was a subsequent therapy in 10 and 13 pts, respectively. cfDNA were available for 36/69 pts with progressive disease; exon 19 deletion or exon 21 L858R detected in 12 samples and T790M in 5 samples.

Conclusions: Treatment with EB compared to E did not result in a statistically significant improvement in PFS in pts with EGFR mutant NSCLC. OS data are immature. A review of subsequent therapies and additional cfDNA analyses are ongoing.

Clinical trial identification: NCT01532089.

Legal entity responsible for the study: Academic and Community Cancer Research United.

Funding: Genentech.

Disclosure: T.E. Stinchcombe: Advisory board related to immunotherapy: Genentech; Advisory board: AstraZeneca; Research funding to institution for clinical trials: Genentech/Roche and AstraZeneca. P.A. Janne: Consultant: BI, Pfizer, Roche/Genentech, Chugai, Ariad, AstraZeneca, Merrimack, Acea Bioscience; Research funding: Astellas, AstraZeneca, BI; Post-marketing royalties: Dana Farber Cancer Institute for intellectual property on EGFR mutations licensed to Lab Corp. E.M. Bertino: Advisory board: BI. E.E. Vokes: Consultant/advisory roles: AstraZeneca, Genentech. All other authors have declared no conflicts of interest.

1445P A phase II study of first-line afatinib for patients aged 75 or older with EGFR mutation-positive advanced non-small cell lung cancer: North East Japan study group trial NEJ027

T. aiba[1], Y. Minegishi[2], O. Yamaguchi[3], S. Kuyama[4], S. Watanabe[5], K. Usui[6], M. Mori[7], O. Hataji[8], T. Nukiwa[9], S. Morita[10], K. Kobayashi[11], A. Gemma[12]

[1]Respiratory Medicine, Sendai Kousei Hospital, Sendai, Japan, [2]Department of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan, [3]Department of Respiratory Medicine, Saitama Medical University International Medical Center, Saitama, Japan, [4]Department of Respiratory Medicine, National Hospital Organization Iwakuni Clinical Center, Iwakuni, Yamaguchi, Japan, [5]Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [6]Division of Respirology, NTT Medical Center Tokyo, Tokyo, Japan, [7]Department of Thoracic Oncology, National Hospital Organization Toneyama National Hospital, Toyonaka, Japan, [8]Respiratory Center, Matsusaka City Hospital, Matsusaka, Japan, [9]Tohoku University, Sendai, Japan, [10]Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine 54 Kawahara-Cho,Shogoin,Sakyo-Ku, Kyoto, Japan, [11]Department of Respiratory Medicine, Saitama Medical University Internatl Medical Centre, Saitama, Japan, [12]Division of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan

Background: The aim of this study was to assess the efficacy and safety of afatinib, an epidermal growth factor receptor (EGFR) tyrosin kinase inhibitor (TKI), for elderly Japanese patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC).

Methods: NEJ027 was single-arm, multicenter, open-label phase II study of first-line afatinib monotherapy. Patients aged 75 or older with stage IIIB/IV or recurrent non-squamous NSCLC harboring EGFR mutations were enrolled. The patients received afatinib at a start dose of 40mg/day until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR), and the secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety profile.

Results: Between January 28, 2016, and September 14, 2017, a total of 38 patients with a median age of 77 years (range, 75-91) were enrolled (15 males; 21 Eastern Cooperative Oncology Group performance status 0; all adenocarcinoma; 23 EGFR exon 19 deletion mutation) in safety analysis and 37 in the full analysis set. The ORR was 75.7% (95% confidence interval: CI 61.9-89.5) and DCR was 89.2%. The median PFS was 14.3 months (95% CI 9.9-not reached). The common grade 3 or 4 adverse events were diarrhea (10 [26.3%]), stomatitis (5 [13.2%]), rash (2 [5.3%]), appetite loss (5 [13.2%]), nail abnormality (4 [10.5%]) and pneumonitis (2 [5.3%]). 30 patients (78.9%) required 1 step or more dose reduction.

Conclusions: Although the percentage of patients requiring dose reduction seemed relatively higher than that in previous studies, first-line afatinib at a start dose of 40mg/day was found to be well-tolerated by dose adjustment and effective in elderly patients with advanced non-squamous NSCLC harboring EGFR mutations.

Clinical trial identification: UMIN000017050.

Legal entity responsible for the study: North East Japan Study Group.

Funding: Japan Agency for Medical Research and Development.

Disclosure: O. Yamaguchi: Honoraria: Bristol-Myers Squibb, Ono Pharm and AstraZeneca. S. Watanabe: Grants: Boehringer Ingelheim, during the conduct of the study; Grants and personal fees: Boehringer Ingelheim, personal fees: Chugai Pharma, Ono Pharmaceutical, Lilly, AstraZeneca, Taiho Pharmaceutical, Pfizer, Bristol-Myers Squibb and Novartis Pharma. M. Mori: Lecture fees: Boehringer Ingelheim. O. Hataji: Lecture fees: Novartis, Boehringer Ingelheim; Research fundings: Novartis, Boehringer Ingelheim, Kyorin Pharm, Bayer Health Care, Daiichi Sankyo, Glaxo Smith Kline. S. Morita: Corporate-sponsored research: Boehringer Ingelheim; Honorarium: Boehringer Ingelheim. K. Kobayashi: Advisory board: AstraZeneca. A. Gemma: Lecture fee: Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1446P Management of leptomeningeal metastases in EGFR mutated non-small cell lung cancer: Analysis of tyrosine kinase inhibitors sequence

R. Flippot[1], E. Auclin[2], P. Biondani[3], E. Le Rhun[4], J. Adam[5], D. Planchard[6], C. Caramella[7], C. Le Pechoux[8], L. Lacroix[9], A. Gazzah[10], L. Mezquita[6], B. Besse[11]

[1]Medical Oncology, Gustave Roussy, Villejuif, France, [2]Oncology, Hopital European George Pompidou, Paris, France, [3]Oncology, Hôpital Paul Brousse, Villejuif, France, [4]Neuro-oncology, Neurosurgery Department, Roger Salengro Hospital, Lille, France, [5]Pathology, Institut Gustave Roussy, Villejuif, France, [6]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [7]Radiology, Gustave Roussy, Villejuif, France, [8]Radiation Therapy, Institut Gustave Roussy, Villejuif, France, [9]Biology, Institut Gustave Roussy, Villejuif, France, [10]Drug Development Department, Institut Gustave Roussy, Villejuif, France, [11]Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France

Background: Non-small cell lung carcinomas (NSCLC) with leptomeningeal metastases are associated with poor outcomes. Tyrosine kinase inhibitors (TKI) in EGFR-mutated (EGFRm) tumors might have substantial activity. Impact of TKI sequence on survival and clinical benefit is unknown.

Methods: Consecutive patients (pts) from 2 institutions with EGFRm NSCLC and LM were included. Retrospective collection of clinical, pathological and radiological data was performed. Overall survival (OS), Progression-free survival (PFS), clinical response rate (CRR) and disease control rate (DCR; stable disease $>$ 2 months or clinical response) were assessed. Evaluation of TKI sequence and dose modifications in pts who had LM progression with first-line TKI was performed.

Results: Seventy pts were enrolled from Apr. 2003 to Feb. 2018. Median age was 54 [26-79], 73% were female and 85% non-smokers. Median time from initial diagnosis to LM onset was 17.5 months (m) [0-106], and pts received a median of 2 [1-7] prior therapies before LM onset. Median OS from LM onset was 7m [95% CI 6-9]. After LM diagnosis, pts received a median of 2 [1-6] lines of systemic therapy. Forty pts received 2nd-line TKI after LM progression under TKI, with a 2nd-line median PFS of 3m [95% CI 2-not reached], CRR 38%, DCR 73%. In pts who switched treatment at LM progression (N = 36), 21 switched from any TKI to erlotinib ("E",53%), 10 maintained erlotinib with either dose increase or concurrent bevacizumab ("HD-E", 22%), 2 switched from erlotinib to afatinib or gefitinib ("A/G", 6%), and 4 with T790M mutation switched from any TKI to osimertinib ("O", 11%). Pts with E had 6-months PFS of 41%, median OS of 6 months [95% CI 3-7], and DCR of 62%. Both pts with A/G had absolute OS $<$ 2m. Pts with HD-E had a median OS of 3 months [2-6] and a DCR of 80%. In T790M-mutated pts, O provided a median OS of 10 months [6-10] and a DCR of 100%.

Conclusions: TKIs in LM from EGFRm NSCLC provide disease control in most pts. Switch from afatinib/gefitinib to erlotinib provided extended survival for patients who progressed with first-line TKI. A higher dose of erlotinib might rescue resistance to erlotinib in subsets of pts.

Legal entity responsible for the study: Gustave Roussy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1447P Risk of not receiving second-line therapy is high in EGFR mt+ pts: Real world data of certified lung cancer centers on treatment sequence in EGFR mt+ pts

J. Roeper[1], M. Falk[2], S. Schatz[3], M. Tiemann[3], C. Wesseler[4], G. Wiest[4], S. Sackmann[5], D. Ukena[5], L.C. Heukamp[6], F. Griesinger[7]

[1]University Department Internal-Medicine-Oncology, Pius Hospital Oldenburg, University of Oldenburg, Oldenburg, Germany, [2]Molecular Pathology, Hematopathology Hamburg, Hamburg, Germany, [3]Molecular Pathology, Hematopathology Hamburg, Hamburg, Germany, [4]Department of Oncology, Asklepios Klinik Harburg, Hamburg, Germany, [5]Department of Pneumology, Klinikum Bremen-Ost, Bremen, Germany, [6]Molecular Pathology, NEO New Oncology, Cologne, Germany, [7]University Department Internal Medicine-Oncology, Pius Hospital Oldenburg, University of Oldenburg, Oldenburg, Germany

Background: Recently FLAURA study demonstrated significant PFS and numeric OS benefit for Osimertinib 1st line vs. 1st gen. TKI's Erlotinib/Gefitinib. The number of pts switching from 1st gen. to 3rd gen. TKI (30%) appeared to be low and it is questionable whether these data represent real world sequencing treatment patterns. Therefore, we investigated the sequence pattern, i.e. the percentage of 2nd line therapy in EGFR mt+ pts in 3 certified lung cancer centers in Germany.

Methods: Data of 912 of 1477 pts tested for EGFR mutations were analyzed between 2009-2017. 140/144 pts with an activating EGFR mt + (16%) and treated with systemic therapy (4 pts received no therapy) were identified and their treatments were captured as well as their outcome. 36 pts were treated before accessibility to 3rd generation TKI and 104 pts after accessibility to 3rd generation TKI.

Results: 130/140 pts were treated with 1st line TKI and 10 received 1st line chemotherapy. 17 pts are still on 1st line TKI, 8 pts were lost to follow-up, 3 pts died while on 1st line TKI. 112 pts were candidates for 2nd line therapy. 34/112 (30%) of these pts did not receive 2nd line therapy. Causes for not receiving 2nd line therapy were pts refusal (n = 2), bad PS (n = 26) frequently due to CNS metastases, fast progression and death (n = 6). After accessibility of 3rd gen. TKI, 20 of 66 (30%) pts did not receive 2nd line therapy. Median OS of the overall cohort was 27 months (n = 140), median OS of pts receiving 2nd line (n = 78) vs. no 2nd line (n = 62) was 36 vs. 14 months ($p < 0.0001$). After accessibility of 3rd gen. TKI 30/104 pts (29%) receive a 3rd gen. TKI after 1st line or 2nd line therapy. Median OS of pts receiving (n = 30) and not receiving 3rd gen. TKI (n = 110) was 55 months vs. 22 months ($p < 0.0001$).

Conclusions: In real world, a significant number of pts treated with 1st or 2nd gen. TKI do not reach 2nd line therapy even when 3rd gen. TKI were accessible. Reasons for not receiving 2nd line therapy are in most cases deterioration of PS and lack of possibility to test for T790M in the minority of cases (n = 28/66, 42% were not tested). These data, although favorable for the small and very selected cohort of pts treated with Osimertinib, might argue for the most effective therapy in 1st line for pts with EGFR mt+ tumors.

Legal entity responsible for the study: Carl von Ossietzky University Oldenburg Department of Internal Medicine-Oncology.

Funding: Has not received any funding.

Disclosure: J. Roeper: Advisory boards: Roche, Boehringer Ingelheim. M. Falk: Advisory boards: Boehringer Ingelheim, Pfizer, Roche. M. Tiemann: Advisory boards: Novartis, Boehringer-Ingelheim, Roche, AstraZeneca; Scientific support: Novartis. F. Griesinger: Advisory boards: Ariad, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Celegene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Roche; Travel support: Ariad, AstraZeneca, Boehriger Ingelheim, Bristol-Myers Squibb, Celegene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, oche; Scientific support: Ariad, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celegene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche. All other authors have declared no conflicts of interest.

1448P Patterns of recurrence to Osimertinib in T790m positive NSCLC: A Swiss cohort study

S. Schmid[1], D. Klingbiel[2], S. Aeppli[1], C. Britschgi[3], O. Gautschi[4], M. Pless[5], S.I. Rothschild[6], L. Wannesson De Nicola[7], W-D. Janthur[8], D. Foerbs[9], I. Demmer[9], W. Jochum[9], M. Früh[1]

[1]Department of Oncology / Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland, [2]Swiss Group for Clinical Cancer Research Coordinating Center, SAKK, Bern, Switzerland, [3]Department of Hematology and Oncology, Universitätsspital Zürich, Zurich, Switzerland, [4]Medical Oncology, Cantonal Hospital Lucerne, Lucern, Switzerland, [5]Oncology/Hematology, Kantonsspital Winterthur, Winterthur, Switzerland, [6]Onkologie, Universitätsspital Basel, Basel, Switzerland, [7]Oncology, IOSI - Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland, [8]Onkologie, Kantonsspital Aarau ZOHT, Aarau, Switzerland, [9]Pathology, Kantonsspital St. Gallen, St. Gallen, Switzerland

Background: Osimertinib (Osi) is an EGFR-TKI that potently inhibits both EGFR-sensitizing and EGFR T790M resistance mutations in non-small cell lung cancer (NSCLC). Identification of oligo-progression (PD) on Osi may allow local treatment and continuation of Osi. Metastatic patterns at the time of acquired resistance to Osi are poorly understood.

Methods: We retrospectively analyzed 50 pre-treated T790M+ NSCLC patients who received Osi at 7 Swiss centers. Oligo-PD was defined as PD in $\leq$ 5 lesions. Archived pre-treatment and fresh biopsies at PD were analyzed for mutational profiling.

Results: Median age was 62 years (range: 37-89), 64% females, 86% had a PS ≤ 1, 54%/13% were never/current smokers. Patients had one (44%), two (34%) or more (22%) prior treatment lines. At diagnosis, patients had EGFR exon 19 deletion (74%), L858R exon 21 mutation (24%) and concomitant exon 18/ exon 20 mutation (2%). Before Osi start, T790M was detected in blood (28%) or tumor tissue (72%). Median follow-up was 15.3 (IQR: 8.6-21.6) months. Overall response rate was 83%, median progression-free survival 15.1 months (IQR: 6.4-20.1), median overall survival 25.1 months (IQR: 16.7-not reached [NR]) and median treatment duration 18.1 months (IQR: 10.1-23.5). At data cut off, PD had occurred in 26 patients (52%). There were 73% oligo- vs. 27% systemic PD. Median treatment duration in patients with oligo-PD was 19.6 vs 6.5 months if systemic PD. The number of progressive lesions in oligo-PD patients were 1 (32%), 2 (37%), 3 (26%), and 5 (5%). Main sites of PD were lung (n = 14), bone (n = 10), lymph nodes (n = 6), liver and pleura (n = 5 each), and brain (n = 4). 12 patients with oligo-PD continued treatment with Osi beyond progression, ten of them after local therapy (8x radiotherapy, 2x surgery). Median time of treatment beyond PD was 10.7 months in patients with oligo-PD (IQR: 5.7-NR). Analyses of pretreatment and post-PD tumor tissue from a subset of patients will be presented.

Conclusions: In patients with acquired resistance to Osi, we observed a high rate of extracranial oligo-PD. Outcomes of patients with oligo-PD were favorable with the majority continuing Osi in addition to local therapy, supporting the concept of Osi treatment beyond progression in combination with local therapy of progressing lesions.

Legal entity responsible for the study: Kantonsspital St. Gallen.

Funding: Institutional funding from AstraZeneca for molecular analysis.

Disclosure: S. Schmid: Research funding (Institutional): AstraZeneca, BMS Advisory (Institutional): Boehringer Ingelheim. S.I. Rothschild: Consulting/Advisory Role (Institutional): BMS, AstraZeneca, Lilly, Boehringer Ingelheim, Eisai, Roche, Novartis, Merck Serono, MSD Oncology, Astellas Pharma, Bayer, Pfizer, Takeda; Research funding (institutional): Boehringer Ingelheim, AstraZeneca, BMS, Eisai, Merck Serono; Travel, Accommodation: Roche, Lilly, BMS, AstraZeneca, Merck Sharp and Dohme, Amgen. W-D. Janthur: Advisory boards: Roche, Boehringer Ingelheim, Takeda, MSD. M. Früh: Advisory Board AstraZeneca. All other authors have declared no conflicts of interest.

1449P Efficacy of afatinib in the clinical practice: First results of the GIDEON trial: A prospective non-interventional study (NIS) in EGFR mutated NSCLC in Germany

W.M. Brueckl[1], E. Laack[2], M. Reck[3], F. Griesinger[4], H. Schäfer[5], C. Kortsik[6], T. Gaska[7], J. Rawluk[8], S. Krüger[9], K. Kokowski[10], S. Budweiser[11], A. Schueler[12], S. Kiessling[12]

[1]Dept. of Internal Medicine 3, Klinikum Nürnberg, Universitätsklinik der Paracelsus Medizinischen Privatuniversität, Nuremberg, Germany, [2]Hemato-Oncology, Hamburg, Germany, [3]Airway Research Center North, German Center for Lung Research, LungenClinic Grosshansdorf, Grosshansdorf, Germany, [4]Dept. of Hematology and Oncology, Pius Hospital, Oldenburg, Germany, [5]Department of Pneumology, SHG-Clinic, Voelklingen, Germany, [6]Dept. of Pneumology, KKM St.Hildegardis Krankenhaus, Mainz, Germany, [7]Hematology and Oncology, Bruederkrankenhaus St. Josef, Paderborn, Germany, [8]Klinik für Innere Medizin I, Universitätsklinikum Freiburg Klinik für Innere Medizin Hämatologie, Onkologie und Stammzelltransplantation, Freiburg, Germany, [9]Dept. Pulmonology, Florence-Nightingale-Hospital, Düsseldorf, Germany, [10]Dept. of Pneumology, Krankenhaus München Bogenhausen Med. II Abteilung, Munich, Germany, [11]Department of Internal Medicine III, Division of Pulmonary and Respiratory Medicine, RoMed Clinical Centre, Rosenheim, Germany, [12]Boehringer Ingelheim Pharma GmbH & Co. KG, Germany, Ingelheim Am Rhein, Germany

Background: Afatinib is an irreversible ErbB family blocker, which is approved as monotherapy for the treatment of advanced non-small cell lung cancer (NSCLC) patients with activating EGFR mutations. Here we report the first interim analysis of the NIS GIDEON, which was initiated to investigate the efficacy and tolerability of Afatinib in first line treatment in the daily clinical routine in Germany.

Methods: EGFR-mutated NSCLC patients were treated with Afatinib according to label until progression, death or discontinuation due to patients' or physicians' decision. Efficacy (objective response rate, ORR; disease control rate, DCR and progression-free survival, PFS) was prospectively assessed by investigators and additional data about tolerability under everyday treatment conditions were documented.

Results: A total of 151 pat. were enrolled in the study and received Afatinib treatment. EGFR mutations comprised exon 19 deletions (Del19, 56.6 %), L858R point mutations (21.9 %) and uncommon mutations (18.5 %). Median age was 67 years (38-89) with 91 Pat. ≥65 years (60.3%). Pat. started treatment on 40mg/d (72.8 %) Afatinib or < 40mg/d (25.8 %). Dose reductions during the course of therapy were frequent, 61.8 % with 40mg/d starting dose and 53.8% with <40mg/d. ORR for the total treated population was 73% with a DCR of 90 %. ORR was similar according to different subgroups, e.g. mutation type and age. mPFS at the time of analysis was 12.9 Mon. and in the group of pat. ≥65 years 13.7 Mon. OS date are not mature yet. The most frequent documented AEs were diarrhea and rash/acne, with 11.6 % of pat. discontinued treatment due to drug related AEs.

Conclusions: Afatinib is a standard therapy for patients with activating EGFR mutations in Germany. The first results of this prospective NIS confirm the robust clinical data for Afatinib in the clinical routine setting, especially in the elderly population, which is underrepresented in clinical trials. A starting dose of < 40 mg Afatinib in selected pat. does not seem to be inferior in terms of efficacy.

Clinical trial identification: NCT02047903.

Legal entity responsible for the study: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

Funding: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

Disclosure: W.M. Brueckl: Payments for membership on advisory boards: Boehringer Ingelheim. M. Reck: Honoraria for lectures and consultancy: Hoffmann-La Roche, Lilly, Boehringer Ingelheim, Abbot, AstraZeneca, Celgene, BMS, MSD, Merck, Novartis and Pfizer. S. Krüger: Honoraria, Advisory boards and lectures: Boehringer Ingelheim. A. Schueler, S. Kiessling: Employee: Boehringer Ingelheim Pharma GmbH & Co. KG. All other authors have declared no conflicts of interest.

1450P Osimertinib treatment for patients with EGFR exon 20 insertion positive non-small cell lung cancer

B. van Veggel[1], A. van der Wekken[2], S. Hashemi[3], R. Cornelissen[4], K. Monkhorst[5], D. Heideman[6], T. Radonic[6], E.F. Smit[7], E. Schuuring[8], J. De Langen[1]

[1]Thoracic Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital (NKI-AVL), Amsterdam, Netherlands, [2]Pulmonary Diseases, University of Groningen, Groningen, Netherlands, [3]Pulmonary Diseases, VU University Medical Center, Amsterdam, Netherlands, [4]Pulmonary Diseases, Erasmus MC, Rotterdam, Netherlands, [5]Pathology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, Netherlands, [6]Pathology, VU University Medical Center, Amsterdam, Netherlands, [7]Pulmonary Diseases, The Netherlands Cancer Institute, Amsterdam, Netherlands, [8]Pathology, University Hospital Groningen (UMCG), Groningen, Netherlands

Background: Epidermal growth factor receptor (EGFR) exon 20 insertions are identified in 4-10% of al EGFR mutations in non-small cell lung cancer (NSCLC) and are generally associated with primary resistance to first and second generation EGFR tyrosine kinase inhibitors (TKIs). In vitro and preclinical animal studies have shown that osimertinib exerts antitumor activity in EGFR exon 20 insertion positive NSCLC cell lines. We report on a cohort of advanced stage NSCLC patients, harboring an EGFR exon 20 insertion, that was treated with osimertinib.

Methods: 17 patients with advanced NSCLC harboring an EGFR exon 20 insertion were treated with osimertinib 80 mg once daily, in four institutions in the Netherlands. Data were obtained retrospectively. EGFR mutation status was assessed by next-generation sequencing. Progression free survival (PFS), disease control rate (DCR) and objective response rate (ORR) were assessed using RECIST v1.1.

Results: Median age was 63 years (range 35 – 81), 71% was female and median number of prior systemic treatments was 1 (range 0 – 3). Ten patients (59%) received prior platinum-based chemotherapy, and 2 patients afatinib, one patient experienced stable disease for 11 months, the other patient showed progression. Among all patients treated with osimertinib, we observed 1 partial response, 13 patients with stable diseases and 3 with progressive disease as best response (ORR 6%). Two patients were still on osimertinib treatment at the cut-off date. Median PFS was 3.7 months (95% CI: 2.3 – 5.4 months). Six of seventeen patients (35%) achieved DCR at five months.

Table: 1450P

Patient	Number of prior treatments	Prior platinum based chemotherapy	Prior EGFR TKI	Best RECIST response	PFS (months)
1	2	Yes	no	SD	4.0
2	1	Yes	no	SD	1.6
3	2	Yes	no	PR	0.7
4	1	Yes	no	PR	0.7
5	2	Yes	no	SD	3.8
6	1	Yes	no	SD	3.0
7	3	Yes	no	SD	9.3
8	1	Yes	no	SD	17.0
9	1	No	no	SD	3.7
10	1	Yes	no	SD	17.2
11	0	No	no	PR	3.1
12	0	No	no	SD	2.6
13	0	No	no	SD	6.5
14	3	Yes	afatinib (SD)	SD	7.9
15	1	No	afatinib (PD)	PD	1.7
16	0	no	no	SD	8.3
17	0	no	no	SD	1.4

EGFR, epidermal growth factor receptor; RECIST: Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression free survival

Conclusions: Osimertinib has limited antitumor activity in patients with EGFR exon 20 mutated NSCLC, with an ORR of 6%. A subset of patients (35%) seems to derive benefit from osimertinib treatment with durable disease control for more than five months.

Legal entity responsible for the study: J. de Langen.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1451P The characteristics and clinical outcome of metastatic NSCLC harboring uncommon EGFR mutation at Thailand's tertiary referral center

J. Chantharasamee[1], N. Poungvarin[2], P. Danchaivijitr[1], S. Techawatanawanna[1]

[1]Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Clinical Pathology, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: An uncommon EGFR-mutant NSCLC is a rare subset of NSCLC. Prevalence and clinical outcome of this entity remain unclear. Several studies have reported the benefit of EGFR-tyrosine kinase inhibitor in patients harboring complex or uncommon EGFR mutations but there are insufficient data to determine the advantage of EGFR-TKI over chemotherapy. This study aimed to review the prevalence and clinical outcome of treatment of uncommon EGFR-mutant patients in real-world practice.

Methods: We retrospectively reviewed medical records of 681 patients tested for EGFR mutation NSCLC during 2014-2018 to collect the mutational status and to compare the survival outcomes between the patients treated with EGFR-TKI and chemotherapy.

Results: At a median follow-up of 19.1 months, 317 (47%) patients were identified with EGFR-mutant NSCLC. Twenty-eight patients (8.8%) harbored uncommon EGFR mutations. Of those 28 patients, the most frequent single mutation was exon20 insertion (21%, n = 6); 5 were L861Q and 4 were G719X. 13 (46%) patients had compound mutations: 4 were G719X plus S768I; 4 were de novo T790M plus either L858R or deletion(del)19; 2 were L858R plus del19; 1 was L858R plus Ex20Ins; 1 was del19 plus KRAS mutation, and 1 with G719X plus E709A was found in squamous cell carcinoma. History of tobacco use was found in 50% of patients. 100% of male patients with G719X mutation were smokers. 57% of the 28 patients were treated with EGFR-TKI, mostly 1st generation, and 29% were treated with chemotherapy alone. The objective response rate was 56% in the TKI group. Median progression-free survival (PFS) in the TKI group was 10.2 months. 5-year overall survival (OS) rate was 34%. Patients treated with TKI had significantly better 5-year OS rate than those who had never received TKI (54% vs. 17%, 95%CI 1.23-14.66, p log-rank= 0.02). The longest OS was 73.6 months in a patient with del19 plus de novo T790M.

Conclusions: This study demonstrated the benefit of 1st generation EGFR-TKI was greater than with chemotherapy alone in the patients with uncommon or compound EGFR mutation NSCLC. Rare EGFR mutations can be detected in squamous cell carcinoma. There was a high prevalence of smoking among the male patients with G719X-mutant NSCLC.

Legal entity responsible for the study: Jomjit Chantharasamee.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1452P Combination of the S49076 with gefitinib in NSCLC patients progressing on EGFR-TKI and harboring MET/AXL dysregulation

S. Viteri[1], G-C. Chang[2], R. Chiari[3], B.C. Cho[4], F. Ciardiello[5], G. Curigliano[6], T. Hida[7], D.H. Lee[8], W.T.D. Lim[9], C-C. Lin[10], A. Martinez[11], H. Murakami[12], I. Natsume[13], M. Nishio[14], L. Paz-Ares[15], R.A. Soo[16], V. Cattan[17], E. Gandossi[18], H. Heck[19], K. Park[20]

[1]Servicio Oncología Médica, Instituto Universitario USP Dexeus, Barcelona, Spain, [2]Oncology, Taichung Veterans General Hospital, Taichung, Taiwan, [3]S.C. Oncologia Medica, Azienda Ospedaliera di Perugia S. Maria della Misericordia, Perugia, Italy, [4]Medical Oncology, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea, [5]Dipartimento Medico di Internistica Clinica e Sperimentale, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [6]Early Drug Development for Innovative Therapies Division, Istituto Europeo di Oncologia, Milan, Italy, [7]Department of Thoracic Oncology, Department of Thoracic Oncology, Aichi, Japan, [8]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea[9]Clinical Trial and Epidemiological Sciences, National Cancer Centre Singapore, Singapore, [10]Department of Oncology, National Taiwan University Hospital, Taipei City, Taiwan, [11]Servicio Oncología Médica, Vall d'Hebron University Hospital, Barcelona, Spain, [12]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [13]Department of Oncology, Yokosuka Kyosai Hospital, Yokosuka Kyosai, Japan, [14]Thoracic Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [15]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [16]Haematology-Oncology, National University Hospital, Singapore, [17]Translational Research, Servier France, Suresnes, France, [18]Servier Oncology, Servier France, Suresnes, France, [19]Dpt of Pharmacokinetics, Servier, Suresnes, France, [20]Div. of Heamatology/Oncology, Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: EGFR T790M mutation is the most common acquired mechanism of resistance in NSCLC patients treated with EGFR-TKI. Alternative mechanisms include activation of the receptor tyrosine kinases MET or AXL. S49076 is a multi-target inhibitor and a potent ATP-competitive TKI that targets MET, AXL and FGFR1/2/3. Here we report phase 1 molecular and safety data of resistant patients without the EGFR T790M mutation that were treated with S49076 combined with gefitinib.

Methods: A dose-escalation of S49076 in combination with gefitinib 250 mg once daily was conducted using a modified Bayesian Continual Reassessment Method. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events (AEs), v4.0. Resistant patients were selected according to a tumor molecular profile including presence of the activating EGFR mutation, absence of T790M and with at least one of the following: MET amplification, or MET or AXL overexpression.

Results: The molecular profile screening has been performed in 46 EGFR/T790M-negative tumour samples. In total, 23/46 met the molecular eligibility criteria: 21 with MET dysregulation (11 MET amplification, 20 MET overexpression and 4 both MET / AXL dysregulations), and 2 with AXL overexpression only. Fourteen patients were treated: 4 received the 500 mg dose and 10 received the 600 mg dose, which was considered as the recommended dose. Related AEs included diarrhoea, paronychia, asthenia, nausea, vomiting, ALAT and ASAT increase, anaemia, peripheral oedema and yellow skin, mostly grade 1-2. One patient experienced a DLT at 600 mg (grade 3 stomatitis); 2 patients experienced 3 serious related AEs (asthenia, atrial fibrillation and diarrhoea). No grade 4-5 AEs were reported. Concomitant intake of gefitinib did not appear to modify the S49076 PK profile as compared to previous data. Limited anti-tumour activity was observed in the 12 evaluable patients: 1 partial response and 9 stable diseases.

Conclusions: S49076 combined with gefitinib is well tolerated and data are consistent with the overall safety profile of each drug. The observed frequency of MET dysregulation was comparable to those reported in the literature whereas AXL overexpression was lower than expected.

Clinical trial identification: EudraCT: 2015-00264631.

Legal entity responsible for the study: Servier group.

Funding: Servier group.

Disclosure: S. Viteri: BMS: Speaker bureau/ Consultant: Roche G.-C. Chang: Honoraria: Hoffman-La-Roche, Merck Sharp & Dohme, BMS, BI, Pfizer, AstraZeneca, Eli Lilly, Compagny Oncology. G. Curigliano: Speaker: Roche, Pfizer, Novartis. T. Hida: Research funding: Novartis, Pfizer, AstraZeneca. D.H. Lee: Honoraria: AstraZeneca, BMS, Ono Pharm, Merck, Lilly, BI, Pfizer, Novartis, CT Cube, Takeda, Roche, Samyang Biopharma, BMS, Janses, MSD, Mundipharma, CJ Healthcare. H. Murakami: Honoraria, Speaker, Grants and Research: AstraZeneca, BMS, Ono Pharm, Merck, Lilly, Chugai Pharm, BI, Pfizer, Taiho, Novartis. M. Nishio: Speaker fees as Honoraria, Consultant, Research funding: Ono Pharmaceutical, Bristol Myers Squibb, Pfizer, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Boehringer ingelheim, MSD, Novartis, Daiichi Sankyo Healthcare, Merck Serono, Astellas. L. Paz-Ares: Honoraria: Roche, Lilly, MSD, BMS, Novartis, Pfizer, Boehringer Ingelheim, AstraZeneca, Merck Serono, Amgem, Clovis Oncology. R.A. Soo: Honoraria, Advisory board, Research: AstraZeneca, BMS, Merck, Lilly, Roche, BI, Pfizer, Taiho, Novartis. V. Cattan, E. Gandossi, H. Heck: Employee: Servier. K. Park: Advisor/consultant: Astellas, AstraZeneca, BI, BMS, Clovis, Daiichi Sankyo, EliLilly, GSK, Hanmi, KHK, MSD, Novartis, Roche Research fund; AstraZeneca. All other authors have declared no conflicts of interest.

1453P Afatinib dose intensity and clinical efficacy in advanced EGFR-mutated non-small cell lung cancer: UK multicentre real-life data

C. Escriu[1], M. Sallam[2], L.P. del Carpio[3], N. Tokaca[4], L. Solway[5], R. Shah[6], A. Fouzia[7], Q. Ghafoor[5], S. Popat[8], P.E. Postmus[9]

[1]Medical Oncology, The Clatterbridge Cancer Center, Merseyside, Merseyside, UK, [2]School of Medicine, University of Liverpool, Liverpool, UK, [3]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [4]Medical Oncology, The Royal Marsden NHS Foundation Trust, London, UK, [5]Oncology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [6]Medical Oncology, Maidstone and Tumbridge Wells NHS Trust, Maidstone, UK, [7]Medical Oncology, The Clatterbridge Cancer Center, Merseyside, UK, [8]Medicine, The Francis Crick Institute, London, UK, [9]Respiratory Diseases, Leiden University Medical Center (LUMC), Leiden, Netherlands

Background: The second-generation afatinib has shown longer Progression-Free Survival (PFS) than gefitinib in the first line treatment of advanced EGFR mutated lung cancer, and has excellent penetration into the central nervous system. It is licensed at a starting dose of 40mg/day, but in real-life practice dose reductions due to toxicity are common. As for other targeted agents, it is questionable if dose selection should be based on biological active dose instead of maximum tolerable dose. Here we aimed to identify the frequency of afatinib dose reductions and analyse their impact in survival outcomes in the UK real-life population.

Methods: Patients with EGFR-mutated lung cancer treated with afatinib between April 2014 and December 2017 in four UK centres were retrospectively identified. The frequency of dose reductions and response rates was quantified. Dose Intensity (DI; average daily dose over the total treatment period) was calculated and patients were grouped into DI $>$ 30mg/day and DI $\leq$ 30mg/day; PFS and Overall Survival (OS) curves were plotted.

Results: 98 patients were identified. The median treatment duration was 8.5 months (range 01.-42.7), and mean DI 30.6mg/day. 85 patients started at 40mg/day and 13 at 30mg/day. They required dose reductions in 65% (n = 55) and 46% (n = 6), respectively. The starting dose did not influence response rates. 50 patients (51%) received a DI $\leq$ 30 and 48 patients (49%) received a DI $>$ 30. A lower DI did not significantly influence PFS (HR 0.65(0.37-1.14); p = 0.127) or OS (HR 0.58(0.28-1.20); p = 0.14), but showed a trend to better outcomes. Patients with brain metastasis (n = 11(22%) DI $\leq$ 30 and n = 14(29%) DI $>$ 30) had similar clinical outcomes regardless of DI, and patients that required a reduction to the lowest dose of 20mg/day (n = 28) achieved similar PFS (HR 0.58(0.3-1.14); p = 0.113) and OS (HR 0.41 (0.16-1.08); p = 0.062) as the rest (n = 70).

Conclusions: Our results suggest equal clinical efficacy in patients treated with a lower DI of afatinib, and a reduced need for dose reductions in patients starting at 30mg/day. Prospective tolerability and efficacy of afatinib starting at 30mg/day will be quantified in a phase II UK study.

Legal entity responsible for the study: The Clatterbridge Cancer Centre NHS Trust.

Funding: Has not received any funding.

Disclosure: R. Shah: Advisory board: Boehringer Ingelheim. Q. Ghafoor: Consultancy: Roche, AstraZeneca, Boehringer Ingelheim, Pfizer. S. Popat: Honoraria, consulting and research funding: Boehringer Ingelheim. P.E. Postmus: Paid member of advisory board: Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1454P EGFR tyrosine kinase inhibitors in non-small cell lung cancer: Nationwide register-based cohort study in Sweden

S. Bergström[1], H. Nordahl Christensen[2], F. Wiklund[3], M. Bergqvist[4]

[1]Oncology, Gävle Hospital, Gävle, Sweden, [2]Nordic-Baltic, AstraZeneca, Södertälje, Sweden, [3]Stockholm, Statisticon AB, Stockholm, Sweden, [4]Radiation Sciences, Umeå University, Umeå, Sweden

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are recommended as first-line treatment for EGFR mutation-positive NSCLC by international and Swedish clinical guidelines. However, knowledge on treatment patterns of TKIs in a real life clinical setting is limited. The aim was to describe disease characteristics and comorbidities of stage IIIB/IV NSCLC patients receiving first line TKI, and treatment patterns related to switch, re-challenge, and discontinuation.

Methods: All patients with stage IIIB/IV NSCLC during 2010-2015 were identified in the national Swedish Cancer Registry, and linked with data on dispensed EGFR-TKI drugs and comorbidity from Swedish national health registries. First line TKI treatment was defined from date of first dispensed EGFR-TKI drug (gefitinib, erlotinib, afatinib) until a treatment gap of minimum 90 days or switch to another EGFR-TKI drug within the same drug class.

Results: Of 9,992 stage IIIB/IV NSCLC patients (mean age 70 years, female 49%), 1419 (14%) received first-line TKI treatment. Overall, 59% of TKI treated patients (median age 68 years) were female, 44% had at least one comorbidity, 85% had adenocarcinoma, and 89% were stage IV. TKI treatment patterns changed during the observation period. Initiation of TKI treatment declined from 23% to 9% in 2010 and 2015, respectively. However, median time from diagnosis to treatment initiation was shorter (from 7 to 2 months) at the end of observation, and the median treatment length was prolonged particularly for patients diagnosed in later years (from about 2 to 6 months in 2013 and 2015, respectively). Switching and re-challenge patterns were more common at the end of the observation period.

Conclusions: This is the first large nationwide study on patients receiving first-line TKIs in routine clinical practice in Sweden. Changes in TKI treatment patterns, such as shorter time to treatment initiation, prolonged treatment length, and more TKI switching and re-challenging during the observation period, may reflect extension of EGFR testing. Correctly targeted patients according to clinical guidelines, may contribute to an extended survival of this patient population.

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: H. Nordahl Christensen: Employee: AstraZeneca. All other authors have declared no conflicts of interest.

1455P Comparative analysis of overall survival using propensity score between first- and second-generation EGFR-TKI: Real world data of 1354 patients with EGFR mutant NSCLC

K. Ito[1], K. Murotani[2], A. Kubo[3], E. Kunii[4], H. Taniguchi[5], J. Shindo[6], K. Asada[7], K. Imaizumi[8], K. Tanaka[9], N. Inui[10], M. Okuno[11], O. Hataji[1], S. Hayai[12], T. Abe[6], T. Kimura[12], T. Tsuda[5], T. Yamaguchi[13], Y. Oya[13], T. Yoshida[14], T. Hida[13]

[1]Respiratory Center, Matsusaka Municipal Hospital, Matsusaka, Japan, [2]Biostatistics Center, Graduate School of Medicine, Kurume University, Kurume, Japan, [3]Division of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine, Nagakute, Japan, [4]Department of Respiratory Medicine, Respiratory Tract Oncology Center, Nagoya City West Medical Center, Nagoya, Japan, [5]Department of Internal Medicine, Toyama Prefectural Central Hospital, Toyama, Japan, [6]Department of Respiratory Medicine, Ogaki Municipal Hospital, Ogaki, Japan, [7]Department of Respiratory Medicine, Sizuoka General Hospital, Sizuoka, Japan, [8]Department of Respiratory Medicine, Fujita Health University School of Medicine, Toyoake, Japan, [9]Internal Medicine 2, Hamamatsu University School of Medicine, Hamamatsu, Japan, [10]Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Hamamatsu, Japan, [11]Department of Respiratory Medicine, Aichi Cancer Center, Aichi Hospital, Okazaki, Japan, [12]Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, Japan, [13]Department of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [14]Laura & Isaac Perlmutter Cancer Center, New York University, New York, NY, USA

Background: We constructed a data set of EGFR-mutant NSCLC patients (pts) and compared the overall survival of first-generation (1G) and second-generation (2G) EGFR-TKIs in clinical practice using propensity score.

Methods: We reviewed the available data of all EGFR-mutated NSCLC pts who received EGFR-TKI therapy between Jan 2008 and Aug 2017 in the 11 institutions in Japan. The primary endpoint was OS. When comparing OS between 1G and 2G EGFR-TKIs, the propensity scoring was performed using two methods; matching and IPTW with adjusted factors (age, sex, smoking history, histology, EGFR mutational subtype, clinical stage, ECOG PS, line of treatment, brain metastasis) which were previously described in the statistical plan. The statistical plan had been opened prior to statistical analysis. (Clinical Trial information: UMIN000030121)

Results: A total of 1400 pts from 11 institutions were enrolled in this study, and the data from the 1354 pts who received EGFR-TKI alone was analyzed (gefitinib, N = 726; erlotinib, N = 413; afatinib, N = 215). Median age was 70, [range, 28-99] and 61.3% were female. The mutational status was exon 19 deletion in 671 pts, L858R in 571 pts, and minor or compound mutation in 112 pts. 95.1% were histologically diagnosed with adenocarcinoma, and 81.1% were with 0 to 1 of ECOG PS. Median OS (months [95%CI]) were 30.9 [27.7-33.9] in 1G (gefitinib, 32.2 [28.4-36.4]; erlotinib, 28.1 [24.9-33.4]), and 38.6 [32.2-NR] in 2G (afatinib), respectively. The trend of longer OS for afatinib against first-generation EGFR-TKIs remained even after adjusted by propensity score. (unadjusted, HR 0.682, p = 0.0031; adjusted by IPTW, HR 0.783 p $<$ 0.0001; adjusted by matching [1:2], HR 0.747, p = 0.0629) Subgroup analysis showed that the patients with exon 19 deletion had significantly longer overall survival benefit from afatinib therapy than 1G EGFR-TKI. (vs. gefitinib, p = 0.0016; vs. erlotinib, p = 0.0135).

Conclusions: From this analysis of 1354 data records, using propensity scoring, afatinib had a trend of longer OS compared with gefitinib and erlotinib.

Clinical trial identification: UMIN000030121.

Legal entity responsible for the study: Aichi Cancer Center Hospital.

Funding: Boehringer Ingerheim.

Disclosure: K. Ito: Research funding: Boehringer Ingelheim, Chugai Pharmaceutical Co, Novartis, GlaxoSmithKline, Daiichi Sankyo, Ono Pharmaceutical Co; Honoraria: Boehringer Ingelheim, Chugai Pharmaceutical Co, Eli Lily, Ono Pharmaceutical Co, MSD, AstraZeneca. A. Kubo: Honoraria: Chugai Pharma, Boehringer Ingelheim, Taiho Pharmaceutical, AstraZeneca, Novartis, Eli Lilly; Research Funding: Chugai Pharma, Boehringer Ingelheim, Eli Lilly. H. Taniguchi: Lecture Fees: AstraZeneca, Ono Pharm, Daiichi Sankyo, Chugai Pharm, Boehringer Ingelheim, Kyowa Hakko Kirin Co, Otsuska Pharm. K. Imaizumi: Research Funding: Taiho Pharm, Boehringer Ingelheim; Honoraria: Boehringer Ingelheim, Chugai Pharm, AstraZeneca, Ono Pharm, MSD, Eli Lilly. O. Hataji: Lecture Fees: Novartis, Boehringer Ingelheim; Research Fundings: Novartis, Boehringer Ingelheim, Kyorin Pharm, Bayer Health Care, Daiichi Sankyo, Glaxo Smith Kline. T. Yamaguchi: Honoraria: Boehringer Ingelheim, Chugai Pharm, AstraZeneca, Ono Pharm, MSD, Eli Lilly. Y. Oya: Honoraria: Boehringer Ingelheim, Chugai Pharm, AstraZeneca, Ono Pharm, MSD, Eli Lilly, T. Hida: Research fund:

Boehringer Ingelheim, Chugai, Novartis, AstraZeneca, Pfizer, Astellas, Clovis Oncology, Taiho Pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

1456P Phase IV, open-label, multicentre trial of afatinib in patients (pts) aged ≥70 yrs with NSCLC harbouring common (Del19/L858R) EGFR mutations: Preliminary results

K.L. Reckamp[1], P. Gilman[2], B. Halmos[3], M. Jahanzeb[4], J. McCann[5], H. Paripati[6], L.C. Seneviratne[7], J.A. Wallace[8], B. Rueter[9], A. Esler[10], E. Dowling[11], M. Koczywas[12]

[1]Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA, USA, [2]Cancer Center, Lankenau Medical Center, Wynnewood, PA, USA, [3]Department of Oncology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA, [4]Sylvester Comprehensive Cancer Center, University of Miami, Deerfield Beach, FL, USA, [5]D'Amour Center for Cancer Care, Baystate Regional Cancer Program, Springfield, MA, USA, [6]Division of Hematology/Oncology, Mayo Clinic, Phoenix, AZ, USA, [7]Los Angeles Hematology/Oncology Medical Group, Los Angeles Cancer Network, Los Angeles, CA, USA, [8]Department of Hematology/Oncology and Geriatrics, UChicago Medicine: Ingalls, Harvey, IL, USA, [9]CMDA Oncology, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA, [10]Statistics, Syneos Health, Raleigh, NC, USA, [11]Study Management and Conduct, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA, [12]Department of Medical Oncology and Therapeutic Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Background: The irreversible ErbB family blocker, afatinib, is approved for first-line treatment of metastatic NSCLC harbouring non-resistant EGFR mutations. While afatinib has demonstrated a predictable and manageable safety profile in pts with EGFR mutation-positive (EGFRm+) NSCLC, elderly pts are often under-represented in clinical trials. Here, we summarise the current status of, and preliminary data from, an ongoing Phase IV trial of afatinib in elderly pts with Del19/L858R EGFRm+ NSCLC (NCT02514174).

Methods: Pts aged ≥70 yrs with Stage IV/recurrent Del19/L858R EGFRm+ NSCLC naïve to prior systemic therapy have been enrolled to sites in the USA. Pts receive afatinib QD (starting dose 30 mg/day) until disease progression/intolerable AEs. Dose reduction to 20 mg/day is permitted in the case of select Grade 2/≥3 AEs. The primary endpoint is the occurrence of AEs leading to dose reduction. Secondary endpoints include occurrence of Grade ≥3 diarrhoea and Grade ≥3 rash/acne, stomatitis and paronychia (grouped terms). Other endpoints are AEs by NCI CTCAE grade, objective response (OR), PFS and overall survival. Preliminary safety data are reported here.

Results: As of 7 Feb 2018, 26 pts have been enrolled across 9 sites, and 24 pts have entered into the trial. Twenty-three pts have been treated: 57% female; 30% Asian; 26%/74% ECOG PS 0/1; median age (range) 79 (71–93) yrs. Thirteen (57%) pts remain on treatment. Reasons for treatment discontinuation were progressive disease (26%), AEs (9%), refusal to continue study medication (4%), and other (4%). All pts have had at least one AE of any cause (Grade 3/4: 52%/0%), most commonly (preferred term [PT]) diarrhoea (87%), rash (61%) and fatigue (48%). The most common treatment-related AEs (PTs) reported are diarrhoea (83%), rash (57%) and dry skin (39%), and the most common serious AEs (PTs) reported are vomiting and dehydration (both 9%). Ten (43%) pts have achieved confirmed OR (complete/partial response: 1 [4%]/9 [39%]) and 10 (43%) pts have had stable disease.

Conclusions: In this preliminary analysis, afatinib (30 mg/day) demonstrated a predictable safety profile in pts aged ≥70 yrs with Del19/L858R EGFRm+ NSCLC. Updated data will be presented.

Clinical trial identification: NCT02514174.

Editorial acknowledgement: Laura Winton of GeoMed, an Ashfield company, part of UDG Healthcare plc.

Legal entity responsible for the study: Boehringer Ingelheim.

Funding: Boehringer Ingelheim.

Disclosure: K.L. Reckamp: Consulting fees: Takeda, Tesaro, Euclises, and Boehringer Ingelheim. B. Halmos: Consulting fees, grants/funds: Boehringer Ingelheim, AstraZeneca, Takeda, Eli Lilly, Pfizer, Novartis; Consulting fees: Roche/Genentech, Foundation Medicine, Guardant Health; Grant/funds: Merck, Mirati, Eisai, Genentech. M. Jahanzeb: Grant funding: Boehringer Ingelheim. L.C. Seneviratne: Consulting fees and Honoraria for a Speaker's bureau: Novartis. J.A. Wallace: Honoraria: Genentech. B. Rueter, E. Dowling: Employee: Boehringer Ingelheim. A. Esler: Contracted: Boehringer Ingelheim. M. Koczywas: Honoraria for a Speaker bureau: AstraZeneca. All other authors have declared no conflicts of interest.

1457P Is there a difference in PFS or OS of T790M-mutated NSCLC patients treated with osimertinib either after chemotherapy or immediately after previous target therapy?

C.H. Lai, M-C. Lin, Y-H. Tsai, C-C. Wang

Division of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung City, Taiwan

Background: Osimertinib (Tagresso) is recommended as an option for treating patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed after first-line TKIs. We compared OS and PFS in patients who received osimertinib treatment immediately after previous treatment with TKIs, and those who received osimertinib after their last cycle of chemotherapy.

Methods: This study enrolled a total of 2605 patients who were diagnosed with lung cancer between January 2013 and April 2017. Among these patients, there were 779 patients with inoperable EGFR-mutated NSCLC who had received TKIs as first-line therapy. Furthermore, 166 of these 779 patients who were resistant to TKIs had received re-biopsy. There were 71 patients who received osimertinib therapy for at least 2 weeks since March 2016.

Results: Demographics and clinical characteristics of the 71 patients are described in the table. Among these cases, 26 (36.6%) patients received osimertinib as 2nd-line therapy after first-line TKI therapy. Seventeen (23.9%) patients received osimertinib as 3rd-line therapy, and 28 (39.4%) patients received osimertinib in >= 4th-line setting. The median PFS in patients as 2nd-line therapy was 11.9 months and that was 17.3 months as 3rd-line therapy. The median PFS in patients as >= 4th-line therapy was 9.3 months. Among the 71 patients, there were 34 (47.9%) patients who received it after previous chemotherapy (Group A), and 37 patients (52.1%) who received osimertinib immediately after previous TKI therapy (Group B). The median PFS for Group A and Group B patients was 12.8 months and 11.0 months, respectively ($p = 0.306$). A higher percentage of patients in Group B had progressive disease (8 cases, 21.6%) compared to Group A (2 case, 5.9% ; $\chi^2 = 0.08$). Besides, obesity patients (BMI >= 27) had trend of shorter PFS with osimertinib therapy. (8.4 months vs. 12.6 months, $P = 0.05$).

Conclusions: Our data suggested that T790M-mutated NSCLC patients may have a better response, and longer PFS when treated with osimertinib therapy after previous chemotherapy compared to after previous TKI treatment. Due to the small sample size, our data need to be updated and need further re-analysis.

Legal entity responsible for the study: Chien-Hao Lai; Chin-Chou Wang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1458P Bone metastasis reduces responsiveness to EGFR-TKIs in patients with EGFR-mutated advanced lung adenocarcinoma

X. Zheng, C. Huang, G. Lin

Department of Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China

Background: The impact of bone metastasis on the patient's response to EGFR-TKI therapy is yet to be determined in lung adenocarcinoma (LUAD) patients harboring EGFR mutations.

Methods: This is a retrospective analysis of the efficacy of EGFR-TKIs for LUAD patients with EGFR mutations, comparing patients with bone metastases (BM) and those with no bone metastases (NBM). Regular imaging that evaluated the bone metastasis response was required for patients with BM. Overall response, median progression-free survival (mPFS), and progression patterns were calculated.

Results: Of the 502 patients reviewed, 175 were evaluated (BM 96, NBM 79). Clinical characteristics were balanced between the groups. Median PFS was 11.0 months in the NBM group versus 7.0 months in the BM group, $P = 0.013$. The mPFS was significantly decreased in patients with multiple BM (≥4) compared with those having oligometastases (1-3) or NBM (7.0 months vs. 10.0 months vs. 11.0 months, $P = 0.003$). Multivariate analysis confirmed that bone metastasis was an independent negative predictive factor of PFS, hazard ratio 1.87, $P = 0.003$. The response rate was higher in the NBM group than in the BM group (70.9% vs. 56.3%), $P = 0.046$. Bone was one of the frequent sites of EGFR-TKIs failure, accounting for 52 of 125 (41.6%). Patients with NBM had a remarkably lower rate of bone failure compared to patients with BM, 11.8% vs. 62.2%, $P < 0.001$.

Conclusions: Bone metastasis and multiple metastases in particular, reduce the responsiveness to EGFR-TKIs for LUAD patients with EGFR mutations. Monitoring of bone metastases should be a routine clinical practice in patients with BM.

Legal entity responsible for the study: Fujian Cancer Hospital.

Funding: Fujian Provincial health systemic youth backbone training projects [grant number 2015-ZQN-ZD-9].

Disclosure: All authors have declared no conflicts of interest.

1459P Which of afatinib and gefitinib/erlotinib is the better EGFR-TKI to be followed by osimertinib?

M. Tamiya[1], A. Tamiya[2], H. Suzuki[3], K. Nakahama[2], Y. Taniguchi[2], K. Kunimasa[1], M. Kimura[1], T. Inoue[1], K. Nishino[1], T. Hirashima[3], S. Atagi[2], F. Imamura[1], T. Kumagai[1]

[1]Thoracic Oncology, Osaka International Cnacer Institute, Osaka, Japan, [2]Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan, [3]Thoracic Malignancy, Osaka Habikino Medical Center, Habikino, Japan

Background: In epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC), there are various treatment challenges. Most patients develop resistance and relaps within 1-1.5 years after first-line EGFR- tyrosine kinase inhibitor (TKI) treatment [1st- and 2nd- generation (G) TKIs]. Some studies suggest that afatinib may overcome the tumor heterogeneity.

Methods: We conducted the multi-center retrospective study in patients with EGFR-mutant NSCLC after acquired resistance to EGFR-TKIs appeared at any line of therapy. The outcomes between afatinib followed by osimertinib and 1st-G EGFR TKIs followed by osimertinib (3rd-G EGFR TKI) were evaluated.

Results: We enrolled 111 T790M mutation-positive patients treated with osimertinib. The median age was 69 (range: 39-88) year old. Among them, 33 (29.7%) were male, 100 (90%) were with PS 0-1, and 35 (31.5%) were treated with afatinib followed by osimertinib. The median treatment line with afatinib or 1st-G EGFR TKI followed by osimertinib was 5 or 4. In all patients, the objective response and disease control rates were 63.1% and 77.5%, respectively. The objective response and disease control rates were significantly higher in patients with afatinib followed by osimertinib than in those with 1st-G EGFR TKI followed by osimertinib [82.9% vs 53.9% ($p = 0.0065$) and 91.4% vs 71.1% ($p = 0.032$)], respectively. The median PFS (with <60% events) was longer and in favor of afatinib followed by osimertinib compared with 1st-G EGFR TKI followed by osimertinib (15.7 vs 8.9 months, $p = 0.195$). The follow-up is still ongoing.

Conclusions: Afatinib followed by osimertinib may provide better clinical benefit for NSCLC patients harboring T790M mutation compared with 1st-G EGFR TKIs. Afatinib followed by osimertinib is one of the first line sequential options even if osimertinib can be used as a first line therapy.

Legal entity responsible for the study: M. Tamiya.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1460P Biopsy on progression in EGFR mutation positive (EGFRm) advanced non-small cell lung cancer (aNSCLC) patients (pts): A Canadian experience

Q.S-C. Chu[1], A. Agha[2], N.C. Devost[3], R. Walton[3], S. Ghosh[4], C. Ho[5]

[1]Oncology, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, [2]Medicine, University of British Columbia, Vancouver, BC, Canada, [3]Oncology, AstraZeneca, Toronto, ON, Canada, [4]BioStatistics, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, [5]Medical oncology, British Columbia Cancer Agency, Vancouver, BC, Canada

Background: EGFR tyrosine kinase inhibitors (EGFR-TKIs) are standard therapy for EGFRm aNSCLC. Upon progression, 50-60% will develop the secondary T790M mutation. Recent trials demonstrated improvement in outcomes with osimertinib over standard platinum-based chemotherapy as 2L therapy for T790M-positive EGFRm aNSCLC. To identify T790M, tumour biopsy or plasma testing is necessary. This study aimed to evaluate biopsy procedures and mutational analysis at two Canadian cancer centres.

Methods: BC Cancer-Vancouver and Cross Cancer Institute performed a retrospective review of pts who signed consent to enroll to the AURA2, AURA3 or ASTRIS studies. Pt characteristics, biopsy method, rebiopsy methods/complications, number of rebiopsies performed, and incidence of the T790M mutation were collected.

Results: 84 pts were considered for trial enrolment. 80 signed consent with M:F 32:68%; ECOG 0/1/2: 11/66/23%; smoker/ex-smoker/never smoker: 6/21/73%; exon 19/L858R/other: 60/36/4%; prior curative intent treatment in 18%. 78 pts underwent biopsy, most commonly CT/US-guided biopsy (50%), bronchoscope/EBUS (32%), thoracentesis/surgical biopsy (12%). 3 pts had plasma testing. Type of biopsies were cores (47%), fine needle biopsy (18%), transbronchial biopsy (14%), other (21%). The most common sites for biopsy were lung or nodes (64%). The median number of biopsies performed was 2. Only 8% of pts experienced complications after biopsy. 77% of samples were adequate for T790M testing: 35% performed locally, 65% centrally. Overall, 47 pts were found to have T790M; of which, 44 were enrolled in a trial. Among 40 pts who were ineligible for trials, reasons included: T790M negative (72.5%), decline in performance status/death (15%), inadequate tissue (5%), biopsy refusal, unable to biopsy, and symptomatic brain metastases requiring radiation (2.5% each). Additional data on practice pattern will be presented.

Conclusions: Patients and physicians were amenable to re-biopsy at progression for further tumor characterization and treatment selection. The incidence of complications was low despite the majority being pulmonary biopsies. 23% of the samples were not adequate for molecular analysis.

Legal entity responsible for the study: University of Alberta, Alberta Health Services, Cross Cancer Institute and AstraZeneca.

Funding: AstraZeneca.

Disclosure: Q.S-C. Chu: Honorarium: AstraZeneca, BMS, BI, Eisai, Lily, Merck, Novartis, Roche, Takeda; Research funding: AstraZeneca. N.C. Devost, R. Walton: Employee: AstraZeneca. C. Ho: Honorarium and research funding: AstraZeneca. All other authors have declared no conflicts of interest.

1461P ASTRIS: A real world treatment study of osimertinib in patients (pts) with EGFR T790M-positive non-small cell lung cancer (NSCLC) - European subset

M. Tiseo[1], A. Santo[2], M.J. Hochmair[3], T. Geldart[4], G. Metro[5], E. Hanrahan[6], K. Lamberg[7], T. Moran[8], C. Nyhus[9], A. Paredes[10], J.F. Vansteenkiste[11], D. Vicente[12], M. Miranda[13], J. Rigas[14], F. de Marinis[15]

[1]Medical Oncology, University Hospital of Parma, Parma, Italy, [2]Medical Oncology, University Hospital of Verona, Verona, Italy, [3]Respiratory Oncology Unit, Otto Wagner Spital, Vienna, Austria, [4]Medical Oncology, Poole Hospital NHS Foundation Trust, Poole, UK, [5]Oncology, Santa Maria della Misericordia Hospital, Perugia, Italy, [6]Department of Oncology, St Vincents University Hospital, Dublin, Ireland, [7]Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University Hospital, Uppsala, Sweden, [8]Medical Oncology Service, ICO Badalona-Hospital Germans Trias i Pujol, Badalona, Spain, [9]Oncology Department, Vejle Hospital, Vejle, Denmark, [10]Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA, [11]Respiratory Oncology Unit (Pulmonology), University Hospitals KU Leuven, Leuven, Belgium, [12]Medical Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, [13]Biometrics and Information Sciences, AstraZeneca, Cambridge, UK, [14]GMA Oncology TA, AstraZeneca, Gaithersburg, MD, USA, [15]Division of Thoracic Oncology, European Institute of Oncology, Milan, Italy

Background: Osimertinib is a third-generation, CNS-active EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitising and EGFR T790M resistance mutations. We report results from the European subset of the ongoing global ASTRIS study (NCT02474355).

Methods: Eligible pts receive osimertinib 80 mg once daily. Inclusion criteria: Stage IIIB/IV T790M-positive NSCLC; T790M status confirmed locally by validated test, not restricted by sample type; prior EGFR-TKI therapy received; WHO performance status (PS) 0 – 2; acceptable organ and bone marrow function and no history of interstitial lung disease (ILD) or QTc prolongation. Asymptomatic, stable CNS metastases are permitted. The primary efficacy outcome is overall survival (OS). Second interim data cut-off (DCO) 20 Oct 2017.

Results: From Sept 18 2015, 759 pts were enrolled across 8 European countries and received ≥1 dose of osimertinib: median follow-up 10.9 months (mo) (range <1 – 24), median age 66 yrs (32–92), 24% ≥75 yrs, 69% female, 97% White, 14% WHO PS 2, 44% prior chemotherapy. T790M-positive status was identified from tissue in 290 pts (38%), plasma ctDNA in 415 pts (55%) and from other sources in 53 pts (7%). At DCO, 545 pts (72%) had discontinued treatment (214 [28%] ongoing); 442 pts (58%) had withdrawn from the study, including 268 deaths (35%); median duration of exposure 9.7 mo (<1–25). In pts evaluable for response, investigator-assessed clinical response rate was 55.3% (381/689; 95% CI 51.5, 59.1). Estimated median progression-free survival (PFS) was 9.7 mo (95% CI 8.5, 10.8), with 470 (62%) progressions/deaths. OS data are not mature (OS at 12 mo was 67.4%; 95% CI 63.7, 70.8). Adverse events (AEs) leading to dose modification and treatment discontinuation were reported in 149 pts (20%) and 53 pts (7%), respectively. Serious AEs were reported in 147 pts (19%). ILD / pneumonitis-like events were reported in 22 pts (3%), and QTc prolongation in 7 pts (1%).

Conclusions: In this European dataset from ASTRIS, clinical activity (response and PFS) with osimertinib in patients with T790M-positive NSCLC is similar to that observed in the global ASTRIS population and the wider osimertinib clinical trial programme with no new safety signals.

Clinical trial identification: NCT02474355.

Editorial acknowledgement: The authors would like to acknowledge Tom Hudson, PhD, of iMed Comms, Macclesfield, UK, an Ashfield Company, part of UDG Healthcare plc, for editorial assistance that was funded by AstraZeneca, Cambridge, UK, in accordance with Good Publications Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.

Disclosure: M. Tiseo: Advisory boards and speakers' fee: AstraZeneca, Pfizer, Eli-Lilly, Bristol-Myers Squibb, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Pierre Fabre. A. Santo: Grants/research support/consultancy: AstraZeneca, Boehringer Ingelheim. M.J. Hochmair: Honoria: AstraZeneca, Boehringer Ingelheim, Pfizer, Roche. J.F. Vansteenkiste: Research funding at University Hospitals KU Leuven: MSD; Advisory functions: Apotex, AstraZeneca, Boehringer Ingelheim, MSD, Novartis, Roche; Lectures: AstraZeneca, BMS, MSD, Roche. M. Miranda: Full time employee: AstraZeneca; Shares: AstraZeneca. J. Rigas: Consultant: AstraZeneca; Employee: Kelly Services. F. de Marinis: Honoraria: Bristol-Myers Squibb, AstraZeneca, Roche, Merck Sharp & Dohme. All other authors have declared no conflicts of interest.

1462P Impact of blood-based biomarkers on survival outcomes with pembrolizumab in pre-treated advanced non-small cell lung cancer (NSCLC) patients (pts)

R.Y. Tay, J. Chiramel, E. Montague, F. Wilson, Y. Summers, F.H. Blackhall, R. Califano
Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK

Background: Elevated neutrophil-lymphocyte ratio (NLR), derived NLR (dNLR) and lactate dehydrogenase (LDH) have been identified as potential prognostic/predictive biomarkers to immune checkpoint inhibitors (ICI). The Lung Immune Prognostic Index (LIPI) utilises dNLR and LDH to define prognostic subgroups associated with overall survival (OS) and overall response rate (ORR) to ICI. The objective of this study was to assess progression free survival (PFS) and OS in pre-treated advanced NSCLC pts who received pembrolizumab and to perform a comparative analysis of pre-treatment NLR, dNLR, LDH, LIPI score and PD-L1 tumour proportion score (TPS) on survival, ORR and toxicity.

Methods: Pre-treated advanced NSCLC pts who received pembrolizumab (Jan '17-Jan '18) at The Christie were identified. Baseline demographics, PD-L1 TPS, NLR, dNLR and LDH were collected. Elevated NLR, dNLR and LDH was defined as ≥ 5, ≥ 3 and $\geq$ upper limit normal (ULN), respectively. LIPI score was calculated (Table). Survival analysis was performed using Kaplan-Meier method. Univariate logistic regression models were used to assess patient characteristics on PFS.

Table: 1462P Lung immune prognostic index (LIPI)

Good	dNLR <3 AND LDH <ULN
Intermediate	dNLR ≥3 OR LDH ≥ULN
Poor	dNLR ≥3 AND LDH ≥ULN

Results: 58 pts were analysed; median age: 67, males 66%, non-squamous 64%, 53% had PD-L1 TPS 1-49%. After median follow up of 5.2 months, 38/58 (66%) pts progressed. Median PFS and OS was 3.7m (95% CI 2.52-9.54) and 11.2m (95% CI 6.3-NR), respectively. ORR was 22.4%. A non-significant trend towards longer PFS was observed between LDH <ULN vs ≥ULN (5.5 vs 2.8m; p = 0.4), NLR <5 vs ≥ 5 (5.51 vs 3.7m; p = 0.99), dNLR <3 vs ≥ 3 (5.51 vs 2.66; p = 0.31), PD-L1 TPS ≥50 vs 1-49% (9.54 vs 2.82m, p = 0.29) and LIPI good/int/poor subgroups (5.8 vs 3.02 vs 1.89m; p = 0.23). Impact of blood-based markers on ORR and toxicity will be presented.

Conclusions: Our cohort demonstrated similar survival outcomes to KEYNOTE-010. Baseline NLR, dNLR, LDH, PD-L1 TPS and LIPI score were not significantly prognostic of survival.

Legal entity responsible for the study: The Christie NHS Foundation Trust, Manchester, United Kingdom.

Funding: The Christie NHS Foundation Trust, Manchester, United Kingdom.

Disclosure: R. Califano: Honoraria for consultancy and advisory boards: MSD. All other authors have declared no conflicts of interest.

1463P Updated results of M7824 (MSB0011359C): A bifunctional fusion protein targeting TGF-β and PD-L1, in second-line (2L) NSCLC

L. Paz-Ares[1], T.M. Kim[2], D. Vicente[3], E. Felip[4], D.H. Lee[5], K.H. Lee[6], C-C. Lin[7], M.J.F. Oncala[8], M. Di Nicola[9], R.M. Alvarez[10], I. Dussault[11], C. Helwig[12], L. Ojalvo[13], J. Gulley[14], B.C. Cho[15]

[1]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [2]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [3]Medical Oncology, Hospital Univeritario Virgen Macarena, Seville, Spain, [4]Medical Oncology Service (Lung Cancer Unit), Vall d'Hebron University Hospital, Barcelona, Spain, [5]Department of Oncology, University of Ulsan College of Medicine, Seoul, Republic of Korea, [6]Department of Internal Medicine, Chungbuk National University Hospital, Chungcheongbuk-Do, Republic of Korea, [7]Department of Oncology, National Taiwan University Hospital, Taipei City, Taiwan, [8]Medical Oncology, Hospital Universitario Virgen Del Rocio, Seville, Spain, [9]Medical Oncology and Hematology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [10]Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [11]Clinical Briomarkers, EMD Serono, Billerica, MA, USA, [12]Medical Oncology, Merck KGaA, Darmstadt, Germany, [13]Immuno-Oncology, EMD Serono, Billerica, MA, USA, [14]Genitourinary Malignancies Branch, National Cancer Institute, Bethesda, MD, USA, [15]Medical Oncology, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea

Background: 2L+ overall response rates (ORRs) with PD-(L)1 inhibitors in patients (pts) with advanced NSCLC range from 12% to 19% (PD-L1 unselected), and median PFS ranges from 2.3 to 4.0 mo. Inhibiting the transforming growth factor β (TGF-β) pathway, which promotes tumor immunosuppression, may enhance the response to PD-(L)1 therapy. M7824 is an innovative first-in-class bifunctional fusion protein composed of a human IgG1 monoclonal antibody against PD-L1 fused with 2 extracellular domains of TGF-βRII (a TGF-β "trap").

Methods: Pts with advanced NSCLC unselected for PD-L1 who progressed after 1L standard treatment (no prior immunotherapy) were randomized to receive M7824 500 or 1200 mg (n = 40 each) q2w until disease progression, unacceptable toxicity or trial withdrawal in this expansion cohort of the ongoing, phase 1 trial NCT02517398. The primary objective is to assess BOR per RECIST v1.1; other objectives are dose exploration and safety/tolerability. Tumor cell PD-L1 expression (Ab clone 73-10 [≥80% is comparable to ≥ 50% with 22C3]) was evaluable in 75 pts.

Results: As of March 12, 2018, 80 pts received M7824 for a median of 11.9 (range, 2-66.1) wk, with a median follow-up of 51.1 wk; 10 pts remain on treatment. Investigator-assessed confirmed ORR was 27.5% at 1200 mg and 20% at 500 mg. Clinical activity was observed across PD-L1 subgroups (Table); ORR was 40.7% in PD-L1 + (≥1%) and 71.4% in PD-L1–high (≥80%) pts at 1200 mg. The most common treatment-related adverse events (TRAEs) were pruritus (20%), maculopapular rash (18.8%), decreased appetite (12.5%) and asthenia (11.3%). Grade ≥3 TRAEs occurred in 23 pts (28.8%); 8 pts (500 mg, n = 2; 1200 mg, n = 6) discontinued treatment due to TRAEs. No treatment-related deaths occurred.

Table: 1463P

ORR, n/N; %	500 mg	1200 mg	Total
All PD-L1+	8/40; 20.0 6/31;	11/40; 27.5 11/27;	19/80; 23.8 17/58;
PD-L1 high	19.4 2/6; 33.3	40.7 5/7; 71.4	29.3 7/13; 53.8
Median PFS; OS, mo			
All PD-L1+	1.4; 10.9 1.6;	2.7; NR 6.8;	2.1; 12.2 2.7;
PD-L1 high	10.3 1.5; NR	NR NR; NR	NR 8.1; NR

NR, not reached.

Conclusions: M7824 had promising efficacy, with encouraging PFS and OS, and ORRs at the RP2D of 1200 mg of 40.7% and 71.4% in PD-L1+ and PD-L1 high pts, respectively. Treatment was well tolerated.

Clinical trial identification: NCT02517398.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: E. Felip: Employment: Vall d'Hebron University Hospital; Consultancy: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Guardan Health, Merck Sharp & Dohme Corp, Novartis, Pfizer, Roche, Takeda, Abbvie, Merck; Speakers' bureau: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Guardan Health, Merck Sharp & Dohme Corp, Novartis, Pfizer, Roche, Takeda, Abbvie, Merck. I. Dussault, L. Ojalvo: Employment: EMD Serono. C. Helwig: Employment and Equity Ownership: Merck KGaA. All other authors have declared no conflicts of interest.

1464P KEYNOTE-189 study of pembrolizumab (pembro) plus pemetrexed (pem) and platinum vs placebo plus pem and platinum for untreated, metastatic, nonsquamous NSCLC: Does choice of platinum affect outcomes?

D. Rodriguez Abreu[1], M.C. Garassino[2], E. Esteban[3], G. Speranza[4], E. Felip[5], M. Domine[6], M.J. Hochmair[7], S.F. Powell[8], S.Y-S. Cheng[9], H. Bischoff[10], N. Peled[11], R. Hui[12], M. Reck[13], E.B. Garon[14], M. Boyer[15], F. Grossi[16], R. Jennens[17], J. Yang[18], M.C. Pietanza[19], S.M. Gadgeel[20]

[1]Medical Oncology, Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas, Canary Islands, Spain, [2]Thoracic Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [3]Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain, [4]Oncology, Hôpital Charles Le Moyne, Greenfield Park, QC, Canada, [5]Medical Oncology Service (Lung Cancer Unit), Vall d'Hebron University Hospital, Barcelona, Spain, [6]Oncology, Instituto de Investigación Sanitaria- Fundación Jiménez Diaz, Madrid, Spain, [7]Respiratory and Critical Care Medicine, Otto Wagner Hospital, Vienna, Austria, [8]Hematology and Oncology, Sanford Health, Sioux Falls, SD, USA, [9]Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [10]Oncology, Thoraxklinik Heidelberg, Heidelberg, Germany, [11]Oncology, Clalit Health Services, Soroka Medical Center, Beer Sheva, Israel, [12]Oncology, Westmead Hospital and the University of Sydney, Sydney, Australia, [13]Thoracic Oncology, LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany, [14]Medicine, Division of Heam/Onc, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, [15]Clinical Research, Chris O'Brien Lifehouse, Camperdown, Australia, [16]Oncology, Ospedale Policlinico San Martino, Genoa, Italy, [17]Oncology, Epworth Healthcare, Richmond, Australia, [18]Biostatistics, Merck & Co., Inc., Kenilworth, NJ, USA, [19]Clinical Research, Merck & Co, Kenilworth, NJ, USA, [20]Oncology, University of Michigan, Ann Arbor, MI, USA

Background: In KEYNOTE-189 (NCT02578680), pembro plus pem and platinum provided superior OS (HR 0.49, P < .00001) and PFS (HR 0.52, P < .00001) and had manageable safety vs placebo plus pem and platinum as first-line therapy for metastatic nonsquamous NSCLC. In an exploratory analysis, we assessed outcomes by investigator's choice of carboplatin (carbo) or cisplatin (cis).

Methods: 616 patients (pts) with untreated metastatic nonsquamous NSCLC regardless of PD-L1 TPS without sensitizing EGFR or ALK alteration were randomized 2:1 to 4 Q3W cycles of pembro 200 mg or placebo + pem 500 mg/m^2 + carbo AUC 5 or cis

75 mg/m^2 followed by maintenance pembro or placebo + pem. Randomization was stratified by TPS (<1% vs ≥ 1%), platinum (carbo vs cis), and smoking status (current/former vs never). Primary end points were OS and PFS; ORR and safety were secondary.

Results: Carbo was chosen for 72% of pts in both arms. OS, PFS, and ORR were improved in the pembro plus pem and platinum arm in both carbo and cis recipients (Table). In the pembro vs placebo arm, 83% vs 72% received 4 carbo doses and 81% vs 79% received 4 cis doses. 76% vs 65% and 78% vs 72%, respectively, received ≥5 pem doses. Grade 3-5 AE rates for pembro vs placebo were 70% vs 66% with carbo and 59% vs 65% with cis. Rates of the most common any-grade AEs were generally similar for carbo and cis: nausea 54% with pembro vs 48% with placebo for carbo and 60% vs 63% for cis, anemia 45% vs 48% and 50% vs 44%, and fatigue 44% vs 43% and 33% vs 26%. Rates of acute kidney injury in the pembro arm were 5.1% with carbo and 5.4% with cis.

Conclusions: Pembro plus pem and platinum improved efficacy and was generally tolerable compared with placebo plus pem and platinum regardless of the chosen platinum. These data support the use of both carbo and cis in combination with pembro and pem as first-line therapy for metastatic nonsquamous NSCLC.

Clinical trial identification: NCT02578680, originally posted October 19, 2015.

Editorial acknowledgement: Melanie Leiby, Merck & Co., Inc., Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck Sharp & Dohme, Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Funding: Merck Sharp & Dohme, Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosure: D. Rodriguez Abreu: Lecture honorarium, Travel expenses, and Advisory board: MSD, Bristol-Myers Squibb, Roche-Genentech, and Boehringer Ingelheim. M.C. Garassino: Consultancy and lecture fees: AstraZeneca, Roche, Boehringer Ingelheim. E. Felip: Consulting fees: Boehringer Ingelheim, Eli Lilly, Pfizer, Roche, MSD, and Abbvie; Lecture fees: AstraZeneca, Bristol-Myers Squibb, and Novartis. S.F. Powell: Research support to institution: MSD, Bristol-Myers Squibb, Incyte, Pfizer, Vyriad, Genentech. N. Peled: Advisory board member: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Foundation Medicine, Gaurdant360, MSD, Novartis, NovellusDx, Pfizer, Roche, Takeda; Grant to institution: AstraZeneca, Bristol-Myers Squibb, MSD, Roche. R. Hui: Advisory board member: MSD, AstraZeneca, Novartis, Roche and Speaker Honorarium: MSD, AstraZeneca, Novartis, Bristol-Myers Squibb, Boehringer Ingelheim. M. Reck: Advisory board member and Speakers board: Hoffmann-La Roche, Lilly, AstraZeneca, Celgene, Bristol-Myers Squibb, MSD, Boehringer-Ingelheim, Pfizer, Novartis, Merck. E.B. Garon: Clinical trial funding to institution: Merck, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Boehringer Ingelheim, Pfizer, Novartis, Mirati, Dynavax, Merck & Co., Inc. M. Boyer: Grant support: MSD, AstraZeneca, Genetech/Roche, Amgen, Bristol-Myers Squibb, Pfizer, Novartis, Peregrine Pharmaceuticals. F. Grossi: Advisory board: MSD, Bristol-Myers Squibb, Pierre Fabre, Pfizer, Novartis, Boehringer Ingelheim; Lectures: MSD, Bristol-Myers Squibb, AstraZeneca, Pierre Fabre, Pfizer, Novartis, Boehringer Ingelheim, Amgen, Roche; Research funding: Bristol-Myers Squibb. J. Yang: Employee: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA. M.C. Pietanza: Employee: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA: Stock options in the Company. S.M. Gadgeel: Advisor: Abbvie, AstraZeneca, Genentech/Roche, Ariad/Takeda. All other authors have declared no conflicts of interest.

1465P Phase I dose escalation of pembrolizumab given concurrently with palliative thoracic radiotherapy (RT) for NSCLC

R. Kumar[1], D.P. Walder[1], A. Pejanaute[2], R. Gunapala[3], J. Bhosle[3], N. Yousef[3], S. Popat[3], F. McDonald[3], I. Locke[3], K. Harrington[4], A. Tree[5], S. Lalondrelle[6], R. Huddart[5], M.E.R. O'Brien[1], M. Ahmed[1]

[1]Lung Cancer Unit, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK, [2]Clinical Trials Unit, The Royal Marsden NHS Foundation Trust, London, UK, [3]Lung Cancer Unit, The Royal Marsden NHS Foundation Trust, London, UK, [4]Head and Neck Unit, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK, [5]Urology Unit, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK, [6]Gynaecology Unit, The Royal Marsden NHS Foundation Trust, London, UK

Background: Pembrolizumab is used routinely in advanced NSCLC. Combination strategies, such as with RT are of great interest. We report on safety and tolerability of an open-label phase 1 trial for cohort 1 of pembrolizumab with 2 schedules of palliative RT.

Methods: All cohort 1 patients started with a pembrolizumab dose of 100mg given 2 weeks prior to RT, and then received pembrolizumab 100mg 2-weekly concurrently with RT, followed by maintenance dose 200mg pembrolizumab 3-weekly. The RT was either 20 Gy/5# (low dose RT - LD) or 36 Gy/12# (high dose RT - HD). Cohort 2 pembrolizumab dose will be 200mg, for all doses, with the same RT schedules. Dose limiting toxicity (DLT) period, 2 months from completing RT, is defined as grade (G) 2 pneumonitis, G4 oesophagitis or G2 myelitis.

Results: 3/6 pts in the LD and 6/8 pts in the HD were evaluable for DLTs. Mean age was 61 years, 64% were female, 71% were smokers, ECOG performance status was 1 in 100%. 57% were of non-squamous histology with no driver mutations, and 64% were PD-L1 positive (TPS ≥1%). All pts had adverse events (AEs); G3–4 AEs were seen in 66.7% in the LD and 37.5% in the HD. There were no DLTs. In the LD, G3 AEs included: anaemia (n = 1), back pain (n = 1), bronchitis (n = 1), dyspnoea (n = 1), fatigue (n = 1), hypokalaemia (n = 1), hypophosphataemia (n = 1), and syncope (n = 2). In the HD, 1 pt had drug induced liver injury (G1 ALT, G3 ALP, G2 AST, G1 bilirubin, G4 GGT), and so the cohort was expanded by a further 3 pts. No DLTs were seen. G3 AEs included: pneumonia (n = 1), back pain (n = 1), dehydration (n = 1), radiation dermatitis (n = 1), diarrhoea (n = 1), hyperglycaemia (n = 1), and hypokalaemia (n = 2). 1 pt had G4 urosepsis. In the LD and HD, pts also had RT dermatitis (G1 n = 11, G2 n = 2), RT esophagitis (G1 n = 10, G2 n = 4), and RT pneumonitis (G1 n = 6). With a median follow-up of 7.9 months, median PFS was 1.3 months in the LD and 3.7 months in the HD (HR 0.28, P = 0.056). Median OS was 5.2 months in the LD and 8.3 months in the HD (HR 0.59, P = 0.441). Disease control rate (DCR) was 37.5% in the LD (3 SD) and 62.5% in the HD (3 PR, 2 SD; P = 0.592). DCR did not correlate with PD-L1 status (P = 1.00).

Conclusions: Combining pembrolizumab and palliative thoracic RT appears to be safe and tolerable with both RT doses. This trial continues to recruit to cohort 2.

Clinical trial identification: NCT NCT02587455.

Legal entity responsible for the study: Royal Marsden Clinical Trials Unit, Royal Marsden NHS Foundation Trust, Downs Road, Sutton, United Kingdom.

Funding: Merck Sharp Dohme.

Disclosure: R. Kumar, A. Tree, S. Lalondrelle: Research grants: MSD. D.P. Walder: Research grants: BMS. J. Bhosle: Honoraria: BMS; Travel grants: BMS. S. Popat: Honoraria: MSD and BMS. F. McDonald, K. Harrington, R. Huddart: Research grants and Honoraria: MSD. M.E.R. O'Brien: Research grants: MSD; Honoraria: MSD and BMS. M. Ahmed: Research grants: MSD and BMS. All other authors have declared no conflicts of interest.

Table: 1464P

	Carbo		Cis	
	Pembro + Chemo N = 297	Placebo + Chemo N = 148	Pembro + Chemo N = 113	Placebo + Chemo N = 58
OS, median (95% CI), mo	NR (NR-NR)	11.3 (8.0-NR)	NR (NR-NR)	10.8 (8.1-NR)
HR (95% CI)	0.52 (0.39-0.71)		0.41 (0.24-0.69)	
PFS, median (95% CI), mo	8.6 (7.1-9.2)	4.9 (4.6-5.6)	9.2 (6.9-11.1)	4.8 (4.7-6.0)
HR (95% CI)	0.55 (0.44-0.70)		0.44 (0.30-0.65)	
ORR, % (95% CI)	47 (41-53)	18 (12-25)	49 (39-58)	21 (11-33)

1466P Effects of antibiotic use during immunotherapy in metastatic non-small cell lung cancer

G. Galli[1], M. Poggi[1], G. Fucà1, M. Imbimbo[1], C. Proto[1], D. Signorelli[1], M. Vitali[1], N. Zilembo[1], M. Ganzinelli[1], F. de Braud[1], M.C. Garassino[2], G. Lo Russo[1]

[1]Medical Oncology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [2]Thoracic Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy

Background: Immunotherapy (IO) has improved the outcome of metastatic non-small cell lung cancer (mNSCLC), but only a minority of patients (pts) derives a benefit from treatment (tx). Recent evidences supported a role of gut flora in influencing systemic response against tumors. The use of antibiotics (Abs) may impair the balance of microbiota and negatively affect the efficacy of IO. We aimed at analyzing this topic in a cohort of mNSCLC pts.

Methods: Data about all consecutive mNSCLC pts treated with IO at Istituto Nazionale dei Tumori, Milan, Italy, from 04/2013 to 01/2018 were retrospectively collected. We considered relevant for the analysis the use of Abs between 1 month (mo) before and 3 mos after the beginning of IO. We also evaluated the variable "Ab exposure" (AE), defined as the % "days of ab tx/days of IO". Survival was estimated with Kaplan-Meier method; curves were compared with log-rank test. Cox proportional model was used for multivariate analyses.

Results: We identified 157 cases. Most pts had a performance status (PS) ECOG $\geq$1 (52.2%) and $\geq$2 sites of metastatic disease (86.0%). IO was either an anti-PD1 (62.4%), an anti-PDL1 (32.5%), or a combination anti-PDL1/CTLA4 (5.1%); it was prescribed in first line in 25 pts, in second line in 66 pts, in a more advanced lines in 66 pts. Abs were administered to 27 pts, mostly for pneumonia. The most common were levofloxacin (55.6%), amoxi-clavulanate (25.9%) and ceftriaxone (14.8%). Progression free survival (PFS) and overall survival (OS) did not differ between Ab-treated and Ab-untreated pts (p.18; p.24, respectively). Median AE of the Ab-treated pts was 4.3% (range 0.6%-42.9%). Both PFS and OS were significantly lower in pts with a higher AE than the median one (2.2 vs 7.7 mos, p<.0001; 4.9 vs 16.3 mos, p.0004, respectively). At multivariate analysis with the other significant variables (PS and IO line), the impact of AE on PFS and OS retained significance (p.0003; p.0002, respectively).

Conclusions: These results suggest that the length of Ab tx, rather than their simple use in a defined time frame, may impair the efficacy of IO. Further research is needed to support this evidence. However, it may be advisable to carefully evaluate the prescription of long Ab cycles to mNSCLC pts receiving IO.

Legal entity responsible for the study: Istituto Nazionale dei Tumori.

Funding: Has not received any funding.

Disclosure: M. Imbimbo: Honoraria: BMS. C. Proto: Honoraria: BMS, MSD, Eli Lilly. D. Signorelli: Honoraria: AstraZeneca, Boehringer Ingelheim, BMS. M.C. Garassino: Honoraria: Roche, AstraZeneca, Boehringer Ingelheim. G. Lo Russo: Honoraria: Eli Lilly, BMS, AstraZeneca. All other authors have declared no conflicts of interest.

1467P Efficacy and safety of nivolumab for cytotoxic chemotherapy unfit patients with advanced non-small cell lung cancer: A phase II study

Y. Okuma[1], S. Kitano[2], K. Watanabe[1], M. Yomota[1], Y. Hosomi[3], Y. Zenke[4], N. Yamamoto[5]

[1]Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [2]Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Thoracic Oncology & Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [4]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [5]Developmental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

Background: This single-center phase II study aimed to examine the efficacy and feasibility of nivolumab for patients with advanced non-small cell lung cancer (NSCLC) who were unsuitable for single-agent chemotherapy or targeted agents because of their poor performance status (PS).

Methods: In this study, we enrolled previously treated patients with advanced NSCLC with poor PS of 2–4 without any indication of cytotoxic chemotherapy or targeted therapies. All enrolled patients received nivolumab (3 mg/kg, every 2 weeks) until progression or unacceptable toxicities. In addition, we prospectively obtained peripheral blood mononuclear cells (PBMC) and plasma from patients after obtaining their informed consent before treatment.

Results: Between April 2016 and December 2017, we enrolled 33 patients with NSCLC and poor PS, including 23 patients with PS 3–4. In this study, the response rate was 29.0% (90% confidence interval (CI), 17.7%–43.7%), and the disease control rate was 41.9% in 31 evaluable patients. PS improvement rate was 29.0%. In addition, the median progression-free survival (mPFS), median overall survival (mOS), and 1-year survival rates were 1.5 (95% CI, 1.0–2.7) months, 3.8 (95% CI, 2.4–16.3) months, and 37.6%, respectively. Among patients harboring EGFR-mutations (mut), the mPFS was 2.6 and 1.1 months in EGFR-wild type (wt) and EGFR-mut ($p = 0.015$), respectively, and the mOS was 9.3 and 1.9 months in EGFR-wt and EGFR-mut ($p = 0.029$), respectively. During the study period, treatment-related deaths were observed in 2 patients (6.1%). We obtained blood samples from 75% of the enrolled patients (data will be updated in the meeting).

Conclusions: To the best of our knowledge, this is the first trial to investigate the efficacy of immune checkpoints in patients with advanced NSCLC with poor PS. Although the response rate was similar to those with good PS, shorter survival was observed. Excluding patients harboring driver mutations may enhance treatment efficacy to show a survival benefit even for poor PS patients. Nevertheless, the biomarker investigation warrants focus on the PBMC analysis.

Clinical trial identification: Clinical trial registration: UMIN000020855/UMIN000021734.

Legal entity responsible for the study: Tokyo Metropolitan Komagome Hospital.

Funding: Has not received any funding.

Disclosure: Y. Okuma: Research Funding: Chugai Pharma (Inst). Y. Hosomi: Honoraria: AstraZeneca; Boehringer Ingelheim Japan; Bristol-Myers Squibb Japan; Chugai Pharma; Eli Lilly Japan; Ono Pharmaceutical; Taiho Pharmaceutical; Research Funding: Chugai Pharma (Inst); Eli Lilly Japan (Inst); Ono Pharmaceutical. N. Yamamoto: Honoraria: AstraZeneca; Bristol-Myers Squibb Japan, Chugai Pharma, Eli Lilly Japan, Ono Pharmaceutical, Pfizer; Research Funding: Astellas Pharma (Inst), Bayer (Inst), Boehringer Ingelheim (Inst), Chugai Pharma (Inst), Daiichi Sankyo (Inst), Eisai (Inst), Kyowa Hakko Kirin (Inst), Eli Lilly Japan (Inst), Novartis (Inst), Pfizer (Inst), Quintiles (Inst), Taiho Pharmaceutical (Inst), Takeda (Inst). All other authors have declared no conflicts of interest.

1468P GECP 1605/NIVEX TRIAL nivolumab in the real world: The SPANISH expanded access program experience in pretreated advanced NSCLC

M. Majem Tarruella[1], J. Campillo[2], J.F. Grau Béjar[3], E. Carcereny[4], R. Bernabe Caro[5], Y. Garcia[6], A. Artal-Cortes[7], M. González Cao[8], P. Lianes[9], A. Paredes Lario[10], M. Sereno Moyano[11], X. Mielgo Rubio[12], J.A. Macias[13], M. Provencio Pulla[14], D. Rodriguez-Abreu[15]

[1]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2]Medical Oncology, Hospital Virgen de la Arrixaca, Murcia, Spain, [3]Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Hospital Germans Trias i Pujol, Catalan Institute of Oncology, Badalona, Spain, [5]Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain, [6]Medical Oncology, Corporació Sanitaria Parc Taulí, Sabadell, Spain, [7]Medical Oncology, Hospital Miguel Servet, Zaragoza, Spain, [8]Medical Oncology, QuironSalud Dexeus University Institute, IOR, Barcelona, Spain, [9]Medical Oncology Service, Hospital de Mataró, Mataró, Spain, [10]Medical Oncology, Hospital Donostia, San Sebastian, Spain, [11]Medical Oncology, Hospital Infanta Sofia, Madrid, Spain, [12]Medical Oncology, Hospital Universitario Fundación Alcorcón, Madrid, Spain, [13]Medical Oncology, Hospital Morales Messeguer, Murcia, Spain, [14]Servicio de Oncología Médica, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain, [15]Servicio Oncología Médica, Hospital Insular De Gran Canaria, Las Palmas, Spain

Background: Nivolumab is a standard treatment for second line in patients (pts) with advanced NSCLC. Real world data about toxicity and efficacy of nivolumab is lacking.

Methods: We have analyzed 665 pts from the Expanded Access Program, which included pts with pretreated NSCLC who received $\geq$1dose of nivolumab 3mg/kg q2w from 01/2015 for squamous (Sq) and 06/2015 for non-Sq NSCLC, to 11/2017.

Results: Median age was 61 (32-85) years, 73% were men, 85% had ECOG 0-1, 88% were current/former smokers and 15% had brain M1. 128 (19.2%) pts presented Sq and 537 (80.8%) Non-Sq NSCLC. 7% of pts presented EGFR mutation. PD-L1 was $\geq$1% in 33% of analyzed pts. Nivolumab was administered as 2nd/$\geq$3rd line in 33% and 67% of pts. Post-nivolumab treatment was administered to 25% pts that received nivolumab in 2nd line and to 23% that received nivolumab in 3rd line. After a median follow-up of 8.2 months, the median OS was 8-97 (95% CI 7.69-10.24) months, and the median PFS was 3.23 (95% CI 2.77-3.70) months. Estimated 1-year OS was 42.4% (95%CI 38.5-42.8%) and estimated 1-year PFS was 22.2% (95% CI 19.1-25.3%). No differences in OS or PFS were observed according to histologies. Among pts that received nivolumab in 2nd line, the median OS was 9.8 (95% CI 7.3-12.0) months and the median PFS was 3.3 (95%CI 2.4-4.2) months. Among pts that received nivolumab in $\geq$ 3rd line the median OS was 8.6 (95% CI 7.2-10.0) months and the median PFS was 3.1 (95% CI 2.6-3.7) months. Median OS for pts that received post-nivolumab treatment in 3rd line was 9.3 (95 CI% 7.0-11.6) months. 296 (44.5%) pts presented toxicity to nivolumab, which was grade $\geq$3 in 69 (10.4%) pts. According to the presence of grade $\geq$3 toxicity, the median OS was 14.57 (CI 95% 8.45-20.68) months for pts with and 8.73 (CI 95% 7.50-9.96) months for pts without grade$\geq$3 toxicity ($p = 0.074$). Additional efficacy and safety data, including PS2, brain M1, response to first line, or post-nivolumab treatment will be presented.

Conclusions: Efficacy and safety of nivolumab was in line with previously shown data. There was a trend to a better OS for those pts experiencing grade$\geq$3 toxicity.

Clinical trial identification: NCT03132493.

Legal entity responsible for the study: Spanish Lung Cancer Group.

Funding: BMS.

Disclosure: All authors have declared no conflicts of interest.

1469P EVIDENS: An observational study of nivolumab-treated patients in advanced non-small cell lung cancer (NSCLC) in a real-world setting: Initial results on 1394 patients

A. Dixmier[1], D. Debieuvre[2], C. Raspaud[3], J.B. Auliac[4], N. Benoit[5], P. Bombaron[6], B. Asselain[7], A. Dumont[8], P. Lamoureux[9], N. Goyard[10], D. Moro-Sibilot[11], M. Perol[12], F. Barlesi[13], C. Audigier Valette[14]

[1]Pneumologie et Oncologie Thoracique, C.H.R. Orleans - La Source, Orleans, France, [2]Service de Pneumologie, Hôpital Emile Muller, GHRMSA, Mulhouse, France, [3]Pneumologie, Clinique Pasteur, Toulouse, France, [4]Pneumologie, CH François Quesnay, Mantes La Jolie, France, [5]Pneumologie, Clinique de l'Europe, Amiens, France, [6]Pneumologie-Cancérologie, Hôpital privé Jean Mermoz, Lyon, France, [7]Biostatistics, Institut Curie, Paris, France, [8]Immuno-Oncology Lung Medical Affairs, Bristol-Myers Squibb, Rueil-Malmaison, France, [9]Excellence Opérationnelle Médicale, Bristol-Myers Squibb, Vandoeuvre les Nancy, France, [10]Global Clinical Trial Strategy and Operations, Bristol-Myers Squibb, Rueil-Malmaison, France, [11]Pneumologie, Centre Hospitalier Universitaire de Grenoble Alpes, Grenoble, France, [12]Cancérologie Médicale, Centre Léon Bérard, Lyon, France, [13]Service d'Oncologie Multidisciplinaire et Innovations Thérapeutiques, Aix-Marseille Université; Assistance Publique Hôpitaux de Marseille, Marseille, France, [14]Pneumology, Hospital Sainte Musse, Toulon, France

Background: Nivolumab demonstrated efficacy and safety in patients previously treated for advanced NSCLC in two phase 3 trials: CheckMate 017 and 057. Real-world data in a large unselected population are needed to support these results. EVIDENS aims to describe clinical characteristics of NSCLC patients treated with nivolumab in real-life in France and to assess its efficacy and safety.

Methods: EVIDENS is an observational, multicenter, longitudinal cohort study of adult NSCLC patients treated with nivolumab in a representative sample of general hospitals, university hospitals and private clinics in France. From Dec 2016 to Nov 2017, 186 sites participated in the study. We report here a pre-planned analysis including patients with confirmed NSCLC treated with at least one dose of nivolumab with a minimum of 6 months of follow-up. Kaplan-Meier estimates were derived for PFS and medians with their 95% confidence intervals.

Results: At data cut off April 20, 2018, 1394 NSCLC patients received nivolumab, including 434 (31.1%) with Squamous (Sq)-NSCLC and 960 (68.9%) with non-Sq-NSCLC. Baseline patient characteristics were representative of a standard advanced NSCLC population: median age 66.0 years (range 35-91), 69.2% men, 89.6% current and former smokers, 83.2% PS 0-1. 279 (20.0%) patients had brain metastases and 41 (2.9%) patients had active autoimmune disease. PD-L1 was tested in 187 patients and expressed ($\geq$1%) in 121 (64.7%) patients. Of the 828 non-Sq NSCLC patients tested, 46 (5,5%) had EGFR mutations. Nivolumab was administered in 2nd and $\geq$3rd line for 74.4% and 25.3% of patients respectively. Median PFS since inclusion was 3 months (95%CI 2.96-3.61). Adverse events occurred in 885 (63.5%) patients, including 145 (10.4%) grade 3/4 events.

Conclusions: These preliminary results of EVIDENS confirm both the activity and safety profile of nivolumab in the $\geq$2nd line setting in usual clinical practice, including patient populations under-represented in pivotal clinical trials. Outcomes over a longer follow-up period (minimum potential 12 months) and OS data will be presented during the congress.

Clinical trial identification: NCT03382496.

Legal entity responsible for the study: Bristol-Myers Squibb France.

Funding: Bristol-Myers Squibb France.

Disclosure: A. Dixmier: Bristol Myers Squibb, Roche. D. Debieuvre: Consulting: Roche; Honoraria : AstraZeneca, Chugai, Lilly, Roche, Novartis, Pfizer, MSD, BMS; Funding for research: Roche, AstraZeneca, Lilly, BMS, Boehringer Ingelheim, Chiesi, Chugai, Janssen, Pfizer, MSD, Novartis, GSK, Sandoz; Expertise (board): Roche, Boehringer Ingelheim, Pfizer, MSD, BMS, Novartis; Honoraria (congress invitation): Roche, Boehringer Ingelheim, Novartis, Pierre Fabre, Pfizer, Mundipharma, BMS. C. Raspaud: Novartis, Boehringer-Ingelheim, GSK, Chiesi, BMS, MSD, AstraZeneca, SOS O2, Agir Adom, Lilly. J.B. Auliac: Advisory board: BMS, Roche, AstraZeneca, Boehringer; Grant: BMS, Roche, AstraZeneca, Boehringer, MSD, Amgen, Pfizer. N. Benoit: BMS, AstraZeneca. P. Bombaron: BMS, Novartis, Boehringer Ingelheim, Roche, Amgen. B. Asselain: Scientific Committee, Speaker: BMS. A. Dumont, P. Lamoureux, N. Goyard: Employee: BMS. D. Moro-Sibilot: Advisory board: Roche, Pfizer, AstraZeneca, BMS, MSD, Lilly, Boehringer, Abbvie, Takeda Corporate; Sponsored research: Boehringer, Abbvie. M. Perol: Honoraria for Advisory Board: BMS. C. Audigier Valette: Principal investigator for clinical trials: AstraZeneca, Boehringer Ingelheim, BMS, Novartis, Roche; Consulting/Advisory board: AstraZeneca, Boehringer Ingelheim, BMS, Lilly, Novartis, MSD, Pfizer, Roche; Speaker: AstraZeneca, Boehringer Ingelheim, BMS, Lilly, Novartis, Pfizer, Roche. All other authors have declared no conflicts of interest.

1470P Fractional polynomial network meta-analysis: A different approach to indirectly assess the comparative efficacy of 2L+ cancer immunotherapy (CIT) treatments for metastatic NSCLC

C. Schulz[1], P. Chu[2], C.G. Berardo[3], B. Karthuria[4], J. Foo[5], C. Morel[5], C. Watkins[6], M. Ballinger[7], D.R. Gandara[8]

[1]Department of Internal Medicine II, University of Regensburg, Regensburg, Germany, [2]Health Technology Assessment Group, F. Hoffman-La Roche Ltd., Basel, Switzerland, [3]Global Product Strategy, F. Hoffman-La Roche Ltd., Basel, Switzerland, [4]Product Development Medical Affairs, F. Hoffman-La Roche Ltd., Basel, Switzerland, [5]Medical Oncology, Mapi Group, Houten, Netherlands, [6]Statistics, Clarostat Consulting, Cheshire, UK, [7]Product Development - Oncology, Genentech Inc. - Roche, South San Francisco, CA, USA, [8]Internal Med. Hematology-Oncology, University of California Davis Cancer Center, Sacramento, CA, USA

Background: CIT is associated with delayed onset of clinical effect and long-term (LT) survival, making traditional proportional hazards models less applicable. This study used a novel method, Bayesian fractional polynomial (FP) network meta-analysis

Table: 1470P Ranking outcomes of expected 5-year overall survival (intention-to-treat primary population of 850 pts from the OAK study; extended network including pembrolizumab)

	Unadjusted Analysis			Switching-Adjusted Analysis	
	Median Rank (95% CrI)	SUCRA		Median Rank (95% CrI)	SUCRA
Nivolumab 3 mg/kg	2 (1, 9)	0.881	Atezolizumab 1200 mg	2 (1, 8)	0.903
Atezolizumab 1200 mg	3 (1, 10)	0.865	Nivolumab 3 mg/kg	3 (1, 9)	0.872
Pembrolizumab 2 mg/kg	3 (1, 13)	0.829	Pembrolizumab 2 mg/kg	3 (1, 14)	0.818
Docetaxel 40 mg/m^2 qw	7 (1, 18)	0.592	Ramucirumab + docetaxel 60 mg/m^2	7 (1, 18)	0.594
Ramucirumab + docetaxel 60 mg/m^2	7 (1, 18)	0.589	Docetaxel 40 mg/m^2 qw	7 (1, 18)	0.575
Erlotinib 150 mg	8 (3, 14)	0.570	Erlotinib 150 mg	8 (3, 14)	0.564
Ramucirumab + docetaxel 75 mg/m^2	8 (2, 17)	0.547	Ramucirumab + docetaxel 75 mg/m^2	8 (2, 17)	0.55
Erlotinib 300 mg	8 (1, 18)	0.533	Erlotinib 300 mg	8 (1, 18)	0.536
Pemetrexed or docetaxel	9 (2, 17)	0.519	Pemetrexed or docetaxel	9 (2, 17)	0.518
Docetaxel q3w pooled	9 (4, 15)	0.514	Nintedanib + docetaxel 75 mg/m^2	9 (2, 17)	0.513
Nintedanib + docetaxel 75 mg/m^2	9 (2, 17)	0.513	Docetaxel q3w pooled	9 (4, 16)	0.508
Paclitaxel poliglumex	9 (2, 18)	0.489	Paclitaxel poliglumex	10 (2, 18)	0.477
Docetaxel 75 mg/m^2	11 (7, 15)	0.412	Docetaxel 75 mg/m^2	11 (7, 15)	0.408
Docetaxel qw pooled	12 (5, 17)	0.379	Docetaxel qw pooled	12 (6, 17)	0.369
Pemetrexed 900 mg/m^2	15 (4, 18)	0.259	Pemetrexed 900 mg/m^2	14 (4, 18)	0.288
Pemetrexed 500 mg/m^2	15 (8, 17)	0.239	Pemetrexed 500 mg/m^2	14 (8, 17)	0.256
Placebo	16 (7, 18)	0.195	Placebo	16 (7, 18)	0.178
Pemetrexed 1000 mg/m^2	18 (9, 18)	0.075	Pemetrexed 1000 mg/m^2	18 (9, 18)	0.075

CrI, Credible interval; SUCRA, surface under the cumulative ranking curve; q3w, every 3 weeks; qw, once a week.

(NMA) of time-to-event data, to address challenges in evaluating overall survival (OS) and switching with CIT.

Methods: A systematic literature review identified randomized, controlled, Phase II-IV trials of US- or EU-approved 2L+ treatments for advanced/metastatic NSCLC that enrolled ≥ 10 adult patients (pts) per treatment arm. An FP-NMA was used to estimate time-to-event outcomes: OS (5-y horizon) and progression-free survival (PFS; 2.5-y horizon). Expected survival time reflected the area under the curve over the time horizon. Adjusted analyses accounted for treatment switching. Expected OS times were ranked by median ranking with 95% credible intervals and by surface under the cumulative ranking curve (SUCRA).

Results: Of 25,115 screened publications, 35 studies of chemotherapy (chemo), PD-(L)1 inhibitors, targeted and other non-chemo agents, and placebo were included in the FP-NMA. In this model, all CIT PD-(L)1 inhibitors (nivolumab [nivo], atezolizumab [atezo] and pembrolizumab [pembro] in rank order) had similar estimated 5-year OS and ranked above all other treatments (Table). When adjusted for switching, all 3 CITs remained the highest-ranking treatments, with atezo ranked highest, followed by nivo and pembro. PFS and PD-(L)1 inhibitors' population subgroup results will be shown.

Conclusions: This FP-NMA showed that PD-(L)1 inhibitors had the highest expected 5-year OS amongst 2L treatments and that factors such as switching affected OS benefit. These results, which vary from prior models, suggest that FP-NMA may be a more relevant and viable method for assessing LT clinical benefit in pts treated with CIT.

Editorial acknowledgement: Jeff Frimpter, Health Interactions.

Legal entity responsible for the study: F. Hoffmann-La Roche AG.

Funding: F. Hoffmann-La Roche AG.

Disclosure: C. Schulz: Advisory Role/Expert Testimony: AstraZeneca, Boehringer Ingelheim, Celgene, Lilly, MSD, Novartis, Roche; Honoraria: AstraZeneca, Boehringer Ingelheim, Celgene, Lilly, Novartis, Roche; Financing of Scientific Research: AstraZeneca, BMS, CellAct, Lilly, Novartis, Roche, Pfizer. P. Chu, C.G. Berardo, B. Karthuria: Employee: F. Hoffman-La Roche Ltd. J. Foo, C. Morel: Employee: Mapi Group (an ICON plc company), which received financial support from Roche. C. Watkins: Employee: Clarostat Consulting, which received financial support by Roche. M. Ballinger: Employee: Genentech Inc., a member of the Roche Group. D.R. Gandara: Grants and personal fees: Genentech Inc., a member of the Roche Group.

1471P Prior or concurrent radiotherapy and nivolumab immunotherapy in non-small cell lung cancer

G. Ratnayake[1], M. Shankar[2], K. Roberts[3], R. Mason[4], B.G.M. Hughes[1], Z. Lwin[1], V. Jain[3], K.J. O'Byrne[5], B. Chua[1]

[1]*Cancer Care Services, Royal Brisbane and Women's Hospital, Brisbane, Australia,* [2]*Department of Radiation Oncology, Townsville Hospital, Townsville, Australia,* [3]*Department of Medical Oncology, Mater Adults Hospital, Brisbane, Australia,* [4]*Department of Medical Oncology, Princess Alexandra Hospital, Brisbane, Australia,* [5]*Cancer Services, Princess Alexandra Hospital, Woolloongabba, Australia*

Background: Preclinical and retrospective clinical studies suggest that combining radiotherapy (RT) with programmed cell death protein 1 (PD-1) blockade may elicit a synergistic anti-tumour response. We aimed to assess whether prior or concurrent RT was associated with improved disease control in patients with metastatic non-small cell lung cancer (NSCLC) treated with nivolumab.

Methods: We conducted a retrospective study of patients receiving nivolumab as second or subsequent line therapy for metastatic NSCLC across four tertiary oncology centers. All patients received nivolumab at a dose of 3mg/kg every 2 weeks intravenously. Survival and toxicity data were collected prospectively. Patients were categorized into those who received any RT for NSCLC (with curative or palliative intent, thoracic or otherwise) prior to or during nivolumab therapy, and those with no history of RT for NSCLC. Kaplan-Meier survival analysis was performed for progression-free survival (PFS) and overall survival (OS) following commencement of nivolumab.

Results: 85 patients (32 female, 53 male) received nivolumab between July 2015 and December 2016. Patients had a median age of 67 years (range 42-84) at commencement of nivolumab and were followed up for a median of 15 months. 65 patients (76.4%) received RT prior to or during nivolumab and 20 patients (23.6%) received nivolumab alone. Baseline characteristics of age, performance status, histology, smoking status, sites of metastatic disease and previous therapy were similar between the two groups. Prior or concurrent RT was associated with prolongation of PFS, median 2.8 months with RT versus 1.3 months without RT ($P = 0.02$, HR = 0.494, 95% CI 0.279-0.873). The median OS of the group receiving RT was 6.4 months vs 4.2 months for the no RT group but the difference did not reach statistical significance ($p = 0.20$). RT was not associated with an increase in toxicity and Grade 2 or greater pneumonitis rates were low in both groups (RT 4.6% vs no RT 5%).

Conclusions: RT prior to or concurrent with nivolumab for metastatic NSCLC was associated with superior PFS over nivolumab alone with no evidence of increase in adverse effects. RT may potentiate the effect of anti-PD-1 immunotherapy in NSCLC.

Legal entity responsible for the study: Royal Brisbane and Womens' Hospital, Herston, Queensland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1472P Immunotherapy in elderly patients (≥ 75 yrs) with advanced non-small cell lung cancer (NSCLC): A multicenter Italian experience

A. Luciani[1], L. Toschi[2], S. Fava[3], D. Cortinovis[4], V. Filipazzi[5], A. Tuzi[6], A. Marra[1], S. Rossi[7], A. Rossi[8], M. Blasi[1], M. Violati[1], L. Sala[4], F. Agustoni[4], P. Bidoli[4], S. Zonato[1], D. Ferrari[1]

[1]*Medical Oncology, Azienda Ospedaliera S. Paolo, Milan, Italy,* [2]*Medical Oncology, Istituto Clinico Humanitas, Rozzano, Italy,* [3]*Medical Oncology, Ospedale Civile di Legnano, Legnano, Italy,* [4]*Medical Oncology, Azienda Ospedaliera S. Gerardo U.O. Oncologia Medica, Monza, Italy,* [5]*Medical Oncology, Ospedale Luigi Sacco, Milan, Italy,* [6]*Medical Oncology, Ospedale di Circolo Fondazione Macchi, Varese, Italy,* [7]*Medical Oncology, Istituto Clinico Humanitas, Rozzano, Italy,* [8]*Medical Oncology, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy*

Background: Immunotherapy with anti PD-1 antibodies (mAbs) is the standard of care for the treatment of advanced Non-Small-Cell Lung Cancer (NSCLC). A conspicuous group of patients with advanced NSCLC are more than 75 years old. However, no randomized controlled trial exploring anti PD-1 therapy in older individuals has been published until now and few experiences in clinical practice have been reported. We therefore performed a multicenter retrospective analysis on NSCLC elderly patients treated with anti PD-1 therapy.

Methods: We collected data from seven centers. Inclusion criteria were a diagnosis of advanced NSCLC, age ≥75 years, and treatment with anti-PD-1mAbs (pembrolizumab or nivolumab) in first or following lines. Primary end-points of the study were efficacy, in terms of Disease Control Rate (DCR), Overall Response Rate (ORR), Progression-Free Survival (PFS), and safety, by means of immune-related adverse events (irAEs).

Results: The Clinical records of 72 patients followed since 2015 were analyzed. Median age was 77 years (75-86), males ware more frequently represented (60/72, 83%). A current or previous smoking history was found in 67/72 (93%) patients. Very old individuals (> 80 years old) were 21/72 (29%) and ECOG PS was 0-1 for 49/72 patients (63%). Non-squamous histology was prevalent 45/72, (62%). Brain metastases were found in 6/72 (8%) patients. Most of the patients (58/72, 81%) received nivolumab. For 68 patients, data on DCR, ORR were available. 39/68 (54%) had a DCR, while 17/68 (24%) had an ORR. Less than 10% of the patients had oligoprogression or pseudoprogression (8,3 and 9,7 % respectively). Overall immune-related adverse events occurred in 9/72 (14%) of individuals, 4/10 (40%) of them grade 3/4, being hematological and liver toxicities the most frequent ones (4 and 3%, respectively). At time of analysis, median PFS was 4,4 months (0.5-25 SD 5,53). In the Cox regression analysis, PFS was significantly influenced by DCR and smoking status ($p = 0{,}0001$, OR 17 95% CI 5,4 - 52,3 and $p = 0{,}001$, OR 11 95% CI 2,6-45, respectively).

Conclusions: In our cohort of elderly patients, anti PD-1 agents demonstrated to have a good toxicity profile and an efficacy comparable with the younger population.

Legal entity responsible for the study: I conducted the study recording and collecting clinical data from other colleagues and computing statistical part with other specialists of the San Paolo Hospital in Milan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1473P Immune checkpoint inhibitor efficacy and safety in elderly non-small cell lung cancer patients

T. Kubo[1], H. Watanabe[2], K. Ninomiya[2], K. Kudo[3], D. Minami[4], E. Murakami[5], N. Ochi[6], T. Ninomiya[7], D. Harada[8], M. Yasugi[9], E. Ichihara[2], K. Ohashi[2], K. Fujiwara[4], K. Hotta[10], M. Tabata[1], Y. Maeda[11], K. Kiura[2]

[1]*Center for Clinical Oncology, Okayama University Hospital, Okayama, Japan,* [2]*Respiratory Medicine, Okayama University Hospital, Okayama, Japan,* [3]*Respiratory Medicine, Iwakuni Medical Center, Iwakuni, Japan,* [4]*Respiratory Medicine, Okayama Medical Center, Okayama, Japan,* [5]*Respiratory Medicine, Japanese Red Cross Society Himeji Hospital, Himeji, Japan,* [6]*General Internal Medicine 4, Kawasaki Medical School, Okayama, Japan,* [7]*Department of Respiratory Medicine, Okayama University, Okayama, Japan,* [8]*Thoracic Oncology and Medicine, Shikoku Cancer Center, Matsuyama, Japan,* [9]*Respiratory Medicine, Chugoku Central Hospital, Fukuyama, Japan,* [10]*Center for Innovative Clinical Medicine, Okayama Unversity Hospital, Okayama, Japan,* [11]*Hematology, Oncology, and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*

Background: Immune checkpoint inhibitors (ICIs) offer longer survival than chemotherapy in advanced non-small cell lung cancer (NSCLC). In subset analyses, ICIs extended survival compared to chemotherapy in patients aged ≥65 years, but the effects in patients aged ≥75 years are controversial. We performed multicenter, collaborative, and retrospective analyses of ICI efficacy and safety in NSCLC patients aged ≥75 years.

Methods: We retrospectively studied 434 advanced NSCLC patients who received ICIs from December 2015 to December 2017 at seven centers, and retrospectively applied the G8 screening tool from medical records.

Results: Of 434 patients who received ICIs, 100 were aged ≥75 years (median: 79 years; range: 75–90 years). Five patients with PS 3 were omitted. The histological diagnoses were non-squamous cell carcinoma in 55 (57.9%), squamous cell carcinoma in 40 (42.1%). ICIs were given as a first-line treatment to 20 patients, and as a second- or later-line treatment to 75; 67 (70.5%) patients received nivolumab, and 28 (29.5%) pembrolizumab. The PD-L1 tumor proportion scores (TPS) were <1% in 4 (4.2%), 1-

49% in 10 (10.5%), and ≥50% in 26 (27.4%) and unknown in 55 (57.9%). The objective response rate (ORR) was 35.0% (CR: 0, PR: 7, SD: 6, PD: 5, NE: 2), the median progression-free survival (PFS) was 6.1 months [95% confidence interval (CI): 1.6–7.7], and the median survival time (MST) was 8.7 months [95% CI: 7.9–not reached (NR)] for first-line treatment in patients with TPS ≥50%. The ORR was 20.0% (CR: 0, PR: 15, SD: 18, PD: 31, and NE: 11), the PFS was 2.9 months [95% CI: 1.9–4.6], and the MST was 15.5 months [95% CI: 5.5–NR] for second- or later-line treatment. The median G8 score was 11.5 (range: 5.5–15.5). The MST was longer in the G8 high (>11.5) group than the low (≤11.5) group (NR vs. 8.2 months) ($p = 0.02$). Likewise, the MST was 17.8 months (PS 0–1) vs. 3.1 months (PS 2) ($p < 0.01$). The grade ≥2 immune-related adverse events incidence was 23.3% (thyroid disease: 4.2%; interstitial lung disease: 10.5%).

Conclusions: Although the observation period is short and the data is immature, ICIs were effective and tolerable for patients aged ≥75 years. PS is a simple and exact parameter, but G8 screening is also useful in judging ICI adequacy for the elderly.

Legal entity responsible for the study: Okayama University Hospital.

Funding: Has not received any funding.

Disclosure: T. Kubo: Research Funding: Ono Phamaceuticals. T. Ninomiya: Honoraria: Chugai Pharma and Boehringer Ingelheim. D. Harada: Speakers' Bureau: Kyowa Hakko Kirin,Yakult, AstraZeneca, Lilly Pharma, Bristol Myers Squibbs, Ono Phamaceuticals, Boehringer Ingelheim. E. Ichihara: Honoraria: AstraZeneca, Chugai Pharma, MSD, Lilly Pharma, Boehringer Ingelheim; Research Funding: MSD, Lilly Pharma. K. Ohashi: Honoraria: AstraZeneca, Boehringer Ingelheim, Chugai Pharma, Ono Pharmaceutical; Research Funding: Boehringer Ingelheim, Novartis, Lilly Japan. K. Hotta: Honoraria: AstraZeneca, Nihonkayaku, Chugai Pharma, Novartis, MSD, Lilly Pharma, Bristol Myers Squibbs, Ono Phamaceuticals, Boehringer Ingelheim, Taiho Pharmaceutical; Research Funding: AstraZeneca, Chugai Pharma, Astellas Oncology, Novartis, MSD, Lilly Pharma, Bristol Myers Squibbs, Ono Phamaceuticals, Boehringer Ingelheim. Y. Maeda: Honoraria: Pfizer, Otsuka, Kyowa Hakko Kirin, Eisai, Mochida Pharmaceutical Co. Ltd., Astellas Oncology, Asahi Kasei, Nippon Shinyaku, Yakult, Chugai Pharma, Novartis, BMS UK, Ono Phamaceuticals; Research Funding from Pfizer, Otsuka, Kyowa Hakko Kirin, MSD, Mochida Pharmaceutical Co. Ltd., Eisai, Astellas Oncology, Meiji Seika Kaisha, Asahi Kasei, Nippon Shinyaku, Yakult, BMS UK, Ono Phamaceuticals. K. Kiura: Honoraria: Chugai Pharma, Pfizer, AstraZeneca, Novartis, MSD, Lilly Pharma, Bristol Myers Squibbs, Ono Phamaceuticals, Boehringer Ingelheim, Taiho Pharmaceutical; Research Funding from Chugai Pharma, AstraZeneca, Daiichi Sankyo, Ono Phamaceuticals, Boehringer Ingelheim, Shionogi Pharmaceutical. All other authors have declared no conflicts of interest.

1474P Nivolumab in non-small cell lung cancer: French evaluation of use, current practices and medico-economic approach

F. Grude[1], R. Corre[2], T. Urban[3], J. Bennouna[4], G. De Chabot[3], T. Chatellier[5], F. Denis[6], R. Descourt[7], J-Y. Douillard[8], C. Ricordel[2], O. Molinier[9], F. Pinquie[3], G. Robinet[7], M. Travers[10], B. Moiteaux[11], D. Deniel Lagadec[12], F. Marhuenda[1]

[1]Cancer Observatory, ICO Paul Papin, Angers, France, [2]Pneumology, CHU de Pontchaillou, Rennes, France, [3]Pneumology, CHU Angers, Angers, France, [4]Pneumology, CHU de Nantes - Laennec, Saint Herblain, France, [5]Oncology, Clinique Mutualiste de l'Estuaire, Saint Nazaire, France, [6]Oncology, Clinique Victor Hugo Le Mans, Le Mans, France, [7]Oncology, C.H.U. Brest - Hôpital Morvan, Brest, France, [8]Division of Medical and Scientific Affairs, ESMO - European Society for Medical Oncology, Lugano - Viganello, Switzerland, [9]Pneumology, Centre Hospitalier Du Mans, Le Mans, France, [10]IAE, Université de Nantes, Nantes, France, [11]IAE, University of Nantes, Nantes, France, [12]Cancer Observatory, CHRU Brest, Brest, France

Background: In 2016, nivolumab could be prescribed according to French registration in stage IIIB/IV NSCLC after disease progression with prior platinum-based chemotherapy and TKI therapy for patients with EGFR mutation. The Observatory of Drugs, Medical Devices and Therapeutic Innovations (OMEDIT), a network from the Health Ministry has evaluated the use, current practices and medico-economic approach in the Bretagne and Pays de la Loire areas.

Methods: All consenting adult patients with stage IIIB/IV NSCLC who initiated nivolumab (3 mg/kg every 2 weeks) in 2016 were included. Minimum follow-up for survival was 12 months. Sex, age, mutation profile, toxicities, Clinic Benefit (CB: pts with complete/partial response/stable disease as the best response), progression-free survival (PFS) and overall survival (OS) have been studied for ECOG PS 0-1 pts (according to registration).

Results: 377 pts with squamous (113 pts), non-squamous (197) and undifferentiated (67) NSCLC have been included. The median number of courses was 8 (1-54). 140 pts (37%) had 1 to 4 courses, 67 pts (18%) 5 to 8 courses and 170 pts (45%) more than 8. 247 pts were treated in 2nd line, 98 in 3rd line. All lines combined, CB was experienced by 212 pts (56%). For these pts, median course was 17 (1-54), mPFS and mOS were 4.6 months and 15.0 months, respectively. No difference on survival has been noticed according to histology, treatment line, age (cut-off 70 y), grade III/IV toxicity. However, mPFS and mOS were lower in ECOG PS ≥ 2 pts than in PS0-1 pts: 2.4 months vs 4.6 m ($p < 0.01$) for PFS and 3.7 m vs 15.0 m ($p < 0.001$) for OS. 20% of pts presented grade III/IV toxicities. These pts presented a better CB (74% vs 56%, $p = 0.002$). In 2016-2017, this treatment, for pts initiated in 2016 only, cost 15.8 million euros (drug, hospitalisation and transportation). 86% of these costs were dedicated to pts who experienced CB.

Conclusions: In a real-life setting, survival outcomes and toxicities with nivolumab in advanced NSCLC are comparable to literature data. ECOG PS ≥ 2 pts presented shorter survival than PS0-1 pts. Interestingly, 86% of the cost incurred for these treatments was to pts with CB. Updated data will be shown at the meeting.

Legal entity responsible for the study: Cancer Observatory, OMEDIT B and PL.

Funding: Has not received any funding.

Disclosure: R. Corre: Board, invitation Congress: BMS. J-Y. Douillard: CMO: ESMO. O. Molinier: Expert advice: BMS. All other authors have declared no conflicts of interest.

1475P Radiological identification of rapid progressions in advanced NSCLC patients treated with nivolumab

P.F. Simões da Rocha[1], E. Ripoll[2], A. Corbera[1], M. Hardy-Werbin[1], A.F. Fernandez-Alarza[2], M. Orrillo[1], À. Taus[1], E. Arriola[1]

[1]Medical Oncology, Hospital del Mar, Barcelona, Spain, [2]Radiology Department, Hospital del Mar, Barcelona, Spain

Background: With the wide introduction of anti-PD-1 agents in the treatment of NSCLC, the unusual patterns of response are now observed more frequently in the clinical setting. One of the major concerns for clinicians is hyperprogression, perceived as a reality by many but for which there is still discussion and has no standard definition. The aim of our work was to analyse the patterns of response to nivolumab in a homogeneously treated population of patients with NSCLC and identify cases with hyperprogression.

Methods: Between December 2015 and August 2017, 42 patients with NSCLC were treated with Nivolumab at 3mg/kg every 2 weeks. A retrospective evaluation of the CT scans (previous to baseline, baseline before nivolumab, subsequent scans after nivolumab) was performed by a thoracic radiologist. Tumour growth rate was defined as the percentage of variation by RECIST1.1 over time. It was calculated for the pre and post-nivolumab period (RECIST%/time (days)). We defined hyperprogressors as those patients whose tumour growth was 2 times greater on nivolumab than in the pre-nivolumab period.

Results: RECIST 1.1 evaluation was feasible in 40 patients. Best response was a partial response in 17.5% patients, including 4 cases (10%) of pseudoprogression and 2 cases with delayed response (after 1st scan). Thirty percent and 52.5% of patients showed stable disease and progressive disease, respectively. Among the 20 patients who developed progression by RECIST 1.1 on nivolumab, 16 experienced a more rapid progression in the post-nivolumab period (median % of change/t 0.6 Vs 0.3 in the pre-nivolumab period; $p = 0.02$)). Sixty percent (12/20) of progressing patients were hyperprogressors according to our definition (30% of the total population). No differences between hyperprogressors vs rest of progressors according to age, performance status, treatment line, gender or histology was observed.

Conclusions: Rare patterns of response (pseudoprogression, hyperprogression) must be considered in the evaluation of patients treated with immunotherapy. Unexpectedly rapid progressions are observed on immunotherapy. Standardized definitions and mechanisms for these events warrant further investigation.

Legal entity responsible for the study: Hospital del Mar.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1476P Role of immunotherapy (I) for advanced, pre-treated, non-squamous NSCLC (APNS-NSCLC): Preliminary data of a pooled analysis with network meta-analysis

C. Cherubini[1], M. Papi[1], L. Gianni[2], C. Gianni[2], S.V.L. Nicoletti[1], M. Fantini[1], L.A. Lazzari Agli[1], D. Tassinari[1]

[1]Oncology, Ospedale Infermi, Rimini, Italy, [2]Oncology and Haematology, Ospedale Infermi, Rimini, Italy

Background: To assess the role of I for second line treatment of APNS-NSCLC.

Methods: A pooled analysis of the final data of the CA209057, the KEYNOTE-010 and the OAK trial was performed. Overall Survival (OS) was the primary end point of the trial. The outcomes of patients with PD-L1 expression of 1%-49% (PD-L1 1%-49%), PD-L1 expression <1% (PD-L1<1%) or mutated-EGFR (EGFR+) were analyzed comparing any checkpoint inhibitor with standard chemotherapy. An indirect comparison with network meta-analysis was performed between the different checkpoint inhibitors whenever a significant difference was observed in the pooled analysis. Direct and indirect comparisons were performed using a random effect model.

Results: The outcome of 1720 patients was analyzed. 313 patients had been treated with Atezolizumab (A), 292 with Nivolumab (N), 270 with Pembrolizumab (P), and 845

with Docetaxel (D). The preliminary results were detailed in the table (Legend. CI95%: 95% Confidence Interval; *: Pooled Analysis; **: Network Meta-Analysis).

Table: 1476P

	OS Hazard Ratio	CI95%	
A vs D (PD-L1 1%-49%)	0.571	0.423-0.771	P < 0.001
N vs D (PD-L1 1%-49%)	0.62	0.467-0.882	P = 0.001
P vs D (PD-L1 1%-49%)	0.76	0.604-0.956	P = 0.019
I vs D (PD-L1 1%-49%)*	0.66	0.555-0.786	P < 0.001
A vs N (PD-L1 1%-49%)**	0.921	0.609-1.392	P = 0.696
A vs P (PD-L1 1%-49%)**	0.751	0.541-1.043	P = 0.087
N vs P (PD-L1 1%-49%)**	0.816	0.597-1.116	P = 0.491
N vs D (PD-L1<1%)	0.9	0.66-1.214	P = 0.491
A vs D (PD-L1<1%)	1.04	0.619-1.747	P = 0.882
I vs D (PD-L1<1%)*	0.933	0.72-1.21	P = 0.601
P vs D (EGFR+)	0.88	0.453-1.71	P = 0.706
N vs D (EGFR+)	1.18	0.693-2.004	P = 0.542
I vs S (EGFR+)*	1.052	0.695-1.594	P = 0.81

Conclusions: Our data seem to confirm the role of I for APNS-NSCLC with PD-L1 1%-49%. On the contrary, not-significant benefits in terms of OS seem to emerge for patients with PD-L1<1% or EGFR+ expression. Likewise, no significant differences seem to emerge from the indirect comparisons between A, N and P for patients with a PD-L1 1%-49% expression. Although all these data need to be analyzed with caution, as expression of indirect comparisons, waiting further conformations from clinical trials they can support clinicians for daily clinical practice.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1477P Evaluation of progression-free survival (PFS) and one-year (1y) survival as surrogate endpoints (SE) in previously treated advanced non-small cell lung cancer (adNSCLC) in the era of immuno-oncology (IO)

S. Zhao, Z. Zhang, T. Zhou, Y. Zhang, L. Zhang

Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: The advent of IO has led to greater availability of effective subsequent treatments and extended survival of patients, increasingly complicating the evaluation of overall survival (OS) in adNSCLC trials. To expedite drug developments and allow timely approvals of potentially effective agents for previously treated adNSCLC, we assessed the validity of PFS and 1y survival as SE in 2nd-line adNSCLC trials, especially in those containing immunotherapies.

Methods: We conducted a systemic literature search of 2nd-line adNSCLC trials. A weighted linear regression analysis between post 2nd-line treatments and OS was performed to establish the necessity of SE in 2nd-line trials. Adopting Buyse's criteria for surrogacy, a two-stage meta-analytic validation model was used to assess associations between SE and OS at patient-level and trial-level. The strength of association was quantified by the coefficient of determination (R^2). R^2 >0.6 was defined a priori as clinically relevant. Results were validated with leave-one-out cross validation methods.

Results: Of 1680 studies identified, 85 trials with 146 arms and 25,698 patients were included. Data of 22,804 patients from 50 trials (103 arms) were used for surrogacy assessment. A significant correlation between percentages of post 2nd-line treatments and OS improvements was identified (R^2 [95% confidence interval] =0.347 [0.345-0.351], $P_{Pearson}$ <0.0001, $P_{Spearman}$ <0.0001). PFS showed weak patient-level (0.100 [0.098-0.101]) and trial-level (0.064 [0.059-0.069]) associations with OS, while 1y survival strongly correlated with OS at both levels ($R^2_{patient}$=0.707 [0.704-0.708]; R^2_{trial}=0.829 [0.828-0.831]). Subgroup analysis of IO trials yielded similar results (PFS: $R^2_{patient}$=0.177 [0.128-0.200], R^2_{trial}=0.835 [0.791-0.918]; 1y survival: $R^2_{patient}$=0.965 [0.960-0.968], R^2_{trial}=0.778 [0.734-0.856]).

Conclusions: A valid SE is needed in 2nd-line adNSCLC trials in the era of IO. PFS poorly correlated with OS at both patient-level and trial-level, while 1y survival showed the potential of being a valid SE in future 2nd-line adNSCLC trials.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1478P Efficacy of second-line nivolumab after early time to progression on first-line cytotoxic chemotherapy in patients with advanced non-small cell lung cancer (NSCLC)

T. Ota, K. Kirita, H. Udagawa, S. Umemura, S. Matsumoto, K. Yoh, S. Niho, K. Goto

Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Some previous studies showed chemo-resistance was associated with upregulation of programmed cell death ligand 1 (PD-L1) and mutation burden in NSCLC. Recently, immune checkpoint inhibitors are available to treat NSCLC, whereas efficacy of immune checkpoint inhibitor in patients showing early progression to first-line cytotoxic chemotherapy remains unknown.

Methods: We retrospectively collected medical records of advanced NSCLC patients who received second-line nivolumab treatment after cytotoxic chemotherapy in our hospital. Early progression was defined as exacerbation less than 16 weeks from the initiation of first-line chemotherapy. The patients were divided according to time to progression (TTP) of first-line therapy for <16, and ≥16weeks and were evaluated efficacy of second-line nivolumab.

Results: Fifty-one patients were received nivolumab treatment as second-line therapy after first-line line cytotoxic chemotherapy failure from February 2016 to April 2017, 22 patients were in the TTP <16 weeks group and 29 patients were in the TTP ≥16 weeks group. The median TTP of first-line cytotoxic chemotherapy was 17.0 weeks (95% CI 8.0-23.1 weeks). The median progression-free survival (PFS) of second-line nivolumab was 6.7 months (95% CI 3.2 -11.2 months). The median PFS was 11.3 months in the TTP <16 weeks group versus 3.7 months in the TTP ≥16 weeks group (hazard ratio, 0.44; 95% CI, 0.21–0.88, P = 0.019). The objective response rate was 55% versus 18% (P = 0.005) and the complete response rate was 5% vs 0%. The median overall survival was not reached and 11.3 months, respectively (hazard ratio, 0.68; 95% CI, 0.30–1.46, p = 0.32). On multivariate analysis, TTP <16 weeks (hazard ratio, 0.39; 95% CI, 0.17-0.83, p = 0.015) and non-sq histology (hazard ratio, 0.33; 95% CI, 0.16-0.69, p = 0.004) were significantly favorable factors for PFS.

Conclusions: Among patients with advanced NSCLC that had early progressed during or after primary cytotoxic chemotherapy, nivolumab was effective as second-line therapy.

Legal entity responsible for the study: National Cancer Center Hospital East.

Funding: Has not received any funding.

Disclosure: H. Udagawa: Honoraria: Ono, Bristol-Myers Squibb, MSD, Taiho, Chugai, AstraZeneca and Amco. S. Umemura: Honoraria: Ono. S. Matsumoto: Honoraria: Ono, Bristol-Myers Squibb. S. Niho: Honoraria: Bristol-Myers Squibb. K. Goto: Grant: Ono; Honoraria: Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1479P First analysis of patients (p) with stage IV non-small cell lung cancer (NSCLC) of the thoracic tumor registry (RTT) of the Spanish Lung Cancer Group (SLCG)

E. Carcereny Costa[1], D. Rodriguez-Abreu[2], M. Guirado[3], R. López-Castro[4], B. Massutí[5], J. Bosch Barrera[6], E. Nogueron Martnez[7], M.A. Sala Gonzalez[8], M. Domine Gomez[9], E. Del Barco Morillo[10], S. Cerezo Gonzalez[11], M. Dorta Suarez[12], J. Casal Rubio[13], C. Camps[14], M.A. Muñoz[15], R. de las Peñas[16], J.A. Ortega dominguez[17], J.L. Gonzalez-Larriba[18], R. Bernabe Caro[19], M. Provencio Pulla[20]

[1]Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain, [2]Servicio Oncología Médica, Hospital Insular De Gran Canaria, Las Palmas, Spain, [3]Medical Oncology, Hospital General Universitario de Elche, Elche, Spain, [4]Medical Oncology, Hospital Universitario Clínico de Valladolid, Valladolid, Spain, [5]Oncología Médica, Hospital General Universitario Alicante, Alicante, Spain, [6]Medical Oncology, Catalan Institute of Oncology (ICO)-Hospital Universitari Josep Trueta, Girona, Spain, [7]Oncologia, Complejo Hospitalario Universitario de Albacete, Albacete, Spain, [8]Medical Oncology, Hospital De Basurto, Vizcaya, Spain, [9]Medical Oncology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [10]Medical Oncology, Complejo Hospitalario Universitario De Salamanca, Salamanca, Spain, [11]Medical Oncology, Hospital General Mancha Centro, Alcazar De San Juan, Spain, [12]Medical Oncology, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz De Tenerife, Spain, [13]Medical Oncology, Hospital Meixoeiro, Vigo, Spain, [14]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain, [15]Medical Oncology, Instituto Valenciano De Oncologia, Valencia, Spain, [16]Medical Oncology, Consorcio Hospitalario Provincial de Castellon, Castellon, Spain, [17]Oncology, Hospital QuironSalud, Malaga, Spain, [18]Medical Oncology, Hospital Clinico Universitario San Carlos, Madrid, Spain, [19]Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain, [20]Servicio de Oncología Médica, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain

Background: In September 2016, the SLCG began a RTT in 53 Spanish hospitals. In this study, we present data on patients with NSCLC with advanced disease.

Methods: The study comprises all the patients included in the RTT since September 2016 with stage IV disease. Progressionfree survival (PFS) and overall survival (OS) were evaluated with the Kaplan-Meier curves and the groups were compared using the Log-rank test. The variables related with the patients that were analyzed included: age, gender, smoking habit, comorbidities, performance status (PS) by ECOG and histology of the tumor. The molecular tests performed in the group of patients with advanced disease were also analyzed. We also analyzed the treatment received in this patient cohort.

Results: Out of the total of 2361 patients included, diagnosed between July 1991 and April 2018, 1194 had stage IV NSCLC. Mean age was 63.2 years, 824 (69%) were males, 473 (39.6%) active smokers and 475 (39.8%) ex-smokers. The most frequent histology

was adenocarcinoma, in 894 patients (74.9%), and squamous cell, in 220 patients (18.4%). A total of 78.6% (938) of the patients had some type of comorbidity: HBP (38.5%), dyslipidemia (28.1%), diabetes mellitus (16.3%) and COPD (14.7%). A total of 978 patients (81.9%) underwent some type of molecular test. The EGFR analysis was performed in 900 patients (75.4%), and was positive in 25.6%. ALP was analyzed in 763 patients (63.9%), mostly by IHC (44.7%), 5.2% being positive by this method. Of the total, 158 patients (13.2%) did not receive any treatment, 530 patients (44.4%) received 1 treatment line, 295 patients (24.7%) two lines, 128 patients (10.7%) three lines, and 30 patients (2.5%) 4 or more lines. A total of 60.9% of the patients received a platinum doublet in first line, the most commonly used being the combination of platinum with pemetrexed (34%). 1171 patients are evaluable for overall survival, with a median survival of 17.4 m (95% CI 14.6-20.2 m).

Conclusions: In this cohort of patients, the clinical characteristics are those expected for this group of patients with advanced disease. However, a greater percentage than that expected of the EGFR mutations appears, perhaps due to a population supraselection.

Legal entity responsible for the study: Spanish Lung Cancer Group / Grupo Español de Cáncer de Pulmón (SLCG/GECP).

Funding: Lilly, Msd, Novartis.

Disclosure: All authors have declared no conflicts of interest.

1481P Extra-cost of brain metastases in patients with non-squamous non-small cell lung cancer (NSCLC): A French national hospital database analysis

N. Girard[1], D. Cozzone[2], L. de Léotoing[3], C. Tournier[3], A. Vainchtock[3], B. Tehard[2], A. Cortot[4]

[1]Oncology, Institut Curie, Paris, France, [2]National Access & Pricing, Roche S.A.S - France, Boulogne-Billancourt, France, [3]Consultancy, HEVA, Lyon, France, [4]Oncology, CHRU de Lille, Lille, France

Background: To assess the incremental cost associated with the management of patients with primary non-squamous non-small cell lung cancer (NSCLC) with brain metastases (BM) at the time of diagnosis

Methods: A retrospective database analysis was performed using the French exhaustive Hospital medical information database (PMSI). Patients with metastatic lung cancer were identified through a combination of ICD-10 diagnosis codes: C34* for lung cancer combined with at least one metastasis code (C77*, C78*, C79*). All such patients hospitalised with metastatic lung cancer for the first time in 2013 were eligible. Those with at least one prescription of bevacizumab or pemetrexed at the index stay or during the 24-month following period were considered to have non-squamous NSCLC. Two cohorts were identified, one with BM and one with metastases at other sites. For each patient, total in-hospital medical resource consumption associated with the initial stay in 2013 and with any follow-up stays in the following 24 months was documented. Costs were attributed from official French national tariffs and expressed in 2017 Euros.

Results: The study included 1,529 patients with other metastases (62.6 ± 9.8 years old; 69.0% of men) and 971 patients with BM (58.6 ± 9.1 years old; 59.3% of men). The mean number of hospitalisations in the 24-month follow-up period was 17 per patient with other metastases and 21 per patient with BM. >99% of patients in both groups received chemotherapy. 57.7% patients with BM and 12.9% patients with other metastases were managed by radiotherapy. 37.2% patients with BM and 23.5% patients with other metastases received palliative care. 942 patients with other metastases and 695 with BM died during hospitalisation within two years (61.6% vs 71.6%). The associated cost was € 2,979 per patient-month for those with BM and € 2,426 for those with other metastases, representing a differential cost of € 553 per month. Radiotherapy (+€164/month) and palliative care (+€130/month) were the principal drivers of the incremental cost).

Conclusions: The presence of BM at the time of diagnosis of non-squamous NSCLC carries a significant burden, and ways of lowering it are needed.

Legal entity responsible for the study: Bertrand Tehard.

Funding: Roche SAS France.

Disclosure: N. Girard, A. Cortot: Member of advisory board for this project: Roche SAS. D. Cozzone: Employee: Roche SAS. L. de Léotoing, C. Tournier, A. Vainchtock: Employee: HEV, Roche SAS contracted with HEVA to conduct analyses on this project. B. Tehard: Employee: Roche SAS France.

1482P Localablative treatment for synchronous oligometastatic lung cancer: A propensity score analysis of 180 patients

N. Frost[1], A. Tessmer[2], A. Schmittel[3], V. van Laak[4], S. Ochsenreither[5], B. Temmesfeld-Wollbrück[1], B. Schmidt[4], N. Suttorp[1], M. Witzenrath[1], C. Grohe[2]

[1]Department of Infectious Diseases and Pulmonary Medicine, Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, [2]Department of Pulmonary Medicine, Evangelische Lungenklinik Berlin-Buch, Berlin, Germany, [3]Onkologie Seestrasse, Schwerpunkt Hamatologie und Onkologie, Berlin, Germany, [4]Department of Pulmonary Medicine, DRK-Klinikum Berlin-Mitte, Berlin, Germany, [5]Charité Comprehensive Cancer Center, Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Background: Localablative treatment (LAT) improves outcome in lung cancer with oligometastatic disease (OMD) and potentially leads to long term survival. The aim of this retrospective study was to evaluate and quantify the additional benefit of LAT in synchronous OMD and to further identify prognostic factors for outcome and survival.

Methods: A propensity score matched pairs analysis was performed on a set of patient and disease variables in 180 patients, treated for synchronous OMD (including non-small cell and neuroendocrine lung cancer) with ≤4 metastatic lesions between 2000 and 2016 in 3 specified lung cancer centers in Berlin, Germany. Patients had either received LAT for all sites of disease (intervention group) by surgery or stereotactic ablative body radiation, or standard chemotherapy, if necessary combined with a palliative-intended local treatment (control group).

Results: Median follow-up time was 32.2 and 18.8 months for the intervention and control group, respectively. Substantial benefits in median progression free survival (PFS, 25.1 vs. 8.2 months; HR, 0.30; 95% CI, 0.21-0.43; $p < 0.001$) and overall survival (OS, 60.4 vs. 22.5 months; HR, 0.42; 95% CI, 0.28-0.62; $p < 0.001$) were associated to LAT. Histology of adenocarcinoma (PFS: HR, 0.58; 95% CI, 0.37-0.91; $p = 0.02$; OS: HR, 0.53; 95% CI,0.33-0.86; $p = 0.01$) and small primaries (T1a; PFS: HR, 0.36; 95% CI, 0.18-0.70, $p = 0.003$; OS: HR, 0.39; 95% CI, 0.18-0.84; $p = 0.02$) also predicted a favorable prognosis concerning PFS and OS. Nodal stage (N0-2 vs. 3; HR, 0.49; 95% CI, 0.25-0.97; $p = 0.04$) and number of metastases (1 vs. 2-4; HR, 0.63; 95% CI, 0.41-0.96; $p = 0.03$) were associated with an extended PFS, whereas initial ECOG-PS (0-1 vs. 2; HR, 0.42; 95% CI, 0.20-0.91; $p = 0.03$) predicted OS.

Conclusions: LAT was the strongest predictor for PFS and OS in patients with OMD and ≤4 metastases. Survival observed in the control group identifies OMD as a subset of lung cancer with a generally more favorable prognosis.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1483P Initial treatment in patients (pts) diagnosed with non-small cell lung cancer (NSCLC) in Denmark from 2005-2015: The SCAN-LEAF study

J.B. Sørensen[1], S. Ekman[2], P. Horvat[3], D. Layton[4], J. Kim[4], M. Rosenlund[4], A. Juarez-Garcia[5], M. Daumont[6], H.C. Jacobs[5], L. Lacoin[6], O.T. Brustugun[7], M. Planck[8]

[1]Department of Oncology, Rigshospitalet, Copenhagen, Denmark, [2]Department of Oncology, Karolinska University Hospital-Solna, Stockholm, Sweden, [3]Real World Evidence Solutions, IQVIA, London, UK, [4]Data Science, IQVIA, London, UK, [5]Worldwide Health Economics & Outcomes Research, Bristol-Myers Squibb, Uxbridge, UK, [6]Worldwide Health Economics & Outcomes Research, Bristol-Myers Squibb, Braine-L'Alleud, Belgium, [7]Department of Oncology, Radiumhospitalet, Oslo, Norway, [8]Division of Oncology and Pathology, Skane University Hospital-Lund, Lund, Sweden

Background: Describing initial treatment (tx) post-NSCLC diagnosis is important in order to understand clinicians' intent in routine care, based on pt/disease characteristics and disease stage at diagnosis. The SCAN-LEAF project aims to describe the epidemiology, clinical care and outcomes of NSCLC pts in Scandinavia. Here, we report initial tx and outcomes among pts with incident NSCLC in Denmark from 2005-2015.

Table: 1483P

	Stage I (N = 4138)	Stage II (N = 2322)	Stage IIIA (N = 3594)	Stage IIIB (N = 3735)	Stage IV (N = 16,486)
Initial treatment, %					
Surgery	68.6	64.9	30.9	5.9	2.8
Surgery with neoadjuvant or adjuvant SACT	7.8	29.4	18.0	3.5	1.5
Radiotherapy only	20.2	14.2	16.7	18.7	19.2
SACT and radiotherapy	1.8	7.1	24.4	25.1	19.6
SACT only	2.5	5.9	18.6	35.7	34.3
Untreated (ie, none of the above)	6.9	8.0	9.5	14.5	24.1
SACT regimen in initial treatment, %	12.1	42.4	61.0	64.3	55.4
No SACT in initial treatment, %	87.9	57.6	39.0	35.7	44.6

Methods: The Danish cohort, established by linkage of Danish national registries, includes all adult pts with incident NSCLC from 2005-2015 (follow-up until Dec 2016). Initial tx includes lung surgery, radiotherapy (RT) and systemic anticancer therapy (SACT) captured through procedure codes (no drug names); it is defined as the first tx received at any time after diagnosis associated with any other tx received within 12 wks of this first tx start. Further analyses will assess the changes in initial tx patterns and overall survival over time, using the Kaplan–Meier method.

Results: Of the 31,939 pts with incident NSCLC, mean age was 68.4 yrs (13.3% ≥80 yrs) and 48.0% were women. TNM stage distribution (stage I, II, IIIA, IIIB, IV, missing) was 12.9%, 7.3%, 11.2%, 11.7%, 51.6% and 5.2%, respectively. 54.4% had non-squamous cell carcinoma and 26.5% squamous cell carcinoma. Initial tx is shown in the table. The proportion of pts receiving SACT (alone or with surgery/RT) was 12.1%, 42.4%, 61.0%, 64.3% and 55.4% in stages I–IV, respectively. The proportion of untreated pts increased from 6.9% in stage I to 24.1% in stage IV.

Conclusions: From 2005-2015, half of NSCLC pts were diagnosed at stage IV. Most pts at stage I and II were treated with surgery, adjuvant/neoadjuvant SACT being relatively uncommon. At stage III, most pts received SACT either as adjuvant/neoadjuvant tx (1/5 of stage IIIA), associated with RT (1/4 of stage IIIA/B) or alone (1/5 of stage IIIA; 1/3 of stage IIIB). Only half of metastatic pts received SACT, highlighting a significant unmet treatment need in NSCLC.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: S. Ekman: Grants: Bristol-Myers Squibb, during the conduct of the study. P. Horvat, D. Layton, J. Kim, M. Rosenlund: Employee: IQVIA. A. Juarez-Garcia: Employee: Bristol-Myers Squibb. H.C. Jacobs: Personal fees: Bristol-Myers Squibb, during the conduct of the study. L. Lacoin: Consultant epidemiologist contracted: Bristol-Myers Squibb for the SCAN-LEAF project. All other authors have declared no conflicts of interest.

1484P Treatment patterns in patients (pts) with stage IIIB-IV non-small cell lung cancer (NSCLC) in Sweden: The SCAN-LEAF study

S. Ekman[1], M. Planck[2], J.B. Sørensen[3], P. Horvat[4], D. Layton[5], J. Kim[5], M. Rosenlund[5], A. Juarez-Garcia[6], M. Daumont[7], H.C. Jacobs[6], L. Lacoin[7], O.T. Brustugun[8]

[1]Department of Oncology, Karolinska University Hospital-Solna, Stockholm, Sweden, [2]Division of Oncology and Pathology, Skane University Hospital-Lund, Lund, Sweden, [3]Department of Oncology, Rigshospitalet, Copenhagen, Denmark, [4]Real World Evidence Solutions, IQVIA, London, UK, [5]Data Science, IQVIA, London, UK, [6]Worldwide Health Economics & Outcomes Research, Bristol-Myers Squibb, Uxbridge, UK, [7]Worldwide Health Economics & Outcomes Research, Bristol-Myers Squibb, Braine-L'Alleud, Belgium, [8]Department of Oncology, Radiumhospitalet, Oslo, Norway

Background: A better understanding of real-world treatment (tx) patterns and associated clinical outcomes in the rapidly changing landscape of NSCLC is critical for informing clinical decision-making and maximising pt benefits. The SCAN-LEAF project aims to describe epidemiology, clinical care and outcomes of NSCLC pts in Scandinavia. Here, we report tx patterns and outcomes in pts with incident stage IIIB-IV NSCLC in 2 university hospitals in Sweden.

Methods: This retrospective cohort study includes all adult pts diagnosed with stage IIIB-IV NSCLC from 2012–2015, and followed in Uppsala and Stockholm University hospitals (follow-up until end of 2016). Electronic medical records were extracted and linked with national registries. Lines of therapy (LoTs) were defined using an algorithm based on systemic anticancer therapy (SACT). Descriptive results are shown by histology. Ongoing analyses will assess LoTs by mutation status, time to next LoT and overall survival using the Kaplan–Meier method.

Results: 1625 pts diagnosed at stage IIIB-IV were identified (58.5% of all incident NSCLC). Mean age was 69.1 yrs (13.6% ≥80 yrs) and 49.5% were male. Histology distribution was: 70.9% non-squamous cell carcinoma (NSQ), 17.7% squamous-cell carcinoma (SQ), 10.3% not otherwise specified (NOS) and 3.4% other NSCLC. Of 831 EGFR-tested pts (51.1%), 21.2% had mutant EGFR; of 612 ALK-tested pts (37.7%), 10.0% had ALK translocations; of 33 PD-L1-tested pts (2.0%), 45.5% had PD-L1 expression ≥1%. Overall, 888 pts (54.7%) received a 1st LoT, of whom, 276 received a 2nd LoT (31.1%). SACT regimens are shown in the table.

Table: 1484P

SACT regimens in stage IIIB-IV NSCLC (used in ≥ 5 patients)	All NSCLC	NSQ	SQ	NOS
1st line of therapy, %	(N = 888)	(N = 638)	(N = 119)	(N = 99)
Platinum-based chemotherapy	80.3	77.4	88.2	87.9
Non-platinum single agent	5.2	4.4	6.7	6.1
Tyrosine kinase inhibitor (mainly erlotinib)	14.4	18.0	5.0	6.1
2nd line of therapy, %	(N = 276)	(N = 201)	(N = 40)	(N = 24)
Platinum-based chemotherapy	23.6	19.9	30.0	25.0
Non-platinum single agent	56.5	55.7	62.5	66.7
> Docetaxel	39.5	37.3	47.5	54.2
> Pemetrexed	8.7	10.9	2.5	4.2
> Vinorelbine	8.0	7.5	12.5	8.3
Tyrosine kinase inhibitor	19.6	24.4	5.0	8.3
> Erlotinib	8.4	10.0	5.0	0.0
> Crizotinib	6.9	9.5	0.0	0.0
> Afatinib	2.9	3.5	0.0	4.2

Conclusions: During the 2012-2016 period (mainly prior to immunotherapy reimbursement), approximately half of incident stage IIIB-IV pts received a 1st LoT and only one-third of those received a 2nd LoT, mostly with non-platinum chemotherapy or tyrosine kinase inhibitors. Almost half of stage IIIB-IV NSCLC pts remained untreated after diagnosis (no SACT regimen).

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: S. Ekman: Grants: Bristol-Myers Squibb, during the conduct of the study. P. Horvat, D. Layton, J. Kim, M. Rosenlund: Employee: IQVIA. A. Juarez-Garcia: Employee: Bristol-Myers Squibb. H.C. Jacobs: Personal fees: Bristol-Myers Squibb, during the conduct of the study. L. Lacoin: Consultant epidemiologist contracted: Bristol-Myers Squibb for the SCAN-LEAF project. All other authors have declared no conflicts of interest.

1485P NSCLC with well controlled extra-cranial disease but uncontrolled brain metastases

H.A. Jung[1], K. Park[2], J-M. Sun[3], S.H. Lee[4], J.S. Ahn[5], M-J. Ahn[6], S. Park[7]

[1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Div. of Heamatology/Oncology, Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [3]Hematology/Oncology, Samsung Medical Center, Seoul, Republic of Korea, [4]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Seoul, Republic of Korea, [5]Hematology & Oncology, Samsung Medical Center, Seoul, Republic of Korea, [6]Hematology and Oncology, Samsung Medical Center, Seoul, Republic of Korea, [7]Hematology-oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: Brain metastases are currently both common in clinical oncology and a critical problem, since they negatively affect patients' quality of life as well as survival. In the era of targeted therapy, survival for metastatic, recurrent lung cancer has improved. However, improved systemic treatment modalities have led to prolonged disease courses and subsequently to an increased incidence of brain metastases.

Methods: We recruited patients who were diagnosed with non-small cell lung cancer at a Samsung Medical Center from 2008 to 2017. We collected clinical characteristics and treatment pattern by medical chart review and analyzed their mutation status by NGS (ampliseq and cancer scan).

Results: Among 12918 patients who were diagnosed with non-small cell lung cancer and received chemotherapy, 1566 patients received gamma knife surgery and 1209 patients received whole brain radiotherapy. 3922 were EGFR mutant non-small cell lung cancers and received EGFR tyrosine kinase inhibitors (erlotinib: 1424; gefitinib: 2210; afatinib: 606; dacomitinib: 24). Among EGFR-mutant patients, 663 (16.9%) patients received whole brain radiation therap (WBRT) and 765 (19.5%) received gamma-knife surgery. 320 patients who were diagnosed with ALK-positive non-small cell lung cancer received ALK inhibitors (crizotinib: 308; alectinib 54). Among them 51 (15.9%) received WBRT and 81 (25.3%) patients received gamma-knife surgery. 268 patients received gamma-knife surgery three times or more. 51 patients received gamma-knife surgery five times or more (maximum 14 of gamma-knife surgery). Among them, 27 (52.9%) patients were EGFR mutant and 11 (21.6%) patients were ALK-rearrangement non-small cell lung cancer.

Conclusions: In patients with EGFR-mutant or ALK-rearrangement non-small cell lung cancer, local treatment for brain metastasis was performed frequently. A minority of patients have well controlled extracranial disease but poorly controlled intracranial disease, and in these cases strategies to maintain systemic chemotherapy and persistent topical treatments for brain lesions are also helpful. Further research is needed to find out the unique tumor biology of patients with uncontrolled brain metastases.

Legal entity responsible for the study: SMC IRB.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1486P Risk assessment in brain-only oligometastatic non-small cell lung cancer (BOO-NSCLC) patients (pts): Recursive partioning analysis (RPA) model modification

C. Salvador Coloma[1], D. Lorente[2], C. Escoin[3], J.A. Mendez[1], O. Juan-Vidal[4]

[1]Medical Oncology, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [2]Medical Oncologist, HULa Fe, Valencia, Spain, [3]Medical Oncology, Hospital La Ribera, Valencia, Spain, [4]Medical Oncology, Hospital Universitari i Politécnic La Fe, Valencia, Spain

Background: Brain metastases (BM) have traditionally been associated with adverse outcome. BOO-NSCLC, however, may represent a distinct population subtype in whom a radical therapeutic approach may be feasible. We aimed to assess the impact of the RPA group classification in this population subtype.

Methods: Retrospective analysis of pts with BOO-NSCLC (1-5 BMs as only metastatic site) treated between 2010-2018 at a single institution. RPA classification and other clinical variables was derived from electronic patient records. Survival analyses were performed with Kaplan Meier and uni- (UV) and multivariable (MV) Cox-regression models. Performance of the survival models was assessed by ROC AUCs and weighted c-indices.

Results: 67 pts were identified. Median age: 59 years. The majority were men (71.6%) with adenocarcinoma histology (73.1%). Median-overall survival (mOS) was 20.2 months (95CI%:11.5-28.9). RPA group score was significantly associated with OS: not reached (NR) vs 16.2m vs 4.5m for RPA group I, II and III pts respectively (HR: 5.7; 95%CI: 3-10.8; $p < 0.001$). The model based on RPA only had a ROC AUC of 79.6% and a c-index of 0.743. T-stage (T1-2 vs T3-4), N-stage (N0-N1 vs N2-N3) and histology were associated with OS in UV cox-regression models, and were included in the MV model (Table). The addition of these variables to the RPA model increased the ROC AUC to 92.3% ($p = 0.008$) and c-index to 0.854.

Table: 1486P UV and MV Cox-Regression survival analysis

	UNIVARIABLE		MULTIVARIABLE	
	HR (95%CI)	p-value	HR (95%CI)	p-value
RPA Group	5.7 (3-10.8)	<0.001	10 (4.5-22.6)	<0.001
T-Stage	2.8 (1.4-5.7)	0.004	6.2 (2.7-14.7)	<0.001
N-Stage	2.2 (1.1-4.4)	0.031	1.8 (0.8-3.8)	0.134
Histology	1.2 (1.1-1.4)	0.003	1.4 (1.1-1.6)	<0.001

Conclusions: RPA group classification may adequately stratify BOO-NSCLC pts into favorable, intermediate and adverse prognostic groups. The addition of histology, T-stage and N-stage of the primary tumor may improve the prognostic accuracy of the model. These findings require prospective validation.

Legal entity responsible for the study: University Hospital La Fe.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1487P LURET: Final survival results of the phase II trial of vandetanib in patients with advanced RET-rearranged non-small cell lung cancer

K. Yoh[1], T. Seto[2], M. Satouchi[3], M. Nishio[4], N. Yamamoto[5], H. Murakami[6], N. Nogami[7], S. Kuroda[8], S. Nomura[8], A. Sato[8], K. Tsuchihara[9], T. Kohno[10], S. Matsumoto[1], K. Goto[1]

[1]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [2]Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan, [3]Department of Thoracic Oncology, Hyogo Cancer Center, Hyogo, Japan, [4]Thoracic Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [5]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan, [6]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan, [7]Department of Thoracic Oncology, Shikoku Cancer Center, Matsuyama, Japan, [8]Office of Clinical Research Support, Hospital East, National Cancer Center, Kashiwa, Japan, [9]Division of Translational Informatics, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Kashiwa, Japan, [10]Division of Genome Biology, National Cancer Center Research Institute, Tokyo, Japan

Background: The LURET phase II trial evaluated the efficacy and safety of vandetanib in patients with advanced RET-rearranged non-small cell lung cancer (NSCLC). Among eligible patients included in primary analysis, objective response rate (ORR) met the primary endpoint (53% [90% CI 31-74]). Here, we report a final analysis of survival outcomes in LURET.

Methods: In all, 19 patients with advanced RET-rearranged NSCLC continuously received 300 mg of oral vandetanib daily. The variant types of RET fusion included 10 KIF5B-RET, 6 CCDC6-RET, and 3 unknown. The data cutoff date was Aug 31, 2017, for a final analysis. In this final analysis, the data on progression-free survival (PFS), overall survival (OS) and safety were updated.

Results: At the final data cutoff, 1 patient was still receiving vandetanib without disease progression. Among all 19 patients in the intention-to-treat population, median PFS was 6.5 months (95% CI, 2.8-8.5) as determined by the independent radiology review committee. Median OS was 13.5 months (95% CI, 9.8-28.1) and the overall survival rate at 12 months was 52.6% (95% CI 28.7-71.9). In the subgroup analysis according to the type of RET fusion, median PFS and OS were 2.9 months (95% CI 1.1-15.7) and 10.5 months (95% CI 3.0-18.1) in patients with KIF5B-RET whereas 8.4 (95% CI 4.7-not reached [NR]) and NR (95% CI 9.9-NR) in those with CCDC6-RET. No new adverse events were observed compared with previous studies in unselected NSCLC.

Conclusions: Our results found that vandetanib to be effective in patients with advanced RET-rearranged NSCLC, and that RET rearrangement may be a favorable molecular subgroup of NSCLC suitable for targeted therapy.

Clinical trial identification: This study is registered with UMIN-CTR, number UMIN000010095.

Legal entity responsible for the study: National Cancer Center Hospital East.

Funding: Sanofi, AstraZeneca, the Ministry of Health, Labour, and Welfare of Japan and the Practical Research for Innovation Cancer Control from the Japan Agency for Medical Research and Development, AMED.

Disclosure: K. Yoh, T. Seto, M. Satouchi: Research funding and honoraria: AstraZeneca. M. Nishio, H. Murakami: Speakers' bureau, Research funding and honoraria: AstraZeneca. N. Nogami: Research honoraria: AstraZeneca. A. Sato: Speakers' bureau: AstraZeneca. K. Goto: Research funding: AstraZeneca. All other authors have declared no conflicts of interest.

1488P Vemurafenib in patients (pts) harboring BRAF V600 mutation: Results of non-small cell lung cancer (NSCLC) cohort from the AcSé trial

J. Mazières[1], L. Montané[2], F. Barlesi[3], X. Quantin[4], J. Trédaniel[5], J. Le Treut[6], V. Avrillon[7], A. Lavolé[8], V. Westeel[9], F. Orsini Piocelle[10], E. Pichon[11], L. Thiberville[12], C. Borel[13], P.A. Renault[14], M. Jaffro[1], S. Collot[1], G. Ferretti[15], F. Legrand[16], C. Mahier Ait Oukhatar[17], J.Y. Blay[18]

[1]Thoracic Oncology, Hospital Larrey, Toulouse, France, [2]DRCI, Centre Léon Bérard, Lyon, France, [3]Medical Oncology, Hospital Nord, APHM, Marseille, France, [4]Medical Oncology, Hopital Arnaud de Villeneuve, Montpellier, France, [5]Pneumonology, Hospital Group Paris Saint Joseph, Paris, France, [6]Respiratory Diseases, Intercommunal Hospital Center Aix Pertuis, Aix-en-Provence, France, [7]Medical Oncology, Centre Léon Bérard, Lyon, France, [8]Pneumology, Hospital Tenon, APHP, Paris, France, [9]Pneumology, Hospital Jean Minjoz, Besançon, France, [10]Medical Oncology, Hospital Center Annecy Gennevois, Pringy, France, [11]Pneumology, CHRU Bretonneau, Tours, France, [12]Pneumology, Hospital Charles Nicolle, Rouen, France, [13]Medical Oncology, Centre Paul Strauss, Strasbourg, France, [14]Pneumology, Hospital Center, Pau, France, [15]Radiology, Hospital Michallon, Grenoble, France, [16]Biology, Transfert and Innovation Department, Institut National du Cancer, Boulogne-Billancourt, France, [17]Research and Development, UNICANCER, Paris, France, [18]Medical Oncology, Centre Léon Bérard, Lyon, France

Background: BRAF mutations are found in 2-3% of NSCLC. BRAF inhibitors reportedly have antitumor activity. The French National Cancer Institute (INCa) launched a program giving nationwide access to vemurafenib for cancer pts with BRAF-mutated tumors and supporting molecular screening. We report here the results of the NSCLC cohort.

Methods: BRAF mutational status was assessed on INCa molecular genetic centers by direct sequencing or NGS. Pts with BRAF V600E mutation, progressing after $\geq$1 standard treatment were proposed vemurafenib 960 mg BID. Objective Response Rate

(ORR) was assessed using RECIST v1.1 every 8 weeks. A sequential Bayesian approach was planned to allow early stopping using an inefficacy boundary for ORR of 10%. If no early stopping occurred, the treatment was considered worthy for further evaluation if there was a 90% probability that the estimated ORR is ≥ 30%, the efficacy boundary.

Results: From 10/2014 to 10/2017, 101 NSCLC pts harboring BRAF V600E were enrolled. Median age: 68 years (range 41–85), 68% smokers, 50% females, 100% non-squamous histology and 19% with ECOG PS 2. Most frequent grade ≥3 adverse events (AEs) were asthenia (10% of pts), epidermoid carcinoma (7%), dermatitis (6%) and increased GGT (6%). Three toxic deaths were reported: 1 nausea and vomiting leading to dehydration, 1 pneumonia and 1 neutropenic sepsis. Among the enrolled pts, 100 BRAF V600E NSCLC pts evaluable for the best overall response (BOR), 43 PR, 21 SD, 16 PD, 12 deaths before assessment and 8 not evaluable (no tumor assessment) were observed. The mean objective response rate was 44.9% (95% CI: 35.2; 54.8), the efficacy boundary was reached with a predictive probability greater than 90%. Median duration of response was 6.5 months (5.1-7.3). Median progression-free survival (PFS) was 5.2 months (3.8-6.9) and median OS was 9.3 months. Nine pts were still on treatment at the cut-off date, 91 have stopped vemurafenib (55 PD, 23 AEs, 3 deaths, 1 doctor's decision, 9 patient's decisions).

Conclusions: Vemurafenib provided reasonable response rate and prolonged PFS in BRAF V600E pretreated NSCLC. These results confirm the activity of BRAF inhibitors in these pts and underline the need of integrating BRAF V600E in biomarkers routine screening.

Clinical trial identification: NCT02304809.

Legal entity responsible for the study: UNICANCER.

Funding: ARC Foundation French National Cancer Institute (INCa) Roche.

Disclosure: J. Mazières: Ad Board, Research grant: Roche, BMS, Astra Zeneca. F. Barlesi: Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer and Takeda. V. Avrillon: Advisory Board: Roche, BMS. G. Ferretti: Speaker conference: Boehringer, Roche, GEMS. J.Y. Blay: Advisory Board: Roche, Lilly, Ignyta, Deciphera, Novartis, Bayer, BMS; Corporate-sponsored Research: Roche, Lilly, Ignyta, Deciphera, Novartis, Bayer, Novartis, GSK, AstraZeneca, MSD; Other Substantive Relationships: Surveillance committee of Innate Pharma. All other authors have declared no conflicts of interest.

1489P Treatment patterns and overall survival in patients with BRAF-mutated metastatic non-small cell lung cancer

R.K. Goyal[1], A. Kron[2], J. Wolf[2], J. Mazieres[3], C. Chouaid[4], K.L. Davis[5], M. Perrinjaquet[6], S. Knoll[7]

[1]Health Economics, RTI Health Solutions, Research Triangle Park, NC, USA, [2]Center for Integrated Oncology Cologne Bonn, University Hospital Cologne, Kerpener, Germany, [3]Thoracic Oncology, Hospital Larrey, Toulouse, France, [4]Chest Department, Centre Hospitalier Intercommunal Créteil, Créteil, France, [5]Health Economics, RTI Health Solutions, Research Triangle Park, NC, USA, [6]Life Sciences, Navigant, London, UK, [7]Global Oncology Value and Access (GVA), Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Background: BRAF mutations are observed in 2% – 4% of all non-small cell lung cancer (NSCLC) patients, but few targeted therapies are available, with limited practice level data on utilization and outcomes. This study therefore aims to document, from a "real-world" perspective, treatment patterns, testing characteristics, and overall survival (OS) in patients with BRAF-positive (BRAF+) metastatic NSCLC (mNSCLC).

Methods: This was a multinational, retrospective medical record review of patients with BRAF+ mNSCLC (diagnosed 2005-2016) in EU, Canada and S Korea. Patients were ≥18 years of age at mNSCLC diagnosis ("index") and had ≥12 months of post-index follow-up time, except for patients who died sooner. Study measures included baseline patient characteristics, timing of mutational testing, systemic therapies for mNSCLC, and OS. Kaplan-Meier analyses were conducted to descriptively analyze OS dependent on treatment with a BRAF inhibitor (BRAFi).

Results: Of all patients (n = 76; median age = 64 years), 24% had been tested for BRAF mutation at index; 61% had been tested before initiating the first line of therapy (LOT-1), 79% before LOT-2 and 85% before LOT-3. Chemotherapy was the most common first (76%), second (46%), and third (38%) LOT. BRAFi (+/- a MEK inhibitor) was received by 53% of all patients initiating a systemic therapy (n = 66) in any LOT. Median OS from index was 19.4 months (95% CI = 13.3-22.8) in all patients, 23.4 months (95% CI = 18.5-98.4) in patients treated with BRAFi, and 11.8 months (95% CI = 4.5-20.0) in patients not treated with BRAFi, in any LOT. Three-year OS rates from LOT initiation are summarized in the table.

Conclusions: The majority of confirmed BRAF+ mNSCLC patients were tested for BRAF mutation before initiation of LOT-1. Chemotherapy was the predominant front-line therapy and BRAFi was utilized mainly in second and later LOTs. Median OS was numerically higher in patients treated with BRAFi versus patients not treated with BRAFi in any LOT.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: R.K. Goyal: Employee: RTI Health Solutions, which has received contract research funding in the past 2 years from the following companies for which author has or currently has conducting health outcomes research projects: Novartis, Pfizer, AstraZeneca, Eli Lilly and Company, and Amgen. J. Wolf: Consulting or advisory role to disclose: Abbvie, AstraZeneca, BMS, Boehringer-Ingelheim, Chugai, Ignyta, Lilly, MSD, Novartis, Pfizer, Roche; Research funding: BMS, MSD, Novartis, Pfizer; Travel, accommodations, or expenses: Abbvie, AstraZeneca, BMS, Boehringer-Ingelheim, Chugai, Ignyta, Lilly, MSD, Novartis, Pfizer, Roche. J. Mazieres: Consulting or advisory role: AstraZeneca, Roche, BMS, MSD, Novartis, Pfizer; Research funding: AstraZeneca, Roche, BMS; Travel, accommodations, or expenses: Roche, BMS, Novartis, Pfizer. C. Chouaid: Honoraria: AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, BMS, MSD, Lilly, Novartis and Amgen; Consulting or advisory role: AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, BMS, MSD, Lilly, Novartis and Amgen; Research funding: AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, BMS, MSD, Lilly, Novartis and Amgen; Travel, accommodations, or expenses: AstraZeneca, Boehringer Ingelheim, Roche, BMS, MSD, Lilly. K.L. Davis: Employee: RTI Health Solutions, which has received contract research funding in the past 2 years from the following companies for which I have (or currently are) conducting health outcomes research projects: Novartis, Pfizer, AstraZeneca, Shire, Eli Lilly and Company, Takeda, Celgene. S. Knoll: Stock or other ownership: Novartis, GSK, Roche, Merck KGA, Gilead, Incyte. All other authors have declared no conflicts of interest.

1490P A prospective observational study of HER2 alterations in NSCLCs: HOT1303-A

T. Goda1, I. Kinoshita[1], S. Oizumi[2], K. Nakano2, T. Harada[3], Y. Kawai[4], J. Sakakibara-Konishi5, H. Yokouchi[6], N. Morikawa[7], N. Yamada[8], S. Yamazaki[9], S. Sugawara[10], H. Asahina[5], T. Amano[11], Y. Hatanaka[12], Y. Matsuno[13], H. Nishihara[14], H. Isobe[15], M. Nishimura[16], H. Dosaka-Akita[1]

[1]Department of Medical Oncology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan, [2]Department of Respiratory Medicine, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan, [3]Department of Pulmonary Medicine, JCHO Hokkaido Hospital, Sapporo, Japan, [4]Department of Respiratory Medicine, Oji General Hospital, Tomakomai, Japan, [5]First Department of Medicine, Hokkaido University, Sapporo, Japan, [6]Department of Pulmonary Medicine, Fukushima Medical University, Fukushima, Japan, [7]Division of Pulmonary Medicine, Allergy and Rheumatology, Iwate Medical University School of Medicine, Morioka, Japan, [8]Department of Respiratory Medicine, Iwamizawa Municipal General Hospital, Iwamizawa, Japan, [9]Department of Thoracic Surgery, Keiyukai Sapporo Hospital, Sapporo, Japan, [10]Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Miyagi, Japan, [11]Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan, [12]Research Division of Genome Companion Diagnostics, Hokkaido University Hospital, Sapporo, Japan, [13]Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan, [14]Genomics Unit, Keio Cancer Center, Keio University School of Medicine, Sapporo, Japan, [15]Department of Medical Oncology, KKR Sapporo Medical Center, Sapporo, Japan, [16]Department of Respiratory Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Background: About 5% of NSCLCs have overexpression and amplification of HER2 or its mutations, mostly exon 20 insertions. There are still few data available on roles of HER2 alterations in NSCLCs.

Methods: To determine the frequency and characteristics of HER2 alterations in NSCLCs and to identify patients (pts) eligible for clinical trial of trastuzumab (HOT1303-B), we conducted a prospective observational study of HER2 alterations in pts with advanced NSCLCs without EGFR or ALK mutations. We determined HER2 overexpression by IHC, amplification by dual color in situ hybridization (DISH), and mutation of exons 8, 19, 20 and 21 by direct sequence and that of all the exons by NGS. We also analyzed 48 cancer-related genes by NGS using targeted sequencing kits.

Table: 1489P OS rate from start of LOTs

	LOT-1		LOT-2		LOT-3	
	BRAFi (n = 34)	No BRAFi (n = 28)	BRAFi (n = 28)	No BRAFi (n = 16)	BRAFi (n = 18)	No BRAFi (n = 13)
3-year OS rate (standard error)	33.9% (0.09)	17.1% (0.09)	37.5% (0.10)	22.9% (0.12)	49.5% (0.13)	9.0% (0.09)

Results: Until completion of enrollment of HOT1303-B, 129 eligible pts with advanced NSCLCs including 108 adenocarcinoma pts were enrolled to this study. IHC3+ was observed in 6 pts (4.6%), all of whom showed DISH+. IHC2+/DISH+ were also observed in 6 pts (4.6%). Hotspot mutations (5 exon 20 YVMA insertions and 2 S310F mutations) were detected in 7 pts (5.4%), and non-hotspot mutations including a previously unknown L755_N758delinsPST mutation were detected in 12 pts (9.3%). Amplifications and hotspot mutations were mutually exclusive except a case with IHC2+/DISH+ and S310F. When we defined amplifications and hotspot mutations narrowly as HER2 alterations (18 pts, 14%), they correlated with smoking inversely ($p = 0.03$), but not with age, sex, chemotherapy response or overall survival from 1st line therapy. The 48 gene NGS analysis was conducted in 91 pts. Number of mutated genes per pt (median, 2; range, 0-23) did not correlate with HER2 alterations. The most frequently mutated gene was TP53, mutations of which tended to correlate with HER2 alterations (11/14, 79% vs. 41/77, 53%; $p = 0.08$). Although there were no genes mutations of which were significantly associated with HER2 alterations, HER2 altered tumors had no oncogenic driver mutations including K-RAS and B-RAF.

Conclusions: HER2 alterations were relatively frequently observed. Hotspot mutations and amplifications were almost mutually exclusive and tended to be associated with TP53 mutations. Precise roles of distinct HER2 alterations should be determined in larger cohorts.

Clinical trial identification: UMIN000012552.

Legal entity responsible for the study: Hirotoshi Dosaka-Akita.

Funding: Ministry of Health, Labor and Welfare, Japan.

Disclosure: I. Kinoshita: Honoraria: Chugai Pharma, Novartis. S. Oizumi: Honoraria: AstraZeneca Japan, Lilly Japan. Research funding from Kyowa Hakko Kirin, Pfizer, BMS UK, ONO Pharmaceutial. T. Harada: Honoraria: Taiho Pharmaceutical, AstraZeneca KK, Boehringer Ingelheim, Hisamitu Pharmaceutical. S. Sugawara: Honoraria: AstraZeneca, Chugai Pharma, Nippon Boehringer Ingelheim, Taiho Pharmaceutical, Pfizer, Eli Lilly and Campany, Novartis, Kyowa Hakko Kirin, Bristol-Myers Squibb, Ono Pharmaceutical, MSD K.K. Y. Hatanaka: Advisory Role: GeneticLab, Medicinal Cheistry Pharmaceutical Co.; Speakers' Bureau: Merck Sharp & Dohme, Chugai Pharma, Pfizer; Honoraria: Ono Pharmaceutical, AstraZeneca KK; Research fuding: Roche, Taiho Pharmaceutical, Eisai, Merck Sharp & Dohme. H. Isobe: Speakers' Bureau: Chugai Pharma, Bristol-Myers Squibb Japan, Pfizer. All other authors have declared no conflicts of interest.

1491P A phase II study of trastuzumab monotherapy in pretreated patients with non-small cell lung cancers (NSCLCs) harboring HER2 alterations: HOT1303-B trial

I. Kinoshita[1], T. Goda[1], K. Watanabe[2], M. Maemondo[3], S. Oizumi[4], T. Amano[5], Y. Hatanaka[6], Y. Matsuno[7], H. Nishihara[8], H. Asahina[9], T. Harada[10], K. Goto[11], H. Isobe[12], M. Nishimura[13], H. Dosaka-Akita[1]

[1]Department of Medical Oncology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan, [2]Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan, [3]Division of Respiratory Medicine, Allergy, and Rheumatology., Iwate Medical University School of Medicine, Morioka, Japan, [4]Department of Respiratory Medicine, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan, [5]Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan, [6]Research Division of Genome Companion Diagnostics, Hokkaido University Hospital, Sapporo, Japan, [7]Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan, [8]Genomics Unit, Keio Cancer Center, Keio University School of Medicine, Sapporo, Japan, [9]First Department of Medicine, Hokkaido University Hospital, Sapporo, Japan, [10]Department of Respiratory Medicine, JCHO Hokkaido Hospital, Sapporo, Japan, [11]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [12]Department of Medical Oncology, KKR Sapporo Medical Center, Sapporo, Japan, [13]Department of Respiratory Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Background: About 5% of NSCLCs have high level of overexpression and/or amplification of HER2 or its mutations, mostly exon 20 insertions. Retrospective studies suggest some activity of a Her2-targeted antibody, trastuzumab, for HER2-altered NSCLCs. However, no clinical trial data of trastuzumab monotherapy for HER2-altered NSCLCs are available so far.

Methods: HOT1303-B was a multicenter, single-arm phase II study of trastuzumab for NSCLC patients who were pretreated with two or more regimens and had HER2-altered tumors (IHC 3+ or IHC 2+/dual color in situ hybridization [DISH] +, and/or presence of mutations) identified by a HER2 screening study HOT1303-A and a nationwide genomic screening study LC-SCRUM-Japan. Eligible patients (pts) were treated with trastuzumab 6 mg/kg every 3 weeks (loading dose 8 mg/kg). The primary endpoint was the overall response rate (ORR) using RECIST v1.1. This study required ten pts, with ORR of 10% considered non-promising and 40% promising (one-sided alpha = 0.10; beta = 0.2).

Results: Ten pts were recruited in this trial. The median age was 59 (range 44-74), three pts were female, three pts were never smokers, nine pts had performance status 0-1, and all had adenocarcinomas. The median lines of prior systemic therapy were 3 (range 2-6). There were two pts with IHC 3+, one pt with IHC 2+/DISH +, five pts with exon 20 insertions (four A755_G776insYVMA and one G776>VC) and two pts with S310F mutations without overlapping cases. ORR was 0% (95% CI, 0-26%). Disease control ratio (DCR) was 70% (95% CI, 39-91%). Median progression-free survival was 5.2 months (95% CI, 1.4-6.3). Grade ≥ 3 adverse events occurred only in a patient with grade 3 pneumonitis, which was judged as organizing pneumonia related with tumor progression. OS data will be presented at the meeting.

Conclusions: Trastuzumab monotherapy did not produce response for HER2-altered NSCLCs in this cohort, although DCR and PFS seemed favorable for the heavily treated pts. Additional approaches including combination therapy are required for HER2-targeted therapy using trastuzumab.

Clinical trial identification: UMIN000012551.

Legal entity responsible for the study: Hirotoshi Dosaka-Akita.

Funding: Ministry of Health, Labor and Welfare, Japan.

Disclosure: I. Kinoshita: Honoraria: Chugai Phama, Novartis. M. Maemondo: Advisory role: Chugai Pharma, AstraZeneca, Boehringer Ingelheim, MSD, Bristol-Myers Squibb Japan, Ono Pharmaceutical, Pfizer, Novartis, Taiho Pharmaceutical, Lilly Japan; Research funding: Boehringer Ingelheim, Chugai Pharma, AstraZeneca, Novartis, Sanofi, MSD, Lilly Japan. S. Oizumi: Honoraria: AstraZeneca Japan, Lilly Japan; Research funding: Kyowa Hakko Kirin, Pfizer, BMS UK, Ono Pharmaceuticals. Y. Hatanaka: Advisory role: GeneticLab, Medicinal Chemistry Pharmaceutical Co.; Speakers' bureau: Merck Sharp & Dohme, Chugai Pharma, Pfizer; Honoraria: Ono Pharmaceutical, AstraZeneca KK.; Research funding: Roche, Taiho Pharmaceutical, Eisai, Merck Sharp & Dohme. T. Harada: Honoraria: Taiho Pharmaceutical, AstraZenea KK, Boehringer Ingelheim, Hisamitsu Pharmaceutical. K. Goto: Advisory role: Otsuka; Honoraria: Daiichi Sankyo, Bristol-Myers Squibb, AstraZeneca, Pfizer, Chugai Pharma, Taiho Pharmaceutical, Ono Pharmaceutical, Ono Pharmaceutical, Novartis, Lilly, Boehringer Ingelheim, Quintiles, Merck Serono, SRL Diagnostics, Life Technologies, F. Hoffmann La Roche AG, MSD, AbbVie, RIKEN GENESIS, Nippon Kayaku; Research funding: MSD, AstraZeneca, Taiho Pharmaceutical, Chugai Pharma, Boehringer Ingelhiem, Ono Pharmaceutical, OxOnc, Sumitomo Dainippon, Takeda, Novartis, Daiichi Sankyo, Kyowa Hakko Kirin, Astellas Pharma, Eisai, Lilly, Pfizer, Riken Genesisi, Bristol-Myers Squibb, Merck Serono, Abbvie, Ignyta. H. Isobe: Speakers' Bureau: Chugai Pharma, Bristol-Myers Squibb Japan, Pfizer. All other authors have declared no conflicts of interest.

1492P BPI-9016M, a novel c-Met inhibitor, in pretreated advanced solid tumor: Results from a first-in-human, phase I, dose-escalation study

X. Hu[1], X. Zheng[2], H. Mo[1], X. Cui[2], L. Ding[3], F. Tan[4], P. Hu[2], Y. Shi[1]

[1]Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China, [2]Clinical Pharmacology Research Center, Peking Union Medical College Hospital, Beijing, China, [3]Headquarter, Bettapharma Pharmaceuticals Co.Ltd, Hangzhou, China, [4]R&D center, Bettapharma Pharmaceuticals Co.Ltd, Beijing, China

Background: BPI-9016M (Betta Pharmaceuticals Co, Ltd, Hangzhou, China) is a potent targeted therapy that inhibits MET and Axl. This first-in-human study is to assess the safety, tolerability, and pharmacokinetics (PK) of BPI-9016M in patients with advanced solid tumor, and to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for the phase Ib/II study.

Methods: Method: Eligible patients were enrolled into sequential dose-escalating cohorts from 100 mg to 1000 mg given orally once per day continually following the conventional 3 + 3 design. The primary endpoint was safety and tolerability. MTD was defined as the highest dose level resulting in < 1 of 3 dose limiting toxicities (DLTs). Blood levels of BPI-9016M were evaluated after single and multiple administration (NCT02478866).

Results: Twenty patients were enrolled and treated in 6 of 7 predefined dose cohorts (100 mg n = 4, 200 mg n = 3, 300 mg n = 3, 450 mg n = 4, 600 mg n = 3, 800 mg n = 3), dose escalation stopped at 800 mg due to saturation. All had stage IV non-small cell lung cancer (NSCLC) progressed on previous systemic therapy (including previous EGFR TKI in 16 patients). BPI-9016M was well-tolerated in all dose cohorts without DLT. The incidence of overall and grade 3/4 TRAEs was 85% and 45%, respectively. Common TRAEs included elevated ALT (45%), constipation (30%), elevated bilirubin (25%), and oral paresthesia (25%). Tumor response was seen in 1 patients in the 800 mg dose cohort. Systemic exposure to BPI-9016M (maximum plasma concentration and AUC) increased with increasing dose. Mean time to maximum plasma concentration and half-life were 2 to 5.33 hours and 8.09 to 22.3 hours, respectively. Two metabolites (M1, M2-2) were detected.

Conclusions: BPI-9016M was well tolerated in patients with advanced solid tumor. A phase Ib study is ongoing to investigate the safety and activity of BPI-9016M in patients with c-Met-dysregulated advanced NSCLC (NCT02929290).

Clinical trial identification: NCT02478866.

Legal entity responsible for the study: Bettapharma Pharmaceuticals Co.Ltd.

Funding: Bettapharma Pharmaceuticals Co.Ltd.

Disclosure: L. Ding: Stock owner, leadership, and full-time employee: Bettapharma Pharmaceuticals Co. Ltd. F. Tan: Stock owner: Bettapharma Pharmaceuticals Co. Ltd. All other authors have declared no conflicts of interest.

1493P Clinical characteristics and outcomes of non-small cell lung cancer (NSCLC) patients harboring MET exon 14 splice sites mutations

P. JAMME[1], F. Escande[2], C. Descarpentries[2], M.C. Copin[2], E. Dansin[3], T. Vanparis[4], D. Tulasne[5], S. Baldacci[6], Z. Kherrouche[1], A. Cortot[6]

[1]Institut Pasteur de Lille, Lille, France, [2]Haut de France, Centre Biologie et Pathologie, CHRU Lille, Lille, France, [3] Centre Oscar Lambret, Lille, France, [4]Centre Hospitalier de Boulogne-sur-Mer, Boulogne-sur-Mer, France, [5]Institut Pasteur de Lille, Lille, France, [6]Hopital Calmette, CHRU Lille, Lille, France

Background: MET exon 14 splice sites mutations define a unique subset of NSCLC patients who may benefit from MET inhibitors. Patterns of disease spread and response to chemotherapy in these patients are still poorly known.

Methods: Clinicopathologic characteristics and outcome of patients harboring MET exon 14 splice sites mutations identified in a single molecular center were retrospectively collected.

Results: We identified 39 patients from 12 french institutions between July 2009 and February 2018. Median age was 75 (range 55-91), sex ratio was 1.16 (M/W), 15 patients (38%) were never smokers. histologic type was adenocarcinoma in 31 tumors (79%) pulmonary sarcomatoid carcinoma in 3 tumors (8%) and NOS NSCLC in 5 tumors (13%). MET exon 14 alterations were deletions in 21 patients (54%), point mutations in 14 patients (36%) and delins in 4 patients (10%). Ten patients had a concurrent TP53 mutation, 3 patients had a RAS mutation, and 1 patient had a PIK3CA mutation. Among the 14 patients tested for PDL1 expression, 9 (64%) were PDL1 high ($\geq$50%). The disease was diagnosed at stage IIIB/IV in 24 patients (62%) . Among those, the most frequent metastatic sites at diagnosis were bones (61%), lung (43%), pleura (39%) and brain (13%). 17 patients received at least one line of chemotherapy. Objective response rate for 1st line chemotherapy was 44%. Anti-PD1 agent was initiated in 6 patients, 1 patient (16%) achieved an objective response. MET TKI was initiated in 7 patients. Median overall survival for stage IIIB/IV patients was 8.5 months.

Conclusions: NSCLC patients harboring a MET exon 14 splice sites mutation are characterized by older age, never smoking status in half of the cases, and metastatic spread to bones. Future efforts should focus on identifying predictive markers of response to MET TKIs.

Legal entity responsible for the study: Alexis Cortot.

Funding: Has not received any funding.

Disclosure: P. Jamme: Travel, Accommodations, Expenses: Chugai Pharma; Consulting: Boehringer Ingelheim International. C. Descarpentries: Personal fees: Roche, AstraZeneca and Boehringer. E. Dansin: Honoraria: BMS, MSD, AstraZeneca, Lilly and Roche (research support 2014). S. Baldacci: Personal fees: Lilly, GSK, Pfizer, Roche for activities outside the written work. A. Cortot: Travel, Accommodations, Expenses: AstraZeneca, Pfizer, Roche; Consulting for Boehringer Ingelheim International, Pfizer, Roche, MSD, AstraZeneca; Honoraria: Takeda, BMS; Research funding: Merck, Novartis. All other authors have declared no conflicts of interest.

1494P Risk of lung cancer following pulmonary tuberculosis: A nationwide population-based cohort study, South Korea

S-S. Han[1], J. Heo[2], S-J. Lee[1]

[1]Internal Medicine, Kangwon National University, Chuncheon, Republic of Korea, [2]Internal Medicine, Kangwon National University Hospital, Chuncheon, Republic of Korea

Background: Some epidemiologic studies on lung cancer have reported findings that suggest the possibility of association between lung disease and lung cancer. The association of pulmonary tuberculosis (TB) and lung cancer has attracted attention for several years and has remained controversial. Therefore, we investigated that the relationship between pulmonary TB and lung cancer by considering the time of TB diagnosis in this study.

Methods: This study was used the National Health Insurance Service – National Sample Cohort in South Korea. Patients with pulmonary TB diagnostic codes and treated with anti-tuberculosis in adults over 20 years of age were defined as pulmonary TB patients. It was monitored the incidence of lung cancer after diagnosis of active pulmonary TB. We compared 3,776 patients with pulmonary TB and 18,880 controls matched for sex and age from 2003 to 2013. Multivariate Cox proportional hazard model was used to calculate the adjusted hazard ratio of lung cancer after adjusting for sex, age, house income, smoking status. The incidences of lung cancer were compared according to duration time after TB infection by calculating the incidence rates ratio (IRR).

Results: During the study period, 194 patients were diagnosed with lung cancer. A total of 86 lung cancer patients were diagnosed in 3,776 pulmonary TB patients and 108 patients were diagnosed in 18,880 control group. The IRR in TB group was the higher at 12.26 within 1 year and 3.33 at 1 year to less than 4 years after TB infection compared with the control group. There was a higher risk of lung cancer in pulmonary TB patients compared to control group (HR, 4.18; 95% CI, 3.15-5.56). The risk of lung cancer after pulmonary TB was HR 9.85 (95% CI, 4.57-21.23), 7.14 (95% CI, 3.63-14.05), 3.32 (95% CI, 2.12-5.19) and 2.57(95% CI, 1.40-4.72) respectively under 50s, 50s, 60s and 70s above. As the age increased, HR of lung cancer decreased after diagnosis of pulmonary TB, gradually.

Conclusions: Pulmonary tuberculosis is a risk factor for lung cancer. In patients with pulmonary TB, it may be considered the co-existence of lung cancer and be necessary to carefully observe the occurrence of lung cancer for a certain period of time after diagnosis of pulmonary TB, especially in younger patients.

Legal entity responsible for the study: Seon-Sook Han.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1495P Analysis of the relationship between heading N / L and survival in patients treated with immunotherapy in lung cancer

N. De Dios Alvare, M. Costa Rivas, S. Agraso Busto, A. Alonso Herrero, M.J. Villanueva Silva, D. Pereiro Corbacho, C. García Benito

Oncology, Hospital Universitario Alvaro Cunqueiro, Vigo, Spain

Background: The neutrophil-lymphocyte (N / L) ratio is a marker of general immune response in different stress situations, having shown a relationship between the quotient and the evolution of patients treated with immunotherapy (IT), emphasizing the importance of inflammation in these patients.

Methods: In order to evaluate this relationship in a context of usual clinical practice, a retrospective review of patients with pulmonary neoplasia who received IT treatment in the first line or successive, between November 2015 and December 2017. Data were collected from the clinical history, with attention to baseline neutrophil and lymphocyte numbers, objective response by criteria iRECIST 1.1 and overall survival (OS) defined from the beginning of treatment until death.

Results: Sixty-six patients (22 women and 44 men) with a mean age of 64 years (44-78) were analyzed. 9.1%, 9 patients (p) received immunotherapy as first line treatment, 69.7% (46p) received it as 2nd line and 21.2% (14p) as 3rd line treatment. Regarding the type of IT, 49p (74.2%) received treatment with Nivolumab and 17p (25.8%) were treated with Pembrolizumab. Two stretches of baseline N / L ratios $<=5$ (low) and>5 (high) were defined. Low ratio N / L ($<=5$) was identified in 47p (71.2%) of the patients treated with IT and high ratio N/L (>5) in 19p (20.8%). Of the 47 patients with a low ratio: 22p (46.8%) had some type of response or stabilization of their disease, 15p (31.9%) had progression and 10p (21.3%) received less than months of treatment, 5p for PS reorientation and the other 5p continue with the treatment and are pending reevaluation. Among the 19p patients with high N / L quotient: 4p (21.1%) presented response or stabilization of the disease, 15p (78.9%) presented progression or treatment was interrupted due to deterioration of the ECOG. The average survival in the group with a low N / L ratio ($<=5$) was 87.85 weeks compared to the group with a high N / L ratio (>5) 25.74 weeks ($p<0.05$).

Conclusions: The N / L ratio has been identified in some studies as an adverse prognostic factor in patients treated with IT. Our data from the usual clinical practice support this theory. If these findings are confirmed in future studies, it could be used as a response biomarker for better patient selection.

Legal entity responsible for the study: Fundación Biomédica Galicia Sur.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1496P Intracranial activity of ensartinib in patients with anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer (NSCLC)

H. Wakelee[1], K.L. Reckamp[2], T.A. Leal[3], S.P. Patel[4], G. Blumenschein[5], E. Shum[6], J. Nieva[7], G. Oxnard[8], R.E. Sanborn[9], S. Waqar[10], K. Zeman[11], G. Dukart[12], K. Harrow[13], C. Liang[14], A. Holzhausen[15], L. Horn[16]

[1]Medicine/Oncology, Stanford Advanced Medicine Center, Stanford, CA, USA, [2]City of Hope, Duarte, CA, USA, [3]Medical Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA, [4]Medicine, UC San Diego Moores Cancer Center, La Jolla, CA, USA, [5]Thoracic/Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [6]Medical Oncology, New York University, New York, NY, USA, [7]Clinical Medicine, University of California, San Diego, San Diego, CA, USA, [8]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [9]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA, [10]Washington University Medical School, St. Louis, MO, USA, [11]Medical Oncology, Walter Reed National Military Medical Center, Bathesda, MD, USA, [12]Xcovery Holdings, Inc., Palm Beach Gardens, USA, [13]Clinical Operations, Xcovery Holding Company, LLC, Palm Beach Gardens, FL, USA, [14]CSO, Xcovery Holdings, Inc., Palm Beach Gardens, FL, USA, [15]Xcovery Holdings, Inc., Palm Beach Gardens, FL, USA, [16]Vanderbilt Ingram Cancer Center, Nashville, TN, USA

Background: Ensartinib is a potent ALK small molecule tyrosine kinase inhibitor (TKI). It has shown efficacy in intracranial tumor models. The activity of ensartinib is being evaluated in an ongoing phase 2 study of ALK positive NSCLC patients (pts). As progression due to growth of pre-existing brain metastases (BrM) or development of new BrM is a common mechanism of treatment resistance, we examined the clinical intracranial activity of ensartinib in pts with known BrM (target and/or non-target) at baseline or subsequent central nervous system (CNS) progression.

Methods: Pts who were either ALK TKI naïve (1st line), had received prior crizotinib and no other ALK TKI (2nd line), or had received prior crizotinib and a 2nd generation ALK TKI (3rd line) received ensartinib 225mg QD until disease progression (PD),

unacceptable toxicity or investigator discretion. Tumor assessments were performed locally every 8 weeks. Pts with asymptomatic BrM at baseline were allowed to enroll. To be considered a CNS target lesion, it had to be > 3 mm in diameter and, if previously treated, must have been at least 4 weeks post whole brain radiation therapy with demonstrated tumor growth and may not have been treated by stereotactic radiosurgery.

Results: As of the data cut-off (May 1, 2018), 77 ALK evaluable pts (ALK+ NSCLC pts at > 200mg QD with a post baseline response assessment) were assessed. Overall, 23 pts (30%) had BrM progression (new or existing lesions). For 41 pts who had no BrM at baseline and received ensartinib as 1st line (10 pts), 2nd line (18 pts) or 3rd line (13 pts), only 2 pts (5%) progressed due to the development of BrM. For 36 pts who had BrM at baseline (5 as 1st line, 19 as 2nd line, 12 as 3rd line), 21 pts (58 %) had BrM progression, some at the time of systemic progression. For patients with baseline CNS target lesions, the CNS objective response rate was 100% (n = 3) for 1st line pts, 54% (n = 13) for 2nd line pts, and 33% (n = 3) for 3rd line pts; with a CNS disease control rate of 100% for all pts. Complete CNS responses were observed in 3 pts with target CNS lesions and in 3 pts with only non-target lesions.

Conclusions: The data indicate that ensartinib has promising CNS activity.

Clinical trial identification: NCT01625234.

Legal entity responsible for the study: Xcovery Holdings, Inc.

Funding: Has not received any funding.

Disclosure: H. Wakelee: Research support: Pfizer, Novartis, Xcovery. K.L. Reckamp: Research funds to institution: Xcovery; Consultant and research funds to institution: Ariad. T.A. Leal: Consultant: Takeda, AstraZeneca, Novartis, AbbVie, BMS. G. Blumenschein: Consultant: BMS, Bayer, Clovis, Merck, Celgene, AbbVie, Novartis; Research support: Xcovery, AstraZeneca. E. Shum: Consulting work: Boehringer Ingelheim. J. Nieva: Research support: Merck; Consultant: Genentech and AstraZeneca; Shareholder: Epic Sciences. G. Oxnard: Consulting: Takeda and Ignyta. R.E. Sanborn: Institutional support: Bristol-Meyers Squibb and Medimmune; Research support: Merck (investigator-initiated trial); Advisory boards: Peregrine Pharmaceuticals, Seattle Genetics; travel to research related meetings: Bristol-Meyers Squibb, Five Prime Therapeutics. G. Dukart, K. Harrow, C. Liang, A. Holzhausen: Full time employee and stock options: Xcovery Holdings, Inc. L. Horn: Consulting: Xcovery Holding Company, BMS, BI, Abbvie, Genentech, Merck. All other authors have declared no conflicts of interest.

1497P JNJ-61186372 (JNJ-372), an EGFR-cMET bispecific antibody, in advanced non-small cell lung cancer (NSCLC): An update on phase I results

B.C. Cho[1], J-S. Lee[2], J-Y. Han[3], E.K. Cho[4], E. Haura[5], K.H. Lee[6], J. Bauml[7], R.E. Sanborn[8], M. Curtis[9], E. Attiyeh[9], N. Haddish-Berhane[9], K. Bae[9], R. Knoblauch[9], L. Sherman[9], M.V. Lorenzi[9], K. Park[10]

[1]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Department of Internal Medicine, Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea, [3]Center for Lung Cancer, National Cancer Center, Goyang, Republic of Korea, [4]Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea, [5]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA, [6]Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Republic of Korea, [7]Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA, [8]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA, [9]Clinical Oncology, Janssen Research & Development, Raritan, NJ, USA, [10]Department of Medicine, Samsung Medical Center, Seoul, Republic of Korea

Background: JNJ-372 has demonstrated activity in EGFR and cMET-driven tumor models. In an ongoing phase 1 study of JNJ-372 in patients (pts) with advanced NSCLC, 1050 mg was identified as a recommended phase 2 dose in dose escalation (Part 1) and is being explored in the dose expansion of pts with EGFR-mutated (mut) NSCLC (Part 2).

Methods: Pts were treated with JNJ-372 IV weekly x 4W for cycle 1, then biweekly thereafter. Pharmacokinetic (PK) sampling was taken at multiple time points for all pts in Part 1 and for the first 6 pts in Part 2. Disease evaluations were performed every 8 weeks. Tumors were characterized at baseline through next-generation sequencing of ctDNA and/or tumor tissue.

Results: As of April 13th, 2018, 55 pts received JNJ-372 in Part 1 (n = 30) or Part 2 (n = 25), with 21 pts (38%) continuing therapy. Median age was 63y, 40% were male, 96% were Asian, and median prior systemic therapies was 2. The most frequent (≥15%) adverse events (AEs) were infusion-related reaction (56%), rash/acneiform dermatitis (53%), dyspnea (20%), paronychia (24%), nausea (22%), constipation (18%), stomatitis (18%), decreased appetite (18%), pruritus (16%), fatigue (16%), and peripheral edema (16%). AEs were mostly grade 1-2, with 3 ≥grade 3 treatment-related AEs (myalgia, neutropenia, and peripheral edema, all grade 3). PK was linear and dose proportional at doses ≥350 mg, with faster clearance PK at the 140-mg dose. Of the 30 response-evaluable pts with EGFRmut disease, treated at doses ≥700 mg, there are 8 partial responses (PRs; 4 confirmed PRs). This includes 6 pts with L858R or Exon19del primary mutations, and acquired resistance to first and/or third-generation EGFR tyrosine kinase inhibitors (TKIs), and 2 pts with primary Exon20ins disease. Activity was also observed in 2 pts with EGFRwt disease (squamous cell carcinoma and pleomorphic adenocarcinoma), each with -20% change in sum of largest diameter. The longest duration of treatment was 13.6 months.

Conclusions: JNJ-372 is a novel EGFR-cMET bispecific antibody with a manageable safety profile consistent with EGFR and cMET inhibition. Preliminary evidence suggests JNJ-372 can have activity in EGFR-driven NSCLC, including pts resistant to EGFR TKIs.

Clinical trial identification: NCT02609776 First posted: November 20, 2015.

Editorial acknowledgement: Writing support was provided by Tracy T. Cao, PhD of Janssen Global Services, LLC. and funded by Janssen Global Services, LLC.

Legal entity responsible for the study: Janssen Research & Development.

Funding: Janssen Research & Development.

Disclosure: B.C. Cho: Research funding: Janssen, Novartis, AstraZeneca, Yuhan, Champions Oncology, Abbvie, Dong-A ST, Ono, MOGAM; Honoraria: AstraZeneca, Novartis, MSD, Ono, Roche; Consulting or Advisory role: Janssen, AstraZeneca, Novartis, MSD, Roche, Yuhan; Speakers' bureau: Novartis J-Y. Han: Research funding: Roche. E. Haura: Research funding: Lilly, Novartis, Boehringer Ingelheim, Janssen, Ignyta, Forma Therapeutics; Consulting or Advisory role: Janssen; Patent: Patent pending on PLA technology related to kinase inhibitor sensitivity biomarkers; Travel/Accommodations: Bristol-Myers Squibb, Roche. J. Bauml: Research funding: Merck, Novartis, Carevive Systems, Janssen, Bayer; Consulting or Advisory Role: Clovis, Bristol-Myers Squibb, Celgene, Boehringer-Ingelheim, AstraZeneca, Genentech, Guardant Health. R.E. Sanborn: Research funding: Merck (investigator-initiated study), Bristol-Myers Squibb (institutional research support), MedImmune (institutional research support); Honoraria: AstraZeneca; Consulting or Advisory Role: AstraZeneca, Seattle Genetics, Takeda, Genentech, Abbvie, Celldex; Travel/Accommodations: Janssen. M. Curtis, E. Attiyeh, N. Haddish-Berhane, K. Bae, R. Knoblauch, L. Sherman, M.V. Lorenzi: Employment: Janssen Stock: Johnson & Johnson. All other authors have declared no conflicts of interest.

1498P Optimal interval from preceding radiotherapy (RT) to enhance efficacy of immune check point inhibitors (ICIs): Consecutive analysis of 294 patients with non-small cell lung cancer (NSCLC)

H. Horinouchi[1], Y. Matsumoto[1], S. Murakami[1], Y. Goto[1], S. Kanda[1], Y. Fujiwara[1], N. Yamamoto[1], Y. Nakayama[2], Y. Ohe[1]

[1]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Based on the preclinical findings, preceding RT enhances efficacy of ICIs. Phase III trial (PACIFIC) evaluating efficacy of durvalumab as consolidation after chemo-RT showed significant improvement in progression-free survival (PFS) in patients with stage III NSCLC (Antonia et al., NEJM 2017). Retrospective analysis showed previous RT resulted longer PFS by ICIs (Shaverdian et al., Lancet Oncol 2017). However, the optimal interval between preceding RT and ICIs has not been clarified.

Methods: Between Dec 2015 and Apr 2018, we analyzed consecutive NSCLC patients received ICIs. Patients' characteristics, driver oncogene alteration (EGFR, ALK and ROS1), RT before ICIs (no RT, definitive or palliative thoracic radiotherapy [TRT] and palliative RT for other sites [other RT]) and PFS were investigated. The interval between the initial day of ICIs and the start date of RT (in patients with RT) or first line chemotherapy (in patients without RT) was classified as follows; within 6 months [<6], 6 to 12 months [6-12] and 12 months or longer [>12].

Results: A total of 294 patients with NSCLC received ICIs; male / female: 186 / 108, median age: 66 (range, 32-85), squamous (Sq) / non-Sq: 60 / 234, driver oncogene alteration (positive / negative or unknown): 47 / 247, regimen (nivolumab / pembrolizumab): 235 / 59, RT (no RT / TRT / other RT): 131 / 83 / 80 and interval time categories (<6 / 6-12 / >12): 91 / 74 / 129. Significantly better PFS of ICIs was demonstrated in patients after TRT (HR 0.71, 95% CI: 0.52-0.97). According to the interval time from preceding RT, efficacy of ICIs was especially enhanced with 6-12 month interval from TRT, even after adjusting by PS, sex, age, histology, tobacco history, ICI regimen and driver oncogene status (adjusted HR 0.37, 95% CI: 0.18-0.76).

Table: 1498P PFS of ICIs according to interval from preceding TRT or other RT in comparison with patients without RT

	Total n = 294 HR [95%CI]	Within 6 mo n = 91 HR [95%CI]	6 to 12 mo n = 74 HR [95%CI]	12 mo or longer n = 129 HR [95%CI]
No RT	1	1	1	1
TRT	0.71 [0.52-0.97]	0.98 [0.49-1.98]	0.35 [0.17-0.71]	0.92 [0.59-1.43]
No RT	1	1	1	1
Other RT	1.02 [0.75-1.39]	0.96 [0.56-1.66]	1.22 [0.66-2.27]	0.89 [0.53-1.48]

Conclusions: Efficacy of ICIs was significantly better in patients after TRT especially between 6 to 12 months from preceding RT.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: H. Horinouchi: Research funding: Ono, MSD, Merck Serono, Novartis, Chugai, Astellas, Daiichi-Sankyo and Genomic Health. Y. Goto: Research funding: MSD, BMS, Chugai. S. Kanda: Consulting or advisory role: AstraZeneca Speaker's bureau: AstraZeneca, Bristol Myers Squibb, Chugai, Ono Pharmaceutical Research Funding: Abbvie, AstraZeneca, Bristol Myers Squibb, Ono Pharmaceutical. Y. Fujiwara: Grants and personal fees: BMS, MSD, AstraZeneca, Grants: Abbvie, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Incyte, Merck Serono, Novartis; Personal fees from Taiho, personal fees outside the submitted work: ONO. N. Yamamoto: Research grants: Quintiles, Astellas, Chugai, Esai, Taiho, BMS, Pfizer, Novartis, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, ONO; Advisory role: Eisai, Takeda, OncoTherapy Science, Otsuka, Boehringer Ingelheim; Honoraria: BMS, Pfizer, AstraZeneca, Eli Lilly, ONO, Chugai. Y. Nakayama: Advisory board: AstraZeneca. Y. Ohe: Research funding: AstraZeneca, Ono Pharmaceutical, Bristol-Myers Squibb, Chugai, MSD, Novartis, Kyorin, Dainippon-Sumitomo, Lilly, Pfizer, Ignyta, Kissei; Honoraria: AstraZeneca, Ono, BMS, Chugai, MSD, Novartis, Daiichi-Sankyo, Boehringer Ingelheim, Bayer, Lilly, Pfizer. All other authors have declared no conflicts of interest.

1499TiP Tumor treating fields concurrent with standard of care for stage 4 non-small cell lung cancer (NSCLC) following platinum failure: Phase III LUNAR study

U. Weinberg[1], O. Farber[2], M. Giladi[3], Z. Bomzon[4], E. Kirson[2]

[1]R&D, Novocure, Luzern, Switzerland, [2]R&D, Novocure, Haifa, Israel, [3]Preclinical Research, Novocure, Haifa, Israel, [4]Physics, Novocure, Haifa, Israel

Background: Tumor Treating Fields (TTFields) is a non-invasive, anti-mitotic treatment approved for glioblastoma based on significantly improved survival outcomes in a Phase 3 trial. Efficacy of TTFields in NSCLC has been shown preclinically and the safety confirmed in a phase I/II pilot study combined with pemetrexed. We hypothesize that adding TTFields to immune checkpoint inhibitors or docetaxel following platinum doublet failure will increase overall survival (OS) in stage 4 NSCLC.

Trial design: The LUNAR trial [NCT02973789] is enrolling patients (N = 534), with squamous or non-squamous NSCLC who are stratified per selected standard therapy (immune checkpoint inhibitors or docetaxel), histology (squamous vs. non-squamous) and geographical region. Key inclusion criteria include disease progression while on/after platinum-based therapy, ECOG 0-2, no electronic medical devices in the upper torso, and absence of brain metastasis. Docetaxel or immune checkpoint inhibitors are given at standard doses. TTFields are applied to the upper torso for >18 hours/day, allowing patients to maintain daily activities. TTFields are continued until progression in the thorax and/or liver. Follow-up is performed once q6 weeks using CT scans of the chest and abdomen. On progression in the thorax and/or liver, patients have 3 post-progression follow-up visits and are then followed monthly for survival. The primary endpoint is superiority in OS with TTFields in combination with the standard of care treatments versus (vs) standard of care treatments alone. Key secondary endpoints compare the OS in patients treated with TTFields and docetaxel vs docetaxel alone, and patients treated with TTFields and immune checkpoint inhibitors vs those treated with immune checkpoint inhibitors alone. An exploratory analysis will test non-inferiority of TTFields with docetaxel compared to checkpoint inhibitors alone. Secondary endpoints include progression-free survival, radiological response rate, quality of life based on the EORTC QLQ C30 questionnaire and severity and frequency of adverse events. The sample size is powered to detect a HR of 0.75 in TTFields-treated patients versus control group.

Clinical trial identification: NCT02973789.

Legal entity responsible for the study: Novcoure.

Funding: Novocure.

Disclosure: U. Weinberg, O. Farber, M. Giladi, Z. Bomzon, E. Kirson: Full-time employee: Novocure.

1500TiP eXalt3: Phase III randomized study comparing ensartinib to crizotinib in anaplastic lymphoma kinase positive non-small cell lung cancer patients

L. Horn[1], Y-L. Wu[2], M. Reck[3], H. Wakelee[4], C. Liang[5], K. Harrow[6], V. Oertel[7], T. Mok[8]

[1]Vanderbilt Ingram Cancer Center, Nashville, TN, USA, [2]Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, Guangdong, China, [3]Thoracic Oncology, Krankenhaus Grosshansdorf, Grosshansdorf, Germany, [4]Medicine/Oncology, Stanford Advanced Medicine Center, Stanford, CA, USA, [5]CSO, Xcovery Holdings, Inc., Palm Beach Gardens, FL, USA, [6]Clinical Operations, Xcovery Holding Company, LLC, Palm Beach Gardens, FL, USA, [7]Xcovery Holdings, Inc., Palm Beach Gardens, FL, USA, [8]Clinical Oncology, Chinese University of Hong Kong, Shatin, China

Background: Ensartinib (X-396) is a novel, potent ALK small molecule tyrosine kinase inhibitor (TKI). It is well-tolerated and has shown promising activity in NSCLC patients in a phase 1/2 study in patients that were both ALK TKI naïve and patients that received prior crizotinib, as well as those with CNS metastases. The safety profile of ensartinib appears to be different from other ALK TKIs.

Trial design: In this global, phase 3, open-label, randomized study, approximately 270 patients with ALK+ NSCLC who have received no prior ALK TKI and up to one prior chemotherapy regimen will be randomized with stratification by prior chemotherapy (0/1), performance status (0-1/2), brain metastases at screening (absence/presence), and geographic region (Asia /other), to receive oral ensartinib (225 mg, once daily) or crizotinib (250mg, twice daily) until disease progression or intolerable toxicity. Eligibility also includes patients ≥ 18 years of age, stage IIIB or IV ALK+ NSCLC. Patients are required to have measurable disease per RECIST 1.1, adequate organ function, and an ECOG PS of ≤ 2. Adequate tumor tissue (archival or fresh biopsy) must be available for central testing. The primary endpoint is progression-free survival assessed by independent radiology review based on RECIST v. 1.1 criteria. Secondary efficacy endpoints include overall survival, response rates (overall and central nervous system [CNS]), PFS by investigator assessment, time to response, duration of response, and time to CNS progression. The study has > 80% power to detect a superior effect of ensartinib over crizotinib in PFS at a 2-sided alpha level of 0.05. Phase 3 recruitment began in June, 2016 and currently has 98 active sites in 21 countries. The duration of recruitment will be approximately 28 months.

Clinical trial identification: NCT02767804.

Legal entity responsible for the study: Xcovery Holdings, Inc.

Funding: Has not received any funding.

Disclosure: L. Horn: Consulting: Xcovery Holding Company, BMS, BI, Abbvie, Genentech, Merck. Y-L. Wu: Speaker fees: AstraZeneca, Roche, Eli Lilly. M. Reck: Honoraria for lectures and consultancy: Hoffmann-La Roche, Lilly, BMS, MSD, AstraZeneca, Merck, Celgene, Boehringer-Ingelheim, Pfizer, Novartis. H. Wakelee: Research support: Pfizer, Novartis, Xcovery. C. Liang, K. Harrow, V. Oertel: Full-Time Employee: Xcovery Holding Company. T. Mok: Grant/Research Support: AstraZeneca, BI, Pfizer, Novartis, SFJ, Roche, MSD, Clovis Oncology, BMS, Eisai, Taiho; Speaker's fees: AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, BI, MSD, Novartis, BMS, Taiho; Major Stock Shareholder: Sanomics Ltd.; Advisory Board: AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, BI, Clovis Oncology, Merck Serono, MSD, Novartis, SFJ Pharmaceutical, ACEA Biosciences, Inc., Vertex Pharmaceuticals, BMS, geneDecode Co., Ltd., OncoGenex Technologies Inc., Celgene, Ignyta, Inc.; Board of Directors: IASLC, Chinese Lung Cancer Research Foundation Ltd., Chinese Society of Clinical Oncology (CSCO), Hong Kong Cancer Therapy Society (HKCTS).

1501TiP Afatinib (AFA) plus bevacizumab (BEV) combination after osimertinib (OSIME) failure for aDvanced EGFR-mutant non-small cell lung cancer (NSCLC): A multicenter prospective single arm phase II study (ABCD-study)

A. Hata[1], N. Katakami[2], K. Nishino[3], M. Mori[4], T. Yokoyama[5], T. Kurata[6], M. Tachihara[7], N. Takase[8], H. Daga[9], T. Kijima[10], S. Morita[11], K. Sakai[12], K. Nishio[13], M. Satouchi[14], S. Negoro[8]

[1]Department of Thoracic Oncology, Kobe Minimally Invasive Cancer Center, Kobe, Japan, [2]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [3]Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan, [4]Department of Thoracic Oncology, National Hospital Organization Toneyama National Hospital, Toyonaka, Japan, [5]Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan, [6]Department of Respiratory Medicine, First Department of Internal Medicine, Kansai Medical University, Hirakata, Japan, [7]Department of Respiratory Medicine, Kobe University Hospital, Kobe, Japan, [8]Cancer Center, Takarazuka City Hospital, Takarazuka, Japan, [9]Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan, [10]Respiratory Medicine, Hyogo College of Medicine, Nishinomiya, Japan, [11]Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine 54 Kawahara-cho,Shogoin,Sakyo-ku, Kyoto, Japan, [12]Department of Genome Biology, Kindai University Faculty of Medicine, Osaka-sayama, Japan, [13]Department of Genome Biology, Kindai University Faculty of Medicine, Osaka, Japan, [14]Department of Thoracic Oncology, Hyogo Cancer Center, Hyogo, Japan

Background: 3rd-generation EGFR-TKI, OSIME showed a remarkable efficacy for T790M+ NSCLC. Moreover, OSIME has proven superior progression-free survival (PFS) over 1st-generation EGFR-TKIs in front-line setting, and it will be widely used in front-line and later settings. Various resistant mechanisms were reported: C797S (cis/trans); EGFR uncommon mutations such as E709K and L844V; T790M- conversion; HER2-amp; MET-amp; PIK3CA/BRAF mutations; and histological transformation such as small cell and EMT. AFA is an irreversible EGFR-TKI with a potency as pan-HER inhibitor. Preclinical and clinical studies showed high sensitivity to EGFR uncommon mutations. Preclinical studies also showed a synergistic effect of AFA and BEV after acquired resistance (AR) to EGFR-TKIs. Our previously-conducted phase II study found a promising efficacy of AFA+BEV after AR: response rate (RR), 18.8%; disease control rate (DCR), 90.7%; and median PFS (mPFS), 6.3 months. Notably, preclinical data has suggested EGFR-TKI+BEV combination could overcome MET-associated resistance. Based on the above background, we hypothesize several resistant mechanisms (e.g., C797S (trans), uncommon EGFR mutations, and HER2) to OSIME are sensitive to AFA, and synergism of additional BEV maximizes AFA sensitivity.

Trial design: This ABCD-study is a phase II study conducted by HANSHIN Oncology Group. ECOG PS 0-1 patients with EGFR-mutant NSCLC are enrolled after failure of OSIME. Liquid/histological rebiopsies before enrollment after OSIME failure are essential to examine the resistant mechanisms. Liquid /histological samples are analyzed to confirm gene mutations/fusions and copy-number gain using next-generation sequencers. AFA is prescribed at 30-40 mg QD, and BEV is administered at 15 mg/kg tri-weekly until progression. The primary endpoint is PFS. Sample size of 26 is based on a null mPFS of 4.0 months, an alternative mPFS of 6.0 months, power of 80% and one-sided 15% of type I error. We plan an exploratory analysis regarding differential efficacies according to each resistant mechanism.

Clinical trial identification: UMIN000030545.

Legal entity responsible for the study: The authors.

Funding: Boehringer Ingelheim.

Disclosure: A. Hata: Lecture fee: Boehringer Ingelheim; Financially support analysis of liquid/histological samples: Boehringer Ingelheim. N. Katakami: Honoraria and Research fund: Boehringer Ingelheim. K. Nishino, T. Kurata, M. Tachihara, H. Daga, T. Kijima, S. Morita, K. Nishio, M. Satouchi: Honoraria: Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1502TiP Fostering efficacy of anti-PD-1-treatment: Nivolumab plus radiotherapy in advanced non-small cell lung cancer: The FORCE trial

F. Bozorgmehr[1], A. Hommertgen[2], F. Lasitschka[3], J. Krisam[4], J. Debus[5], J.R. Fischer[6], M. Bischof[7], A. Atmaca[8], S. Wetzel[9], M. Faehling[10], D. Bottke[11], C. Grohe[12], W. Engel-Riedel[13], E. Ingenhoff[14], D.F. Heigener[15], N. Reinmuth[16], C. Schumann[17], M. Wermke[18], M. Thomas[1], S. Rieken[19]

[1]Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany, [2]Department of Radiation Oncology, Heidelberg University Hospital; Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (dkfz), Heidelberg, Germany, [3]Institute of Pathology, Heidelberg University Hospital; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany, [4]Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany, [5]Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany, [6]Department of Thoracic Oncology, Lungenklinik Loewenstein, Loewenstein, Germany, [7]Department of Radiation Oncology, Klinikum am Gesundbrunnen, SLK-Kliniken Heilbronn GmbH, Heilbronn, Germany, [8]Department of Hematology and Oncology, Krankenhaus Nordwest UCT-University Cancer Center, Frankfurt am Main, Germany, [9]Department of Radiation Oncology, Krankenhaus Nordwest, Frankfurt am Main, Germany, [10]Department of Cardiology and Pneumology, Hospital Esslingen, Esslingen, Germany, [11]Department of Radiation Oncology, Hospital Esslingen, Esslingen, Germany, [12]Department of Pneumology, ELK Berlin, Berlin, Germany, [13]Department of Pneumology, City of Cologne Municipal Hospitals, Lung Hospital Cologne Merheim, Cologne, Germany, [14]Department of Radiation Oncology, City of Cologne Municipal Hospitals, Cologne, Germany, [15]Department of Thoracic Oncology, Lungen Clinic Grosshansdorf, Airway Research Centre North (ARCN), Member of the German Center for Lung Research (DZL), Grosshansdorf, Germany, [16]Department of Thoracic Oncology, Asklepios Fachkliniken München-Gauting, Gauting, Germany, [17]Clinic for Pneumology, Thoracic Oncology, Sleep, and Respiratory Critical Care, Klinikum Kempten-Oberallgaeu gGmbH, Kempten, Germany, [18]Medizinische Klinik und Poliklinik I, University Hospital Carl-Gustav-Carus, Dresden, Germany, [19]Department of Radiation Oncology, Heidelberg University Hospital; Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg, Germany, Heidelberg, Germany

Background: Hypofractionated palliative radiotherapy for metastatic lung cancer patients is frequently used in order to ease pain, to increase bone stability, to treat local mass effects or to prolong progression-free survival at critical sites. Recently introduced, immunotherapy for patients with non-squamous non-small cell lung carcinoma (NSCLC) has significantly improved outcome in this cohort. Preclinical and early clinical data suggest that the combination of photon radiation with PD-1-targeting immunotherapies may promote a strong and durable immune response against tumor manifestations both within and beyond radiation targets.

Trial design: In this prospective, two-armed, non-randomized, open-label phase II trial, 130 patients with stage IV non-squamous non-small cell lung cancer in 2nd-line or 3rd-line treatment will be included. 65 patients with a clinical indication for palliative radiotherapy to non-cerebral non-pulmonary metastatic sites will receive nivolumab 240 mg followed by palliative radiotherapy with 5 x 4 Gy = 20 Gy photon radiation, which will be initiated within 72 hours after first nivolumab administration (Group A). 65 patients without an indication for radiotherapy will receive nivolumab (Group B). Nivolumab will be administered every two weeks in both groups and will be continued until progression or until limiting toxicities. The primary endpoint will be the objective response rate according to RECIST criteria 1.1. Secondary endpoints will be progression-free survival according to RECIST 1.1, overall survival, descriptive subgroup analyses according to PD-L1 expression, toxicity and quality of life. An extensive exploratory translational research program attached to this trial will focus on mechanisms of the immune-stimulating effect of radiotherapy and the identification of potential biomarkers predicting response to nivolumab. The FORCE trial will contribute prospective data to the observation that the combination of hypofractionated photon radiotherapy and medical immunotherapy is not only safe but will also promote antitumoral immune responses.

Clinical trial identification: NCT Nr: 03044626 Eudra-CT Nr: 2015-005741-31

Legal entity responsible for the study: AIO-Studien gGmbH.

Funding: Bristol Myers Squibb GmbH & Co. KGaA BMBF / NCT 3.0 BMBF / NCT 3.0.

Disclosure: F. Bozorgmehr: Research funding: BMS; Honoraria: MSD, Novartis. F. Lasitschka: Advisory board memberships: Roche Pharma, BMS; Corporate-sponsored research: Roche, MSD, BMS, Boehringer-Ingelheim, Morphosys, Dianova. J. Debus: Advisory board: Merck; Research support: Siemens, Accuray, Viewray. J.R. Fischer: Honoraria, Advisory boards, Presentations, Consulting: AstraZeneca, BMS, Boehringer Ingelheim, Celgene, MSD, Roche. M. Bischof: Advisory board: BMS. A. Atmaca: Honoraria for Advisory board participation and travel expenses: BMS. M. Faehling: Advisory boards: BMS, Roche, MSD, AstraZeneca. D.F. Heigener: Honoraria for presentations / Advisory board: Boehringer Ingelheim, BMS, Astra Zeneca, Roche, Lilly, Pfizer, Takeda, MSD. Travel expenses: Boehringer Ingelheim, BMS, Astra Zeneca, Roche, Lilly, Pfizer, Takeda, MSD. N. Reinmuth: Honoraria: Roche, Lilly, Novartis, MSD, BMS, Boehringer-Ingelheim, AstraZeneca, Pfizer, Takeda. C. Schumann: Advisory role and lectures: BMS, Astra, Roche, MSD. M. Wermke: Honoraria: BMS, Novartis, Roche, Bayer, Glenmark, AstraZeneca; Travel expenses: AstraZeneca, BMS, MSD, Novartis. M. Thomas: Presentations: Lilly; BMS; MSD; Roche; Pfizer; AstraZeneca; Advisory Boards: Lilly; BMS; MSD; Roche; Pfizer; AstraZeneca; Celgene; Mediolanum. S. Rieken: Honoraria and travel expenses: ELEKTA Inc., Accuray Inc., AstraZeneca GmbH, Brystol Myers Squibb, Lilly, Roche, DGP, DKG, DEGRO, Frauenselbsthilfe nach Krebs e.V., Berufsverband der Pharmaberater IITs and research funding: Brystal Myers Squibb, Accuray Inc., Merck KGaA Consulting or advisory role: Accuray Inc., AstraZeneca GmbH All other authors have declared no conflicts of interest.

1503TiP CheckMate 592: A phase II exploratory study of biomarkers associated with the efficacy of first-line nivolumab (nivo) plus ipilimumab (ipi) in patients (pts) with stage IV or recurrent NSCLC

S. Gettinger[1], T. Beck[2], X. Yang[3], B. Telivala[4], D. Morgensztern[5], V. Velcheti[6], S.S. Ramalingam[7], K. Schalper[8], M. Dajee[9], A. Ranck[10], R. Yang[11], D.R. Spigel[12]

[1]Internal Medicine, Medical Oncology, Yale Cancer Center, New Haven, CT, USA, [2]Research, Highlands Oncology Group, Fayetteville, NC, USA, [3]Hematology and Oncology Department, Bon Secours Saint Francis Cancer Center, Greenville, SC, USA, [4]Clinical Research Department, Cancer Specialists of North Florida, Jacksonville, FL, USA, [5]Medical Oncology, Washington University, St. Louis, MO, USA, [6]Hematology and Oncology Department, Cleveland Clinic, Cleveland, OH, USA, [7]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA, [8]Pathology and Medicine, Yale Cancer Center, New Haven, CT, USA, [9]Translational Medicine, Oncology Biomarkers, Bristol-Myers Squibb, Princeton, NJ, USA, [10]Oncology Clinical Development, Bristol-Myers Squibb, Princeton, NJ, USA, [11]Global Biometric Sciences, Bristol-Myers Squibb, Princeton, NJ, USA, [12]Chief Scientific Officer, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA

Background: Combining PD-1 and CTLA-4 inhibitors can augment antitumor immune responses. In the phase 1 CheckMate 012 study, first-line nivo (anti–PD-1 antibody) plus ipi (anti–CTLA-4 antibody) exhibited a higher objective response rate (ORR) and 2-year overall survival (OS) rate than nivo alone in pts with stage IIIB/IV NSCLC. Pts whose tumors expressed PD-L1 or had a high tumor mutational burden (TMB) showed better outcomes. High TMB was identified in the phase 2 CheckMate 568 (nivo + ipi) and phase 3 CheckMate 026 (nivo alone) studies and validated in phase 3 CheckMate 227 (nivo + ipi) as a potential predictive biomarker, independent of PD-L1 expression. High TMB may result in high expression of neoantigens, which could prime responses to checkpoint inhibitors. Beyond PD-L1 and TMB, there may be other important potential predictive biomarkers. CheckMate 592 (NCT03001882) is a two-part, exploratory, open-label phase 2 study exploring potential biomarkers, including PD-L1 and TMB, among others, and their association with clinical benefit with first-line nivo + ipi for stage IV or recurrent NSCLC.

Trial design: Pts aged ≥18 years with treatment-naïve stage IV or recurrent NSCLC and who had ECOG performance status 0–1 are being enrolled in the United States (parts 1 and 2) and Europe (part 2). Pts are ineligible if they have active autoimmune disease. In part 1, approximately 100 pts will be analyzed according to PD-L1 status (≥1% vs < 1%) before treatment. In part 2, approximately 150 pts will be treated regardless of PD-L1 status. The primary endpoint in part 1 is the association of ORR with baseline TMB, and candidate peripheral blood and tumor biomarkers at baseline and on treatment; secondary endpoints are ORR, disease control rate, response duration, time to response, progression-free survival (PFS), OS, and the association of

enteric biomarkers with efficacy. Primary endpoints in part 2 are the association of ORR with baseline tissue and blood TMB; secondary endpoints are ORR, PFS, OS, safety, and the association of enteric biomarkers with efficacy. The start date was March 2017. The estimated primary completion date is March 2019.

Clinical trial identification: NCT03001882.

Editorial acknowledgement: Professional medical writing and editorial assistance were provided by StemScientific, funded by Bristol-Myers Squibb.

Legal entity responsible for the study: Bristol-Myers Squibb.

Funding: Bristol-Myers Squibb.

Disclosure: S. Gettinger: Research funding: Bristol-Myers Squibb, Genentch, Ariad, Incyte, Pfizer, and Celldex; Consulting fees: Bristol-Myers Squibb, Ariad, Pfizer, and Alexion Pharmaceuticals. X. Yang: Payment to institution: Bristol-Myers Squibb for clinical trial services. D. Morgensztern: Consultant: Abbvie and Bristol-Myers Squibb. V. Velcheti: Consultant: Merck, Bristol-Myers Squibb, Genentech, and AstraZeneca. S.S. Ramalingam: Advisory board meetings: AstraZeneca, Amgen, AbbVie, Bristol-Myers Squibb, Celgene, Lilly, Merck, Genentech, Roche and Takeda. K. Schalper: Grants: Navigate Biopharma, Vasculox/Tioma, Tesaro Inc., Onkaido/Moderna, Takeda, Surface Oncology and Pierre-Fabre; Consultant: Celgene, Shattuck Labs and Moderna Therapeutics. M. Dajee, A. Ranck, R. Yang: Stock ownership and employee: Bristol-Myers Squibb. D.R. Spigel: Consulting role: Novartis and Genentech; Travel, accommodations, and expenses: Novartis, Genentech, and Pfizer. All other authors have declared no conflicts of interest.

1504TiP Nintedanib plus docetaxel in routine clinical practice: VARGADO, a German prospective non-interventional study (NIS) reflecting routine treatment conditions in an evolving NSCLC treatment landscape

C. Grohe[1], I. Zander[2], K. Lüdtke-Heckenkamp[3], W. Blau[4], S. Krüger[5], C. Franke[6], H. Mueller-Huesmann[7], W.M. Brückl[8], N. Basara[9], D. Ukena[10], S. Lang[11], J. Atz[12], R. Kaiser[12]

[1]Department of Pneumology, ELK Berlin, Berlin, Germany, [2]Onkologie, Am Raschplatz, Hannover, Germany, [3]Niels-Stensen-Clinics, Georgsmarienhuette, Osnabrück, Germany, [4]Department of Internal Medicine V, University Hospital Giessen, Giessen, Germany, [5]Department for Pulmonology/Allergology/Sleep Medicine and Respiratory Care, Florence-Nightingale-Hospital, Duesseldorf, Germany, [6]Facharztzentrum, Sonneberg, Germany, [7]Klinik für Hämatologie und Onkologie, Bruederkrankenhaus St. Josef, Paderborn, Germany, [8]Dept. of Internal Medicine 3, Klinikum Nürnberg, Universitätsklinik der Paracelsus Medizinischen Privatuniversität, Nuremberg, Germany, [9]Department of Internal Medicine, Malteser Hospital St. Franziskus, Flensburg, Germany, [10]Department of Pneumology, Klinikum Bremen-Ost, Bremen, Germany, [11]Department of Respiratory Medicine, SRH Wald-Klinikum Gera, Gera, Germany, [12]Medical Affairs Oncology, Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim Am Rhein, Germany

Background: Nintedanib is an oral, triple angiokinase inhibitor approved by the EMA and other countries in combination with docetaxel for the treatment of adenocarcinoma NSCLC patients after first-line chemotherapy. Nintedanib plus docetaxel demonstrated significant and clinically meaningful OS benefits in adenocarcinoma patients, which were more pronounced in patients with aggressive or refractory tumors. During the past years the treatment landscape for advanced NSCLC has changed tremendously impacting individual treatment decisions and choice of adequate treatment sequences. Here we present the ongoing NIS VARGADO study design and set up to assess the efficacy and tolerability of nintedanib plus docetaxel in daily clinical routine in Germany.

Trial design: The NIS VARGADO (NCT02392455) is currently recruiting patients. Four hundred patients are planned to be enrolled at one hundred German centers. Adult NSCLC patients with advanced adenocarcinoma who are initiating treatment with nintedanib according to its label as part of routine clinical practice are eligible. The primary endpoint of the study is the one-year overall survival rate after start of therapy with nintedanib and docetaxel. Progression-free survival is one of the key secondary endpoints. Patients with aggressive or refractory tumors will be analyzed in detail with respect to efficacy in this real world setting. Documentation of patients treated with nintedanib plus docetaxel combination following first-line chemotherapy and/or immunotherapy will allow for analyses on treatment sequence. Analysis of tolerability will comprise the assessment of frequency and severity of adverse events. Furthermore, therapy management under routine conditions will be recorded and assessed.

Clinical trial identification: NCT02392455.

Legal entity responsible for the study: Boehringer Ingelheim Pharma GmbH & Co. KG.

Funding: Boehringer Ingelheim Pharma GmbH & Co. KG.

Disclosure: I. Zander: Consultancy: Boehringer Ingelheim. S. Krüger: Honoraria, Advisory boards and lectures: Boehringer Ingelheim. W.M. Brückl: Payments for membership on advisory boards: Boehringer Ingelheim. J. Atz, R. Kaiser: Employee: Boehringer Ingelheim Pharma GmbH & Co KG. All other authors have declared no conflicts of interest.

1505TiP A phase III, randomized, open-label, multicenter study of SHR-1210 (anti-PD-1 antibody) in combination with pemetrexed and carboplatin as first line therapy in subjects with advanced/metastatic non-squamous non-small cell lung cancer

F. Wu[1], G. Gao[1], C. Zhou1, X. Kang[2], Y. Zhou[2]

[1]Medical Oncology, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China, [2]Department of Clinical R&D - Oncology, Shanghai Hengrui Phamaceutical Co.LTD, Shanghai, China

Background: SHR-1210 is a humanized anti–PD-1 antibody, with immunoglobulin gamma 4 (IgG4) as heavy chain and immunoglobulin kappa (IgK) as light chain expressed in the supernatant of a Chinese hamster ovary (CHO) stable cell line. Antitumor activity data for the ongoing clinical studies of SHR-1210 are currently being evaluated. SHR-1210 is currently being tested in 15 studies in advanced malignancies: 4 in advanced solid tumors, 3 in NSCLC, 2 in hepatocellular cancer (HCC; including 1 in HCC or gastric cancer [GC]), 2 in esophageal cancer (EC), 1 in melanoma, 1 in nasopharyngeal cancer (NPC), 1 in primary liver cancer (PLC), and 1 in classic Hodgkin lymphoma (cHL). Since 22 MAY 2017, 395 patients have been enrolled in this trial.

Trial design: In this trial, 412 patients will be randomly assigned in a 1:1 ratio, to receive either carboplatin-pemetrexed chemotherapy,OR receive SHR-1210 combined with carboplatin-pemetrexed chemotherapy. Randomization will be stratified according to gender and smoking history. All the patients will receive carboplatin(area under the curve 5) plus pemetrexed(500 mg/m^2), all administered as IV infusion on Day 1 of each 3-week cycle for 4 or 6 cycles of the investigator's choice, followed by pemetrexed(500 mg/m^2) every 3 weeks(Q3W) maintenance for the remainder of the study. Patients assigned to the SHR-1210 combined with chemotherapy arm, will additionally receive SHR-1210(200mg) administered as IV infusion on Day 1 of each 3-week cycle, for up to 35 cycles. Patients assigned to the chemotherapy arm will have the opportunity to crossover to receive SHR-1210(200mg) monotherapy every 3 weeks(Q3W) once they experience progression of disease (PD) defined by RECIST 1.1 and meet all crossover criteria.

Clinical trial identification: NCT03134872.

Legal entity responsible for the study: Jiangsu HengRui Medicine Co., Ltd.

Funding: Jiangsu HengRui Medicine Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

1506TiP Phase I study of the AXL inhibitor DS-1205c in combination with osimertinib in subjects with metastatic or unresectable EGFR-mutant NSCLC

D. Planchard[1], P.A. Janne[2], H.A. Yu[3], D. Moro-Sibilot[4], T. Goldberg[5], X. Gu[6], J. Li[5], J. McGill[5], C. Yu[5], E. Slosberg[7]

[1]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [2]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [3]Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [4]Thoracic Oncology Unit SHUPP, PTV, Centre Hospitalier Universitaire de Grenoble Alpes, Grenoble, France, [5]Clinical Development, Daiichi Sankyo Inc., Basking Ridge, NJ, USA, [6]Biostatistics, Daiichi Sankyo Inc., Basking Ridge, NJ, USA, [7]Translational Development, Daiichi Sankyo Inc., Basking Ridge, NJ, USA,

Background: In patients with metastatic EGFR-mutant (EGFRm) non-small cell lung cancer (NSCLC), resistance to EGFR tyrosine kinase inhibitors (TKIs) arises from the T790M EGFR mutation in over half of cases; up-regulation of "bypass track" activity in non-EGFR signaling pathways is observed in other cases. Up-regulation of expression of the AXL tyrosine kinase has been observed in EGFRm NSCLC patients experiencing disease progression on erlotinib, and xenograft studies have supported the role of AXL inhibition in combination with EGFR TKI treatment in overcoming such resistance. DS-1205c is a novel, orally administered, specific small molecule inhibitor of AXL.

Trial design: This is a multicenter, open-label, Phase 1, dose escalation and dose expansion study of DS-1205c in combination with osimertinib in metastatic or unresectable EGFR-mutant NSCLC subjects experiencing disease progression during treatment with erlotinib, gefitinib, or afatinib, and without T790M resistance mutation; or during treatment with osimertinib. Eligible subjects are at least 18 years of age, have ECOG PS 0 or 1, have radiological documentation of disease progression on erlotinib, gefitinib, afatinib, or osimertinib, and have at least one measurable lesion. This study includes two parts: Dose Escalation and Dose Expansion. In Dose Escalation, subjects receive DS-1205c during a run-in period, followed by combination treatment with DS-1205c and 80 mg daily of osimertinib. Escalation of DS-1205c dosing is guided by the modified Continuous Reassessment Method using a Bayesian logistic regression model following the escalation with overdose control principle. In Dose Expansion, subjects receive DS-1205c at the recommended dose for expansion (RDE) determined in Dose Escalation, in combination with 80 mg daily of osimertinib. Primary objectives are to determine safety, tolerability, and RDE of DS-1205c in combination with osimertinib. Secondary objectives are to assess pharmacokinetic parameters of DS-1205a (free form of DS-1205c), osimertinib, and osimertinib active metabolites, and to assess antitumor activity (RECIST v1.1). Retrospective analysis of AXL expression will be conducted using tumor tissue collected prior to study treatment. Enrollment opened in December 2017.

Clinical trial identification: NCT03255083.

Legal entity responsible for the study: Daiichi Sankyo, Inc.

Funding: Daiichi Sankyo, Inc.

Disclosure: D. Planchard: Advisory boards: AstraZeneca, Boehringer, BMS, Celgene, MSD, Novartis, Pfizer, Roche. P.A. Janne: Consultant: AstraZeneca, Boehringer Ingelheim, Pfizer, Merrimack Pharmaceuticals, Roche/Genentech, Chugai Pharmaceuticals, Acea Biosciences, Ignyta, Loxo Oncology, Ariad Pharmaceuticals, Eli Lilly Pharmaceuticals, Araxes Pharmaceuticals, Gatekeeper Pharmaceuticals; Research Funding: Astellas Pharmaceuticals, AstraZenenca, Daiichi Sankyo, Puma, Eli Lilly Pharmaceuticals, Boehringer Ingelheim. Patents, Royalties, Other intellectual property: LabCorp. H.A. Yu: Research funding to institution: AstraZeneca, Novartis, Daiichi, Pfizer; Consulting: AstraZeneca. D. Moro-Sibilot: Roche, Abbvie, Eli Lilly, Boehringer, BMS, MSD, Takeda, AstraZeneca. T. Goldberg, J. Li, J. McGill, C. Yu: Employee: Daiichi Sankyo, Inc. X. Gu, E. Slosberg: Employee and stockholder: Daiichi Sankyo.

1507TiP Ultra-early response capturing in the treatment of non-squamous NSCLC using diffusion-weighted MRI: A prospective multicenter study

G. Heussel[1], N.V. Batora[2], M. Schneider[3], P. Flechsig[4], J. Krisam[5], C. Wiedemann[6], O. Sedlaczek[2], I. Fellhauer[2], H-U. Kauczor[2], M. Thomas[7], H. Golpon[8], J. Vogel-Claussen[9], A. Tufman[10], J. Dinkel[11], A. Guenther[12], S. Janciauskiene[8], H. Sueltmann[13], M. Meister[3], C.P. Heussel[14], F. Bozorgmehr[7]

[1]Department of Diagnostic and Interventional Radiology with Nuclear Medicine, Department of Pneumology, Thoraxklinik at Heidelberg University Hospital; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany, [2]Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany, [3]Translational Research Unit, Thoraxklinik at Heidelberg University Hospital; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany, [4]Department of Diagnostic and Interventional Radiology, Department of Nuclear Medicine, University Hospital Heidelberg; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany, [5]Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany, [6]Thoracic Oncology, Thoraxklinik at Heidelberg University, Heidelberg, Germany, [7]Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany, [8]Department of Pneumology, Hannover Medical School; Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Member of the German Center for Lung Research (DZL), Hannover, Germany, [9]Institute for Radiology, Hannover Medical School; Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Member of the German Center for Lung Research (DZL), Hannover, Germany, [10]Department of Internal Medicine V, University of Munich (LMU); Division of Respiratory Medicine and Thoracic Oncology, Thoracic Oncology Centre Munich; Comprehensive Pneumology Center (CPCM), Member of the German Center for Lung Research (DZL), Munich, Germany, [11]Department of Clinical Radiology, University of Munich (LMU); Comprehensive Pneumology Center (CPCM), Member of the German Center for Lung Research (DZL), Munich, Germany, [12]Department of Internal Medicine, Justus-Liebig University Giessen; Universities of Giessen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research (DZL), Giessen, Germany, [13]Cancer Genome Research Group, German Cancer Research Center (DKFZ); Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany, [14]Department of Diagnostic and Interventional Radiology with Nuclear Medicine, Thoraxklinik at Heidelberg University Hospital; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany

Background: Currently, there is no possibility to detect early tumor response in lung cancer patients within the first days after chemotherapy (CTx) or tyrosine kinase inhibitor (TKI) therapy induction. Using the current gold standard for therapy monitoring, i.e. the measurement of morphologic differences according to RECIST 1.1 by CT and MRI, changes are detected only after weeks or months. Thus, patients may undergo eventually ineffective treatment and suffer from unnecessary toxicity, with both causing relevant costs. This highlights the importance of early response detection to guide and optimize therapy. Monitoring treatment response with diffusion-weighted and dynamic contrast perfusion MR imaging has been proposed for some time as a new powerful tool that will allow determining tumor response much earlier than RECIST.

Trial design: This is an observational, prospective, multicenter, non-randomized, open clinical study. 150 patients with non-squamous NSCLC undergoing systemic treatment receive MRI before and after 1st-line therapy. The first follow-up (FU) MRI for patients undergoing chemotherapy is performed 24 hours post treatment. Patients treated with TKIs undergo MRI at days 7 and 14 after therapy induction. A thoracic MRI protocol is performed, including navigated diffusion-weighted imaging with the acquisition of 6 b-values, while the evaluation will focus on the non-perfusion sensitive b-values 400 and 800 (online calculated trace images) and the apparent diffusion coefficient (ADC). Software-based analysis of user-defined ROIs is used to assess the ADC value inside the tumor. ROIs are put in the solid part of the tumorous lesion. So far, 54 patients (28 TKI, 26 CTx) have been included. Findings will be correlated with routinely performed FU CT-imaging and the clinical outcome during FU visits. Further, an accompanying biomarker program aims to elucidate ultra-early blood-bound signs of apoptosis in correlation with MRI signals. This multicenter study will address the unmet clinical need of ultra-early detection of therapy response in NSCLC in order to translate this promising approach into broad clinical practice.

Legal entity responsible for the study: Claus Peter Heussel.

Funding: German Center for Lung Research (DZL).

Disclosure: H-U. Kauczor: Grant: Siemens; Speakers bureau: Boehringer Ingelheim, Philips; Grant, speakers' bureau: Bracco, Bayer. M. Thomas: Speaker: Lilly, BMS, MSD, Roche, Pfizer, AstraZeneca; Advisory board: Lilly, BMS, MSD, Roche, Pfizer, AstraZeneca, Cellgene, Mediolanum. H. Golpon: Advisory boards: Roche, AstraZeneca, Boehringer Ingelheim, BMS. A. Tufman: Advisory boards: Roche, AstraZeneca, Boehringer Ingelheim. C.P. Heussel: Consultation or other fees: Schering-Plough, Pfizer, Basilea, Boehringer Ingelheim, Novartis, Roche, Astellas, Gilead, MSD, Lilly, Intermune, Fresenius; Research funding: Siemens, Pfizer, MeVis, Boehringer Ingelheim; Lecture fees: Gilead, Essex, Schering-Plough, AstraZeneca, Lilly, Roche, MSD, Pfizer , Bracco, Meda Pharma, Intermune, Chiesi, Siemens, Covidien, Pierre Fabre, Boehringer Ingelheim, Grifols, Novartis, Basilea, Bayer. F. Bozorgmehr: Research funding: BMS; Honoraria: MSD, Novartis. All other authors have declared no conflicts of interest.

1508TiP Durvalumab in frail and elder patients with stage four NSCLC: The DURATION trial

J. Kuon[1], F. Bozorgmehr[2], M.A. Schneider[3], J. Krisam[4], F. Lasitschka[5], M. Serke[6], W. Schuette[7], N. Moosmann[8], W. Gleiber[9], M. Faehling[10], M. Wermke[11], P. Schuett[12], M. Boesche[13], V. van Laak[14], L. Fischer von Weikersthal[15], M. Ulmer[16], C. Meyer zum Büschenfelde[17], J.R. Fischer[18], M. Thomas[19]

[1]Thoracic Oncology, Thoraxklinik Heidelberg, Heidelberg, Germany, [2]Thoracic Oncology, University Hospital Heidelberg, Heidelberg, Germany, [3]Translational Research Unit, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [4]Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany, [5]Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany, [6]Thorakale Onkologie, Lungenklinik Hemer des Deutschen Gemeinschafts-Diakonieverbandes GmbH, Hemer, Germany, [7]Oncology, Hospital Martha-Maria Halle-Doelau, Halle, Germany, [8]Department of Oncology and Hematology, Hospital Barmherzige Brüder, Regensburg, Germany, [9]Medizinische Klinik I, University Hospital Frankfurt, Frankfurt, Germany, [10]Klinik für Kardiologie und Pneumologie, Klinikum Esslingen, Esslingen, Germany, [11]University Hospital Carl-Gustav-Carus, University Hospital Carl-Gustav-Carus, Dresden, Germany, [12]Oncology, Onkologische Schwerpunktpraxis, Gütersloh, Germany, [13]Oncology, University of Greifswald, Greifswald, Germany, [14]Department of Pulmonary Medicine, DRK-Klinikum Berlin-Mitte, Berlin, Germany, [15]Oncology, Hospital St. Marien Amberg, Amberg, Germany, [16]Oncology, Hospital Ludwigsburg, Ludwigsburg, Germany, [17]Clinic for Hematology, Oncology, St. Vincentius Hospital Karlsruhe, Karlsruhe, Germany, [18]Oncology, Klinik Loewenstein, Loewenstein, Germany, [19]Thoraxoncology, Thoraxklinik Heidelberg, Heidelberg, Germany

Background: Elderly patients represent a major population of non-small cell lung cancer (NSCLC) patients in routine clinical practice, yet are underrepresented in clinical trials. In particular, data regarding efficacy and safety in frail or elderly patients with respect to immunotherapy is lacking. Importantly, immunosenescence in elderly patients can result in altered activities of immune-modulating drugs such as PD-1/PD-L1 inhibitors. Thus, there is an urgent need to assess safety and efficiency of such inhibitors in this group.

Trial design: In this prospective, open label, treatment stratified, and randomized phase II study, 200 patients with stage IV NSCLC, >70 years old and/or "frail" (Charlson Comorbidity Index >1) or restricted performance score (ECOG >1), who are amenable for at least chemotherapy with gemcitabine or vinorelbine, will be included. Patients are stratified after a modified CARG Score (a predicting chemotherapy toxicity score): "Fit" patients are treated with doublet chemotherapy (carboplatin/nab-paclitaxel), while "unfit" patients receive monochemotherapy (gemcitabine or vinorelbine). Patients are then 1:1 randomized and receive either 4 cycles of chemotherapy + follow-up every 8 weeks (Arm A/D) or 2 cycles of chemotherapy followed by 2 cycles of durvalumab and subsequent maintenance durvalumab every 4 weeks (Arm B/C). The primary endpoint is the rate of treatment related grade III/IV adverse events (CTCAE V4.03). As secondary endpoints progression-free survival according to RECIST 1.1, overall survival, descriptive subgroup analyses according to PD-L1 expression, and quality of life will be addressed. Geriatric screening assessments and functional tests will be performed to complete the description of a potential "frail" and "elderly" patient cohort (G8-questionnaire, Timed up & go test, 6MWT). Further, a biomarker profiling program will analyse immune-related effects and potentially identify novel response predictors. The DURATION trial will prospectively investigate the safety and tolerability of PD-L1 treatment with durvalumab after chemotherapy in elderly and frail patients and thereby provide new insights into the effect of PD-L1 blockade and the impact of immunosenescence in this important cohort.

Clinical trial identification: EudraCT: 2016-003963-20.

Legal entity responsible for the study: AIO-Studien-gGmbH.

Funding: AstraZeneca, Celgene.

Disclosure: J. Kuon: Honoraria: AstraZeneca, Pfizer. M. Serke: Honoraria: BMS, Celgene, Lilly, Roche. AD boards: AstraZeneca; BMS, Boehringer, Celgene, Hexal, Lilly,

Merck, MSD, Pfizer, Roche, Teva, Abbvie, AIO. M. Faehling: Honoraria: AstraZeneca, BMS, MSD, Roche. M. Wermke: Honoraria: BMS, Novartis, Roche, Bayer, Glenmark, AstraZeneca; Travel cost reimbursements: AstraZeneca, BMS, MSC, Novartis, Glenmark; Research funding: Novartis, Pfizer. M. Thomas: Speaker honoraria: Lilly; BMS, MSD, Roche, Pfizer, AstraZeneca; Advisory boards: Lilly, BMS, MSD, Roche, Pfizer, AstraZeneca, Celgene; Mediolanum Scientific projects: AstraZeneca, BMS, Celgene. All other authors have declared no conflict of interest.

1509TiP Randomized phase II trial of osimertinib with or without local consolidation therapy (LCT) for patients with EGFR-mutant metastatic NSCLC (NORTHSTAR)

Y.Y. Elamin[1], M. Antonoff[2], C. Blakely[3], M. Baggstorm[4], T. Bivona[5], X. Le1, A.V. Louie[6], R.C. Doebele[7], C. Rusthoven[8], P. Lee[3], R. Govindan[4], S.G. Swisher[9], V.A. Papadimitrakopoulou[10], J.V. Heymach[11], D.R. Gomez[12]

[1]Thoracic/Head and Neck Medical Oncology, UT MD Anderson Cancer Center, Houston, TX, USA, [2]Thoracic and Cardiovascular Surgery, UT MD Anderson Cancer Center, Houston, TX, USA, [3]Thoracic Medical Oncology, University of California San Francisco, San Francisco, CA, USA, [4]Internal Medicine, Division of Oncology, Washington University in St. Louis, St. Louis, MO, USA, [5]Medical Oncology, University of California San Fransesco, Aurora, CO, USA, [6]Radiation Oncology, London Health Science Centre, London, ON, Canada, [7]Medical Oncology, University of Colorado, Aurora, CO, USA, [8]Radiation Oncology, University of Colorado, Aurora, CO, USA, [9]Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [10]Thoracic/Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [11]Thoracic Head and Neck, MD Anderson Cancer Center, Houston, TX, USA, [12]Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA

Background: Osimertinib has been shown to be superior to erlotinib or gefitinib in previously untreated patients with EGFR mutant (exon 19 deletion/L858R) NSCLC. Osimertinib is approved for the treatment of patients with metastatic T790M+ NSCLC who have disease progression after EGFR-TKI therapy. The majority of EGFR mutant NSCLC patients who are treated with a TKI ultimately acquire resistance, including those treated with osimertinib. We have recently completed a phase 2 randomized clinical trial demonstrating that patients with oligometastatic NSCLC treated with aggressive local consolidation therapy (surgery or radiation) have improved progression-free survival compared to those patients treated with systemic therapy alone (Gomez et al., Lancet Oncol, 2016). A retrospective review of EGFR-mutant subset of patients enrolled in the trial suggests that EGFR-mutant patients may derive greater benefit from this approach. Thus, two premises underlie the current randomized trial: 1) osimertinib is standard of care for treatment of primary and TKI resistant EGFR-mutant metastatic NSCLC, and 2) the majority of patients treated with osimertinib ultimately become resistant, and LCT has been found to improve outcomes compared to systemic therapy alone.

Trial design: A phase 2 randomized, multicenter, study to evaluate the efficacy of osimertinib with or without LCT for patients with EGFR-mutant metastatic NSCLC. Eligible patients include 1) Previously untreated patients with EGFR-mutant NSCLC (L858R or exon 19 deletion) or 2) NSCLC patients with acquired EGFR T790M that was acquired following progression on first or second generation TKI, this subset of patients must have not received prior third generation TKI. Patients who don't have disease progression after 6-12 weeks of induction osimertinib will be randomized 1:1 to osimertinib continuation or to osimertinib continuation with LCT Primary end point is progression free survival Exploratory biomarkers associated with resistance to osimertinib will be evaluated in tumor tissue and plasma collected at baseline and progression. 140 patients will be enrolled in 5 centers in North America.

Clinical trial identification: NCT03410043.

Legal entity responsible for the study: UT MD Anderson Cancer Center.

Funding: National Comprehensive Cancer Network NCCN, AZ grant.

Disclosure: All authors have declared no conflicts of interest.

1510TiP The GATTO study: A phase I of the anti-EGFR tomuzotuximab (TO) in combination with the anti-MUC1 gatipotuzumab (GAT) in patients with EGFR positive solid tumors

E. Garralda[1], M. van Hoef[2], S. Ochsenreither[3], L. Gianni[4], D. Lorusso[5], W. Fiedler[6], U. Keilholz[7], K. Klinghammer[8], C. Dicke[9], M. Kebenko[9], I. Matos[10], J. Tabernero[11], F. Raspagliesi[12], G. Del Conte[13], B. Habel[14], H. Baumeister[14], A. Zurlo[15]

[1]Early Drug Development Unit, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [2]Clinical Development, Glycotope, Berlin, Germany, [3]Charité Comprehensive Cancer Center, Charité University of Medicine, Berlin, Germany, [4]Oncology, IRCCS San Raffaele, Milan, Italy, [5]Gynecologic Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [6]Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [7]Medical Oncology, Charite Berlin Mitte, Berlin, Germany, [8]Medical Oncology, Charite Comprehensive Cancer Center, Berlin, Germany, [9]Medical Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [10]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [11]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [12]Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [13]Medical Oncology, IRCCS San Raffaele Hospital, Milan, Italy, [14]Laboratory, Glycotope, Berlin, Germany, [15]Clinical Development, Glycotope GmbH, Berlin, Germany

Background: TO (CetuGEX) is a second-generation anti-EGFR antibody that specifically binds to EGFR and acts as a competitive antagonist at the ligand binding site. GAT (PankoMab-GEX) is a novel humanized monoclonal antibody, which recognizes the tumor-specific epitope of mucin-1 (TA-MUC1) expressed on tumor cells. Both antibodies are glyco-engineered to potentiate antibody-dependent cellular cytotoxicity (ADCC). Compelling preclinical evidence suggests a complex interaction between EGFR and cell surface expressed TA-MUC1 in driving neoplastic processes and shows a synergistic antibody dependent cell cytotoxicity activity with the dual targeting of these molecules. Based on this evidence, this study aims to assess the tolerability, safety and preliminary activity of a combination with anti-EGFR and anti-TA-MUC1 glyco-engineered antibodies.

Trial design: The GATTO is an open label phase Ib dose evaluation study in patients with EGFR positive metastatic solid tumors, for whom no standard treatment is available. The proposed doses and schedule are 1200 mg Q2W for TO and 1400 mg Q2W for GAT. A staggered approach will be utilized in order to minimize the number of patients exposed and to evaluate the safety of the combination treatment. The first 6 patients will be enrolled into a safety run-in phase where the number of dose-limiting toxicities (DLTs) will be evaluated. Assuming that the safety criteria are met (ie. observation of 0 or 1 DLT), the dose will remain unchanged and further patients will be recruited at the highest dose level. If this is not the case, a step-wise dose reduction approach will be applied. The antitumor activity of the combined treatment will be evaluated as secondary endpoints including best overall response rate (ORR), duration of objective response (DOR), progression-free (PFS) and overall (OS) survival. Extensive pharmacokinetics (PK) and pharmacodynamics (PD) (cellular immune status, serum and tissue biomarkers) will be also analyzed. As of the beginning of May 2018 the study is ongoing and 6 patients are being treated.

Clinical trial identification: NCT03360734.

Legal entity responsible for the study: Glycotope GmbH.

Funding: Glycotope GmbH.

Disclosure: E. Garralda: Investigator: Glycotope GmbH. M. van Hoef: Consultant: Glycotope GmbH. S. Ochsenreither, L. Gianni, D. Lorusso, W. Fiedler, U. Keilholz, K. Klinghammer, C. Dicke, M. Kebenko, I. Matos, J. Tabernero, F. Raspagliesi, G. Del Conte: Investigator: Glycotope GmbH. B. Habel, H. Baumeister, A. Zurlo: Employee: Glycotope GmbH.

Annals of Oncology 29 (Supplement 8): viii548–viii556, 2018
doi:10.1093/annonc/mdy295

PALLIATIVE CARE

1511O Training oncologists and preparing patients for shared decision making about palliative systemic treatment: Results from the randomized controlled CHOICE study

H.W.M. van Laarhoven[1], I. Henselmans[2], P. van Maarschalkerweerd[2], H. de Haes[2], D.W. Sommeijer[3], P.B. Ottevanger[4], H-B. Fiebrich[5], S.E. Dohmen[6], G-J.M. Creemers[7], F.Y.F.L. De Vos[8], E.M. Smets[9]

[1]Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Medical Psychology, Academic Medical Center, Amsterdam, Netherlands, [3]Medical Oncology, Flevoziekenhuis, Almere, Netherlands, [4]Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [5]Medical Oncology, Isalaklinieken, Zwolle, Netherlands, [6]Medical Oncology, Bovenij Hospital, Amsterdam, Netherlands, [7]Medical Oncology, Catharina Hospital Eindhoven, Eindhoven, Netherlands, [8]Medical Oncology, University Hospital Utrecht, Utrecht, Netherlands, [9]Medical Psychology, Academic Medical Center (AMC), Amsterdam, Netherlands

1512O Automated survival prediction in metastatic cancer patients using high-dimensional electronic medical record data

M.F. Gensheimer[1], A.S. Henry[2], D.J. Wood[2], T.J. Hastie[2], S. Aggarwal[1], S. Dudley[1], P. Pradhan[1], I. Banerjee[2], E. Cho[3], K. Ramchandran[4], E. Pollom[1], A. Koong[1], D. Rubin[2], D.T. Chang[1]

[1]Radiation Oncology, Stanford University School of Medicine, Stanford, CA, USA, [2]Biomedical Data Science, Stanford University School of Medicine, Stanford, CA, USA, [3]Genentech, South San Francisco, CA, USA, [4]Oncology, Stanford University School of Medicine, Stanford, CA, USA

1513PD A prospective study examining cachexia predictors in patients with incurable cancer

O.M. Vagnildhaug[1], C. Brunelli[2], M.J. Hjermstad[3], F. Strasser[4], V. Baracos[5], A. Wilcock[6], M. Nabal[7], S. Kaasa[3], B. Laird[8], T.S. Solheim[1]

[1]The Cancer Clinic & European Palliative Care Research Centre (PRC), Department of Clinical and Molecular Medicine, St. Olav's Hospital & NTNU, Trondheim, Norway, [2]Palliative Care, Pain Therapy and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy, [3]European Palliative Care Research Centre, Institute of Clinical Medicine and Department of Oncology, Oslo University Hospital, Oslo, Norway, [4]Oncological Palliative Medicine, Kantonsspital St. Gallen, St. Gallen, Switzerland, [5]Department of Oncology, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, [6]Hayward House, Nottingham University Hospital NHS Trust, Nottingham, UK, [7]Palliative Care Supportive Team, Hospital Universitario Arnau de Vilanova de Lleida, Lleida, Spain, [8]Edinburgh Cancer Research UK Centre, University of Edinburgh, Edinburgh, UK

1514PD Timing of palliative care referral before and after a cluster randomized controlled trial (RCT) of early palliative care

D. Hausner[1], C. Tricou[1], D. Wadhwa[2], A. Pope[1], M. Giruparajah[1], N. Swami[1], M. Krzyzanowska[3], K. Mah[1], C. Zimmermann[1]

[1]Department of Supportive Care, Princess Margaret Cancer Centre, Toronto, ON, Canada, [2]Medical Oncology, BC Cancer, Kelowna Centre, Kelowna, BC, Canada, [3]Department of Medical Oncology and Haematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

1515PD Randomized clinical trial of an individualized intervention promotes cancer patients' prognostic awareness and reduces CPR received in the last month

C.H. Chen[1], J-S. Chen[2], F.H. Wen[3], J.W-C. Chang[2], W-C. Chou[2], C-H. Hsieh[2], M-M. Hou[2], S.T. Tang[4]

[1]College of Nursing, National Taipei University of Nursing and Health Science, Taipei, Taiwan, [2]Division of Hematology-Oncology, Chang Gung Memorial Hospital-Linkou, Tao Yuan, Taiwan, [3]Department of International Business, Soochow University, Taipei, Taiwan, [4]School of Nursing, Chung Gung University, Taoyuan, Taiwan

1516P Effectiveness of a randomized control trial of an individualized, interactive advance care planning intervention in improving terminally ill cancer patients' psychological symptoms, quality of life and concordance between preferred and received life-sustaining treatments

S.T. Tang[1], J-S. Chen[2], W-C. Chou[2]

[1]School of Nursing, Chung Gung University, Taoyuan, Taiwan, [2]School of Medicine, Chung Gung University, Taoyuan, Taiwan

Background: To examine the effectiveness of an advance care planning (ACP) intervention in facilitating concordance between cancer patients' preferred and life-sustaining treatments (LSTs) received in the last month and in improving quality of life (QOL), anxiety symptoms, and depressive symptoms over the dying process.

Methods: Terminally ill cancer patients (N = 460) were randomly assigned 1:1 to the experimental and control arms. Data were obtained from 430 participants who died through December 2017. The experimental arm received an individualized, interactive ACP intervention tailored to participants' readiness to engage in ACP. The control arm received a sham intervention of education on symptom management. Group allocation was concealed, data collectors were blinded, and treatment fidelity was ensured. Outcome measures included concordance of preferences for and receipt of six LSTs, QOL (McGill Quality of Life Questionnaire scores), as well as anxiety and depressive symptoms (Hospital Anxiety and Depression Scale scores). Intervention effectiveness was evaluated by intention-to-treat analysis.

Results: Concordance between LST preferences and LSTs received were 58.2-77.5% and 59.0-75.7% for the experimental and control arms, respectively. Between-arm differences in concordance between the six preferred and received LSTs were not significantly (odds ratios [95% CI]: 0.966 [0.653, 1.428]-1.107 [0.690, 1.775]). Participants in the experimental arm had significantly lower anxiety (β [95% CI]=-0.583 [-0.977, -0.189], p = 0.004) and depressive (β [95% CI]=-0.533 [-1.036, -0.030], p = 0.038) symptoms than those in the control arm, but QOL did not differ.

Conclusions: Our individualized, and interactive ACP intervention facilitated participants' psychological adjustment to the end-of-life (EOL)-care decision-making process, but did not improve their QOL nor facilitate EOL care that honored their wishes before death. Our findings can ensure clinicians that ACP intervention is not detrimental to patients' psychological well-being, but improves it at EOL.

Clinical trial identification: NCT01912846, 2018/1/24.

Legal entity responsible for the study: Chang Gung University, School of Nursing.

Funding: National Health Research Institutes in Taiwan.

Disclosure: All authors have declared no conflicts of interest.

1517P Current status of the integration of oncology and palliative care in Japan: A nationwide survey

U. Yu[1], K. Sato[2], T. Morita[3], M. Mori[4], C. Shimizu[5], Y. Horie[6], M. Hirakawa[6], T.E. Nakajima[6], S. Tsuneto[7], M. Muto[1]

[1]Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto City, Japan, [2]Department of Nursing, Nagoya University Graduate School of Medicine, Nagoya City, Japan, [3]Division of Supportive and Palliative Care, Seirei Mikatahara General Hospital, Hamamatsu City, Japan, [4]Palliative Care Team, Seirei Mikatahara General Hospital, Hamamatsu City, Japan, [5]Breast Center, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan, [6]Department of Clinical Oncology, St Marianna University School of Medicine, Kawasaki City, Japan, [7]Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto City, Japan

Background: Based on recommendations from several agencies, including the European Society for Medical Oncology, palliative care (PC) services are increasingly recognised as an essential part of oncology care. However, the implementation of integration of oncology and palliative care (IOP) seems to be evolving slowly and detailed progress of IOP remain unclear. This was a cross-sectional nationwide survey to clarify the current status of IOP in Japan.

Methods: We performed comparison between designated cancer hospitals (DCHs) and non-designated cancer hospitals (non-DCHs), since considerable number of patients in Japan are receiving cancer treatment at non-DCHs. We distributed the questionnaire to executives or directors of oncology departments at cancer hospitals in November 2017 and sent a reminder mail later. Our questionnaire was developed based on indicators of IOP with international consensus. We conducted descriptive statistics, t-tests and Cochrane-Armitage trend tests where appropriate. To adjust the difference of inpatient beds scale, estimates at non-DCHs were weighted by the distribution of inpatient beds at DCHs.

Results: Among the 399 DCHs and 478 non-DCHs that were surveyed, 269 (67%) and 259 (54%) responded, respectively. DCHs had significantly more PC resources than non-DCHs did (e.g. both full-time physicians and nurses on a PC team, 53% vs. 14% ($p < 0.001$); the availability of outpatient PC service $\geq$ 3days per week, 48% vs. 21% ($p < 0.001$)). Clinical tools for PC services were well equipped (e.g. symptom management guidelines, 89% vs. 79% ($p = 0.238$); PC referral criteria, 72% vs. 59% ($p = 0.077$)). However, strategies to identify suitable patients for PC referral seemed to be undeveloped (e.g. clinical care pathways, 17% vs. 5% ($p < 0.001$); referral using time trigger, 9% vs 8% ($p = 0.358$); referral using needs trigger, 31% vs. 20% ($p = 0.820$)). Mutual rotation training for both oncology and PC fellows and research opportunities on IOP were limited.

Conclusions: Non-DCHs face a severe lack of PC resources, whereas DCHs might have relatively more resources to enhance IOP. Both education and research opportunities for IOP were limited. Further research is warranted to identify specific barriers to and facilitators for implementation of IOP.

Legal entity responsible for the study: Graduate School of Medicine, Kyoto University.

Funding: Ministry of Health Labor and Welfare in Japan (Health Labor Science Research Grant).

Disclosure: All authors have declared no conflicts of interest.

1518P Access to palliative care before death in French cancer patients during the first two years after diagnosis: The national cancer cohort

M.K. Bendiane[1], A. Janah[1], D. Leufeuvre[2], P-J. Bousquet[2]

[1]Faculté de Médecine, Aix Marseille University, INSERM, IRD, Economics and Social Sciences Applied to Health & Analysis of Medical Information (SESSTIM), Marseille, France, [2]National Cancer Institute, INCa, Paris, France

Background: Palliative care (PC) is a part of a multidisciplinary approach that improves the quality of life of patients with potentially terminal illnesses including cancer. However, referrals to PC occur relatively late for the management of physical and psychological distress. In France, the proportion of patients who actually receive PC is not clear. This study aims to provide the prevalence and characteristics of dead cancer patients who have been referred at least one time to PC, and to identify the delay between PC access and death.

Methods: All people living in France (67 million population) with universal insurance coverage and diagnosed, treated or followed up for a cancer, such as survivors, are included and will be followed up for 25 years. Extracted from SNDS, the cancer cohort contains all healthcare consumption refunded data (i.e hospitalization, outpatient care, medication . . .) for subjects who have undergone cancer-related treatment since 2010. Every year, new cases are included in the cancer cohort. Data were extracted from the French "cancer cohort" databases for all people with cancer-related care between 2013 and 2015. Demographic characteristics, type of cancer, health care consumption, and delay between PC and death were determined.

Results: Of the 310 901 cancer patients included in the Cancer Cohort in 2013, 70 858 (22.8%) died between 2013 and 2015. Of these, the proportion of PC access was 52%. Access to PC of dead cancer patients was different according to age, gender, type of cancer and comorbidities. The median time between diagnosis and death, diagnosis and PC access, and PC access and death, were 225.0 days (Q1-Q3: 84.0 - 418.0), 158.0 days (Q1-Q3: 38.0 - 354.0) and 26.0 days (Q1-Q3: 11.0 - 56.0), respectively.

Conclusions: If more than half of cancer patients in our study had access to PC before death, differences in age and gender were observed confirming the results of previous studies. We also noted that the delay between PC access and death indicates a late referral to PC in the disease trajectory. General practitioners, PC specialists and the community at large need education so that cancer patients have access to quality PC as soon as possible and without necessarily being in near end-of-life situations.

Legal entity responsible for the study: French National Cancer Institute (INCa) - Cohort Cancer Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1519P Anticancer therapy at the end of life of breast, prostate, and colorectal cancer patients

V. Heidt[1], K. Hermes-Moll[1], K. Blaschke[2], V. Lappe[2], P. Ihle[2], I. Schubert[2], W. Baumann[1]

[1]WINHO GmbH, Cologne, Germany, [2]PMV Forschungsgruppe, Universität Köln, Cologne, Germany

Background: The study addresses growing concerns regarding aggressive cancer treatment at the end of life. The extent of anticancer treatment at the end of life of breast, prostate, and colorectal cancer patients aged 60 years and older as well as its development in recent years is investigated.

Methods: Routine data of the statutory health insurance company AOK Hessen in Germany (approx. 1.4 million assured persons in 2014) for 2008-2013 are analyzed. Cancer patients are identified using ICD-10 codes: breast (C50), prostate (C61), and colorectal cancer (C18-21), and validated using inpatient and outpatient diagnoses. The last year before death is examined in 90-days periods and, in addition, the last 90 days in 30-days periods.

Results: Key results are that cancer patients aged 80 years and older less often receive anticancer therapy at the end of life (e.g. women with breast cancer in 2013: 20% in the last 90 days, 6% in the last 30 days before death) than patients aged 60-69 (56% and 29%) or 70-79 (46% and 18%). There is no clear development toward a reduction in anticancer treatment in women with breast cancer at the end of life between 2008 and 2013. The number of anticancer therapies at the end of life in men with prostate cancer aged 60-69 years reduced between 2008 and 2013, especially in the second (2008: 56%, 2013: 49%) and third 90-days period from last (2008: 57%, 2013: 45%) and reached the same level as patients aged 70-79. There are differences in the number of anticancer therapies between men and women with colorectal cancer at the end of life. Especially, women aged 80 and older with colorectal cancer rarely receive anticancer therapy in the year before death (in 2013: 5% in the last 90 days, 1% in the last 30 days before death) compared to men (12% and 5%).

Conclusions: These results support increased sensitivity regarding anticancer treatment at the end of life. To further investigate these results, studies should include cancer staging, general health status, and patient reported outcomes such as quality of life.

Legal entity responsible for the study: WINHO GmbH & Universität Köln / PMV Forschungsgruppe.

Funding: Zentralinstitut für die kassenärztliche Versorgung.

Disclosure: All authors have declared no conflicts of interest.

1520P Perspectives and attitudes towards the integration of oncology and palliative care in Japan: A nationwide survey

U. Yu[1], K. Sato[2], T. Morita[3], M. Mori[4], C. Shimizu[5], Y. Horie[6], M. Hirakawa[6], T.E. Nakajima[6], S. Tsuneto[7], M. Muto[1]

[1]Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto City, Japan, [2]Department of Nursing, Nagoya University Graduate School of Medicine, Nagoya City, Japan, [3]Division of Supportive and Palliative Care, Seirei Mikatahara General Hospital, Hamamatsu City, Japan, [4]Palliative Care Team, Seirei Mikatahara General Hospital, Hamamatsu City, Japan, [5]Breast Center, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan, [6]Department of Clinical Oncology, St Marianna University School of Medicine, Kawasaki City, Japan, [7]Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto City, Japan

Background: Integration of oncology and palliative care (IOP) is recommended by several agencies, including the European Society for Medical Oncology. Given the slow evolution of IOP in practice, several barriers to its implementation may exist. Lack of institutional support is known to be one of the key barriers to IOP. However, institutional recognition towards IOP is less investigated. This was a cross-sectional nationwide survey to clarify the institutional perspectives and attitudes towards IOP in Japan.

Methods: We distributed a questionnaire to executives or directors of oncology departments at cancer hospitals on November 2017 and sent a reminder mail later. Since considerable number of patients are receiving cancer treatment at non-designated cancer hospitals (non-DCHs) in Japan, we performed comparison between designated cancer hospitals (DCHs) and non-DCHs. Questionnaire items were developed based on a comprehensive literature review. We conducted descriptive statistics, t-tests and Cochrane-Armitage trend tests where appropriate. To adjust the difference of inpatient beds scale, estimates of non-DCHs were weighted by the distribution of inpatient beds at DCHs.

Results: In total, 399 DCHs and 478 non-DCHs were surveyed, of which 269 (67%) and 259 (54%) responded, respectively. Most cancer hospitals considered their quality of palliative care (PC) services unsatisfying (75% vs. 76% ($p = 0.674$)), believed that IOP would be beneficial for their patients (85% vs. 89% ($p = 0.933$)) and did not regard it as costly (13% vs. 18% ($p = 0.217$)). DCHs had difficulty in recruiting PC physicians and non-DCHs in recruiting not only PC physicians but PC nurses and mental healthcare professionals. Although both were willing to facilitate an early referral to PC services (55% vs. 60% ($p = 0.001$)), less than 30% of hospitals was planning to increase full-time PC medical staff, inpatient PC beds and funding.

Conclusions: IOP was broadly recognised as beneficial for cancer patients and most institutions were willing to facilitate IOP. However, few institutions were planning to address their limited clinical resources. Strategies, such as the rearrangement of reimbursement systems or education for healthcare professionals, need to be investigated.

Legal entity responsible for the study: Graduate School of Medicine, Kyoto University.

Funding: This research is funded by the Ministry of Health Labor and Welfare in Japan (Health Labor Science Research Grant).

Disclosure: All authors have declared no conflicts of interest.

1521P Evolving concurrent integration of oncology and palliative care at an ESMO designated center over a decade

F. Strasser, T.C. Silzle, E.B. Schmidt

Clinic Medical Oncology & Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Background: Streamlining oncology (Onc) and specialist palliative care (SPC) into integrated patient (pt) care is increasingly a gold standard of optimized cancer care. The ways that integrated Onc/SPC manifests in clinical practice may change over time. Little is known about factors that drive evolution in integrated care practices.

Methods: From a pt's first appointment with outpatient SPC, all visits were chronologically color coded for Onc, SPC, and Neutral (e.g. emergency) or joint visits (Onc/SPC same day). Visual Graphic Analysis revealed 4 patterns of integration (Onc only; SPC only; CONCurrent: permanent exchange of Onc and SPC, $\geq$5 switches, joint visits; SEGmented: alternating periods of Onc or SPC, <4 switches), independent researchers approved reliability of patterns definitions. Data from 2006-2009 (presented 34-ESMO 2009) were compared with 2016-2017. Explanatory factors for patterns evolution were derived from multi-professional, consensual discussion reviewing descriptive statistics (e.g. impact of inpt admission on patterns, pattern stability over 3 months intervals, anticancer treatment administered by SPC, pt characteristics) and further explored in the data.

Results: 345 pts from 2006-09 and 64 from 2016 met eligibility criteria and were included. CONC occurred in 18% in 2006-09 and 45% in 2016 (X^2 (1, N = 409) = 22.66, $p < .001$)], and 14% vs 50% remained in the CONC pattern comparing 3 months intervals. Elimination of inpt visits left 3/4 of patterns unchanged. A double-boarded Onc/SPC physician saw 94% of pts in the 2016 sample and prescribed systemic anticancer treatment in > 1/3 of these visits, 77% of these pts were in the CONC Pattern. Joint Onc/SPC visits were increasing over time, also (bi-)weekly alternating visits by Onc and SPC (double-boarded). Pts of CONC had complex and high needs for palliative interventions, were in phase I studies, or refused standard anticancer treatment, but accepted later.

Conclusions: Concurrent Onc/SPC is an increasing and consistent pattern, not explained by mere bed availability. Prescribing anticancer therapy by a double-boarded physician may foster integration. Further research may determine how CONC affects pt outcomes and the influence of pt and physicians' characteristics.

Legal entity responsible for the study: Cantonal Hospital St.Gallen.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1522P The impact of inclusion in home palliative program and distance to hospital on chemotherapy near end of life

J. Balsalobre[1], A. Checa-Soriano[1], P. Cerezuela-Fuentes[1], M. Martínez-Penella[1], M.J. Martínez-Ortíz[1], J.L. Alonso-Romero[2], M.I. Luengo-Alcázar[1], M.T. García-García[1]

[1]*Medical Oncology, Hospital Universitario Santa Lucia, Cartagena, Spain,* [2]*Medical Oncology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain*

Background: Chemotherapy (CT) near end of life is considered a marker of inadequate palliative care for cancer patients. The objectives of our work were to determine the influence of palliative care at home and the distance between the residence area and the cancer referral center on the interval between last chemotherapy cycle and death.

Methods: A retrospective observational study was conducted in a tertiary care hospital. All cancer patients deceased between January 2013 and June 2014 were included. Clinical, demographical and treatment variables were obtained from medical records.

Results: Our population of 951 patients had a mean age of 63 years; male: 601 (63%), females: 350 (37%). Tumor locations: lung, 261 (28%); colorectal, 125 (13%); breast, 99 (10.7%); pancreas, 79 (8.8%). The table shows an analysis of the CT used in all patients, indicating a high proportion of CT use near the end of life (68% in the last 3 months). Average time elapsed between the end of treatment and death was significantly longer in the group of patients included in home palliative care programs (n = 111; 24.5%) vs. those not included (n = 367; 75.5%): 42.3 vs. 24.7 days ($p < 0.05$). CT was stopped earlier in patients belonging to geographical areas farther from the referral center, with median times between last cycle of CT and death of 14.9 days for patients living near the referral hospital versus 51.9 days for > 70 km ($p = 0.041$) and 58 days for > 100 km ($p = 0.013$).

Table: 1522P Analysis of CT use in all patients

N = 901	n (%)
Treatment No CT CT	198 (22) 703 (78)
Nr of lines of CT 1 2 3 4 or more	441 (49) 198 (22) 135 (15) 127 (14)
Nr of drugs in last line of CT 1 2 3	378 (42) 414 (46) 109 (12)
CT in the last 3 months	604 (67)
CT in the last 4 weeks	405 (45)
CT in the last week	63 (7)

Conclusions: In our population, a high percentage of CT was observed in the final stages of life, including a high use of third and successive lines of treatment. Patients included in home palliative care programs and/or belonging to more distant geographical areas finished active treatment before, thereby suggesting that both factors impact on decision making for patients with advanced cancer. Understanding the factors that determine the use of CT near the end of life may contribute to limit its inadequate indication.

Legal entity responsible for the study: Hospital Universitario Santa Lucia, Cartagena.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1523P Cancer patients' perceptions of palliative care

J. Yoong[1], B. Chosich[1], M. Burgess[1], A. Earnest[2], F. Runacres[1], L. William[1], M. Franco[1], P. Poon[1]

[1]*Supportive and Palliative Care Unit, Monash Health, Melbourne, Australia,* [2]*Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia*

Background: Despite clear benefits and increased efforts towards earlier integration of palliative care (PC) with oncology, there are concerns that PC remains stigmatized and predominantly associated with end-of-life care (EOLC). This project aims to explore current perceptions and understanding of PC in cancer patients.

Methods: Prospective survey conducted in the oncology ward of a tertiary academic hospital in Melbourne, Australia. Over a 4-month period a 16-item questionnaire was distributed to all cancer patients upon admission to the ward (N = 103). Chi-Squared test was used to examine for significant factors related to patients' perceptions of PC.

Results: Ninety-six patients (93%) completed the questionnaire; of which 76% had metastatic cancer. Of the domains explored, salient findings were: 1) Familiarity and experience: 76% had heard of PC; while only 21% had received PC. Self-rating of PC knowledge was varied, and evenly distributed: 31% good/excellent, 36% average and 33% below average/poor. 2) Roles of PC and oncology: 86% believed they could receive concurrent oncology care and 81% believed they could receive anti-cancer treatment whilst receiving PC. Those who had heard of PC were significantly more likely to respond that they could receive concurrent anti-cancer treatment ($p = 0.005$), as well as those who had better self-rated PC knowledge ($p = 0.045$). 3) Perceptions: 45% believed PC was only associated with EOLC. Those more likely to disagree with this statement had received PC services ($p = 0.039$). The majority (77%) felt comforted with PC involvement; this was significantly associated with older age ($p = 0.047$) and

an understanding that oncology ($p < 0.005$) and anti-cancer treatment ($p = 0.013$) could continue. However, 40% felt frightened and 29% felt hopeless about a referral to PC. Notably, 50% felt more comfortable with "supportive care" services (versus PC), 25% were neutral and 25% were not.

Conclusions: This survey had an excellent response rate and results were reassuring that, in general, respondents had an accurate understanding of and positive perceptions of PC. Familiarity and comfort with PC were associated with significantly better understanding of PC. This may reflect overall progress in integration of PC and oncology care.

Legal entity responsible for the study: Research Support Services, Monash Health.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1524P Multicenter feasibility study of physician orders for life-sustaining treatment (POLST) for terminal cancer patients

H.J. An[1], H.J. Jeon[2], J. Cheon[3], S.H. Chun[4], H.A. Jung[5], H.K. Ahn[6], K.H. Lee[7], M-H. Kim[8], J.H. Kim[9], S. Kim[10], S-J. Koh[3]

[1]Department of Medical Oncology, St. Vincent's Hospital, College of Medicine, Catholic University of Korea, Suwon, Republic of Korea, [2]Department of Internal Medicine, Seoul Medical Center, Seoul, Republic of Korea, [3]Department of Oncology, Ulsan University Hospital, Ulsan, Republic of Korea, [4]Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine Catholic University of Korea, Bucheon, Republic of Korea, [5]Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Dongtan, Republic of Korea, [6]Department of Internal Medicine, Gachon University Gil Hospital, Incheon, Republic of Korea, [7]Yeungnam University College of Medicine, Department of Internal Medicine, Daegu, Republic of Korea, [8]Ewha Institute of Convergence Medicine, Seoul, Republic of Korea, [9]Department of Hematology and Oncology, Ulsan University Hospital, Ulsan, Republic of Korea, [10]Department of Nursing, Changwon National University, Changwon, Republic of Korea

Background: Terminally ill patients can draw up Physician Orders for Life-Sustaining Treatment (POLST) with physicians to decide whether they want to suspend life-prolonging treatment near death. We conducted a multicenter, prospective study to assess the feasilibity of completing the POLST in real practice for cancer patients.

Methods: The inclusion criteria were patients with terminal cancer, age $\geq$19, and able to communicate. The purpose and concept of POLST was introduced first, and POLST was discussed with those whom wanted. Primary endpoint of this study was the completion rate of the POLST form in Korea.

Results: From June to December 2017, 336 patients were enrolled from seven hospitals. The median age was 66 (20-97) years, 177 (52.7%) were male, and 203 (60.4%) showed ECOG 3/4. Hepato-pancreato-biliary cancer (26.2%) was the most common, followed by lung (23.2%) and gastrointestinal (19.9%) origins. The mean expected survival duration was 10.6$\pm$7.3 months. At enrollment, 41.2% received hospice care, 29.6% stopped anti-cancer treatment, but 14.0% were in the middle of chemotherapy. The POLST were introduced in 203 patients (60.4%), and 105 patients (31.2%) completed the documentation of POLST. Barriers to introducing POLST were as follows; refusal from family members (29.8%); patients' denial or unawareness of prognosis (13.4%); lack of rapport with patients (13.3%); uncertainty of prognosis or timing (12.6%); guilty feelings (7.5%); and inadequate time/place (7.2%). Patients refused to sign the POLST due to lack of understanding (32.3%), emotional discomfort (32.3%), difficulty in making decision by themselves (29.8%), and denial of prognosis (5.7%).

Conclusions: Only one-third of patients completed the POLST, and various barriers were found among physicians, patients and families.

Legal entity responsible for the study: The authors.

Funding: This study was supported by grants from the Korean Cancer Study Group.

Disclosure: All authors have declared no conflicts of interest.

1525P Palliative care in advanced cancer: A clinical and ethical goal achieved?

J.C. Sanchez[1], R. Gomez-Bravo[1], A.M. Morito Aguilar[1], A. Royuela[1], B. Núñez García[1], T. Tojar[2], A. Ruano Ravina[3], C. Parejo[1], B. Cantos[1], M. Provencio Pulla[4]

[1]Servicio de Oncología Médica, Hospital Universitario Puerta de Hierro, Majadahonda, Spain, [2]Unidad de Cuidados Paliativos, Hospital Universitario Puerta de Hierro, Majadahonda, Spain, [3]Medicina Preventiva, Universidad de Santiago de Compostela, Santiago de Compostela, Spain, [4]Servicio de Oncología Médica, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain

Background: There is a global consensus that at the end of life relief of symptoms and suffering must be guaranteed. It is considered by our national health system as a priority goal in advanced cancer to address all the needs both the patient and the family, and improve their quality of life. Palliative Care Units (PCU) are intended to achieve this objective. In the last months of life, despite these advances, active treatments continue to predominate over palliative care.

Methods: We conducted a retrospective observational study selecting all patients with a first consultation in the Medical Oncology Unit of the Puerta de Hierro University Hospital during 2014 and 2015, who died before December 31st, 2017. Treatments carried out, assessment by a PCU and home palliative care services (HPCS), during the last 6 months of life and place of death (hospital, home or PCU) were reviewed. We aim to assess quality of care evaluating the use of active therapies and PCU using a novel approach considering what was done during the last six months of life.

Results: 622 patients were selected (36% female/64% male), median age of 69 years (IQR 61-76). 89% were stage IV. Lung (32%) and gastrointestinal (31%) cancer were the most frequent. In the last 6 months of life, 59% of patients received chemotherapy (CT), 26% radiotherapy (RT) and 8% undergone surgery. Median time from the last CT and RT to death was 39 days (IQR 23-75) and 57 days (IQR 21-100) respectively. 28% of patients were not assessed by a PCU from whom 52% were first evaluated in the last 30 days before death and 28% had been followed for more than 60 days. Only 44% were followed by HPCS. In patients with HPCS, the number of deaths at home (41%) and at PCU (29%) was significantly higher, with only 30% dying at hospital. By contrast, among those never assessed by HPCS: these figures were 12%, 24% and 64% respectively ($p < 0{,}001$).

Conclusions: 1/3 of patients had never been assessed by a PCU and the selection of patients who benefit from active therapies in the last months of life must be clearly improved. The association between place of death and assessment by a HPCS suggests the efficiency of these units and the benefit of increasing their resources. The objective of a global approach for palliative care to all patients with advanced cancer is close but not achieved yet.

Legal entity responsible for the study: Medical Oncology Department, Puerta de Hierro University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1526P The experience of onco-palliative care multidisciplinary meetings in Hotel Dieu de France University Hospital, an ESMO designated center of integrated oncology and palliative care

A. Houchan[1], T.S. Assi[2], Z. Bakouny[1], E. El Rassy[1], A. Tohme[3], M.C. Mouhawej[3], J.G. Kattan[1]

[1]Hematology-Oncology, Saint Joseph University, Faculty of Medicine, Beirut, Lebanon, [2]Medical Oncology, Institut de Cancérologie Gustave Roussy, Villejuif, France, [3]Palliative Care, Saint Joseph University, Faculty of Medicine, Beirut, Lebanon

Background: Current management strategies of cancer patients are adopting multidisciplinary meetings (MDM) and including the earliest palliative care intervention to improve the quality of life and survival. We have established, since 2015, a monthly onco-palliative care MDM for the management of our cancer patients. This study reports on the role of onco-palliative MDM in Hotel Dieu de France University Hospital, an ESMO Designated Center of Integrated Oncology and Palliative Care.

Methods: All cancer patients referred to the mobile palliative care unit and/or transferred to the palliative care unit, are presented and discussed during the onco-palliative care MDMs held between May 2015 and November 2017. Demographic, clinical and long-term characteristics were obtained from the electronic medical records and retrospectively nalysed. Demographic and survival data were compared between 2015 and 2017.

Results: 245 patients were presented during 20 MDMs. Median age was 68 years (range 59-77) and 58% of patients were male. The most common motive for palliative care consultation was social support (40%). Over the study period, no significant effect on the place of death was retained. However, patients had significant improvement in the symptomatic management of their disease between 2015 and 2017 (41.6% vs 7% in 2015) and better social support (60.7% vs 32.4% in 2015) ($p < 0.0001$). The median survival of patients after the onco-palliative care MDMS was 23 days (19.3- 26.7). No significant difference in survival was noted over the 3 year course ($p = 0.315$). Using the univariate cox regression model, in comparison to 2015, the hazard ratio is 0.780 (0.556 – 1.094, $p = 0.149$) for 2016, and 0.924 (0.3652 – 1.309, $p = 0.656$) for 2017.

Conclusions: The onco-palliative care MDMs is an innovative approach in Lebanon, a small conservative Middle Eastern society. These MDMs were shown to improve the quality of life of cancer patients with better symptomatic and social support. However, no significant impact on survival was demonstrated so far.

Legal entity responsible for the study: Saint Joseph University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1527P End of life resource utilization among patients receiving immunotherapy for advanced cancer

J.T. Burkart[1], S. Patel[1], A.M. Noonan[1], P. Monk[1], C.J. Presley[1], T. Olencki[1], K.L. Kendra[2], G.A. Otterson[1], J. Gustin[3], L. Wei[1], D.H. Owen[1]

[1]Division of Medical Oncology, The Ohio State University James Cancer Hospital, Columbus, OH, USA, [2]Cutaneous Oncology Program, Ohio State University Comprehensive Cancer Center - James, Columbus, OH, USA, [3]Palliative Medicine, Ohio State University, Columbus, OH, USA

Background: Patients (pts) with advanced cancer have high rates of healthcare resource utilization at the end of life (EOL). Immunotherapy (IO) has changed the treatment landscape for many patients with cancer. The impact of IO on resource utilization at the EOL for pts with metastatic disease, including emergency department (ED) visits, hospitalizations, and referrals to hospice is unknown.

Methods: We conducted a single center, retrospective analysis of pts treated with PD-1/L1 or CTLA-4 antibodies alone or in combination from 2011 – 2017. We identified 1,113 pts from electronic health records and present here clinical information for 306 pts with metastatic disease and end of life outcome data for 188 decedents. Survival curves were compared using log-rank test for pts by disease, treatment type, ECOG performance status (PS) at treatment start, and age. Hospice referral rate was compared using Fisher's exact test.

Results: Of the 306 pts, 131 (43%) had melanoma, 42 (14%) had renal cell carcinoma, 33 (11%) had non-small cell lung cancer, 22 (7%) had head and neck carcinoma, and 78 (25%) had another advanced malignancy. Treatment consisted of nivolumab in 130 (42%) pts, ipilimumab in 73 (24%), pembrolizumab in 59 (19%), nivolumab/ipilimumab in 23 (8%), atezolizumab in 9 (3%), and other IO combinations in 12 (4%). Of the 188 (61%) pts who died, 93 (49%) had at least one ED visit in the last month of life, 110 (59%) had at least one hospitalization, and 21 (11%) died in the hospital. Of all pts who died, 156 (83%) had hospice referral with a median of 11 days (range 1-420) between hospice referral and death. Overall survival (OS) was not associated with disease type ($p = 0.11$) or treatment ($p = 0.832$), but was associated with ECOG PS ($p = 0.013$). Referral to hospice did not vary by disease type ($p = 0.945$), treatment type, ($p = 0.809$) or age ($p = 0.432$), but did vary by ECOG PS ($p = 0.006$). Death within 72 hours of hospice referral rate varied significantly by inpatient or outpatient referral ($p = 0.002$).

Conclusions: Hospitalizations and ED visits are frequent at the EOL among pts who received IO for advanced malignancies. There was a high referral rate to hospice, but the median time between hospice referral and death was short. Interventions to decrease aggressive EOL care are needed.

Legal entity responsible for the study: Jarred Burkart.

Funding: Has not received any funding.

Disclosure: A.M. Noonan: Paid member of a data safety monitoring board from 2016-2017: Helsinn. All other authors have declared no conflicts of interest.

1528P Palliative chemotherapy for patient with advanced tumor and poor performance status: Are oncologists' hopes of benefit justified?

V.F. Vasconcellos, R.R.C.C. Bonadio, G. Avanco, M.V. Negrão, R. Riechelmann

Medical Oncology, ICESP - Instituto do Câncer do Estado de São Paulo, Sao Paulo, Brazil

Background: The recommendation to use palliative chemotherapy (PC) in patients (pts) with advanced cancer and poor performance status (ECOG-PS) is controversial and could be harmful. However, in routine practice some oncologists still recommend it. We sought to identify the outcomes and related prognostic factors of PC in these pts treated in a large academic cancer center.

Methods: We retrospectively reviewed all consecutive pts with poor ECOG-PS metastatic solid tumors who received PC during hospitalization for symptom control from January 2015 to September 2017. Eligible pts had ECOG-PS 3/4 and started first line PC or had ECOG-PS ≥ 2 and started second or further lines. Pts with known chemo-sensible tumors (germ cell, ovary, small cell lung cancer) and primary central nervous system were excluded. The primary end point was survival rate within 30 days from the date of first cycle. Logistic regression was used to identify prognostic factors associated with this mortality rate.

Results: We identified 228 consecutive pts. The median age was 56 years old, 133 pts (58%) were female, 150 pts (66%) were chemotherapy-naïve and almost half of pts had primary gastrointestinal tumors. 21.9%, 66.7% and 11.4% pts had ECOG-PS 2, 3 and 4, respectively. With a median follow-up of 49 days, 224 pts (98.2%) died. Nearly two thirds ($N = 142$) of pts died while hospitalized, with 31 (13.8%) dying while in ICU, 27 pts (12%) died in a hospice and 2 pts passed away at home. The median overall survival was 38.5 days and the survival rates within 30 and 60 days of chemotherapy were 55.7% and 38.5%, respectively. In the multivariate analysis, ECOG-PS 3/4 (OR 2.45; $p = 0.015$) and baseline values of anemia (OR 0.41; $p = 0.034$), hypercalcemia (OR 2.71; $p = 0.410$) and elevated total bilirubin level (5.14; $p < 0.001$) were significantly associated with 30-day mortality.

Conclusions: Most pts with advanced cancer and poor performance status clearly do not benefit from PC, especially those with ECOG-PS 3/4, hypercalcemia and elevated bilirubin. Transparent conversation with pts and their families about prognosis and the inefficiency of PC in this setting is crucial to avoid futile interventions.

Legal entity responsible for the study: Comitê de Ética e Pesquisa ICESP - Instituto do Câncer do Estado de São Paulo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1529P Integration of oncology and palliative care

S. Kaasa[1], J.H. Loge[1], T. Albreht[2], E. Bruera[3], A.T. Caraceni[4], A. Cervantes[5], I.J. Higginson[6], K. Jordan[7], P. Sjøgren[8], P. Stone[9], C. Zimmermann[10], T. Lundeby[1]

[1]Department of Oncology, Oslo University Hospital, Oslo, Norway, [2]Department of Health Care, National Institute of Public Health of Slovenia, Ljubljana, Slovenia, [3]Palliative, Rehabilitation & Integrative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]Palliative Care, Pain Therapy and Rehabilitation, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [5]Department of Medical Oncology, University of Valencia, Valencia, Spain, [6]Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, King's College London, London, UK, [7]Innere Medizin V - Hämatologie, Onkologie, Rheumatologie, University of Heidelberg, Heidelberg, Germany, [8]Department of Oncology, University of Copenhagen, Copenhagen, Denmark, [9]Marie Curie Palliative Care Research Department, University College London, London, UK, [10]Department of Supportive Care, Princess Margaret Cancer Center, Toronto, ON, Canada

Background: Integration of oncology and palliative care (PC) combines two paradigms: the tumour-directed approach, which is the main focus of oncology, and the host-directed approach, which is the focus of PC. Contemporary PC aims to prevent, treat and reduce symptoms and suffering and to preserve and improve quality of life. A Lancet Oncology Commission was written on how PC and oncology can be integrated by combining these two approaches focusing content, models, organization of cancer care, public health, politics, education and research.

Methods: An international panel was established, consisting of experts in oncology, PC, public health and psycho-oncology. Literature searches were conducted, author meetings were held, and an interactive writing process was conducted.

Results: Integration is a complex process that involves various components of the health care system. The published RCTs on integration demonstrate health gains, but how and when to integrate is uncertain. Still, early delivery of specialist palliative care promotes patient-centeredness including shared-decision making, family involvement and regular use of patient-reported outcome measures. Barriers to integration include the perception of PC as end-of-life care, deficient planning at local, national and international levels, and insufficient infrastructure and funding. Furthermore, death and dying are stigmatized. The present competence in combined oncology and PC varies substantially and must be defined at all levels. The commission proposes to use standardized care pathways (SCPs) and multidisciplinary teams (MDTs) to promote integration. Integration raises new research questions: how much, when and how should PC be delivered and what is the minimum model for good care?

Conclusions: Integration involves the transition from a dualistic perspective - the tumor and the host- to a combined perspective. Integration must be recommended by health care authorities and decision-takers, followed by resource allocation and priority-setting. In all areas, the present volume of PC is too small to support integration on a broad scale. Implementation of integrated models is best secured by MDTs and SCPs. The combined perspective must be reflected in care models, education and research funding.

Legal entity responsible for the study: Oslo University Hospital.

Funding: Has not received any funding.

Disclosure: S. Kaasa, J.H. Loge: Stockholder: Eir-solution. T. Albreht: Grants: European Commission and Ministry of Health of Slovenia, during the conduct of the study; Grants and personal fees: Pfizer Oncology, outside the submitted work. A.T. Caraceni: Grants: Molteni; Grants and personal fees: Italfarmaco; Personal fees: Sandoz, Pierre Fabre Institute; Gants: Gruenenthal, Ipsen, outside the submitted work. K. Jordan: Personal fees: MSD, Helsinn, Tesaro, Amgen, Pfizer, Merck, Hexal, outside the submitted work. All other authors have declared no conflicts of interest.

1530P Understandability of the standard arabic translation of the EORTC QLQ-C15-PAL questionnaire by Egyptian patients with incurable cancer

H.F. Masoud[1], S-E. Abdelmoneim[1], M.F. Ismael[1], S.A. Alsirafy[2]

[1]Clinical Oncology Department, Alexandria Faculty of Medicine, Alexandria, Egypt, [2]Palliative Medicine Unit, Kasr Al-Ainy Center of Clinical Oncology & Nuclear Medicine, Kasr Al-Ainy School of Medicine, Cairo, Egypt

Background: Many of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires is translated into standard Arabic. However, standard Arabic is not the language used for daily life communication in Arab countries where each country has its own local dialect. The aim of this study was to explore the understandability of the current standard Arabic version of the EORTC QLQ-C15-PAL by Egyptian advanced cancer patients with different educational levels.

Methods: The study included 100 adult patients with incurable cancer and different educational levels. Literate patients were asked to read the standard Arabic QLQ-C15-

PAL questionnaire and to state whether or not they understand each of its 15 questions. For illiterate patients, the questions (as they are written without explanation) were read for them.

Results: The median age of patients was 54 years (range: 27-78) and 56% were males. The education level was illiteracy in 49% of patients, less than high school in 18%, high school or equivalent in 18% and more than high school in 15%. The average number of questions understood by the whole group was 11 (range: 6 –15). Only 7 questions (1, 2, 5, 7, 10, 11 and 15) were understood by > 80% of patients. The average number of understood questions differed significantly according to the education level of patients ($p < 0.001$). The average number of understood questions was almost similar among illiterate patients and those with less than high school education with no significant difference between them (9.4 and 9.6, respectively; $p = 0.814$). Similarly, there was no significant difference in the average number of understood questions between high school and more than high school educated patients (13.8 and 14.5, respectively; $p = 0.102$).

Conclusions: The results suggest that the current standard Arabic translation of the EORTC QLQ-C15-PAL should only be used with patients with a high school level of education and above. There is a need to translate the EORTC QLQ-C15-PAL into "Egyptian" Arabic; otherwise, a vulnerable group of patients (illiterates and those with less than high school education) will not be included in studies using the EORTC QLQ-C15-PAL.

Legal entity responsible for the study: Alexandria Faculty of Medicine, Alexandria Clinical Oncology Department.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1531P How to practice oncology with a supportive and palliative care ambulatory unit: A French experience (HOASIS)

A. Gonzalez Moya[1], H. Bourgeois[2]

[1]Radiation Oncology, Centre Jean Bernard, Le Mans, France, [2]Medical Oncology, Clinique Victor Hugo Le Mans, Le Mans, France

Background: Early outpatients palliative care (EPC) in patients with metastatic cancer has been shown to impact quality of life and decrease healthcare utilization, but data describing these benefits are limited and referrals to palliative care services are often late. Our Ambulatory Unit named HOASIS offers an interdisciplinary approach to cancer management for patients.

Methods: HOASIS was created in March 2017 to receive EPC patients in order to foster autonomy and quality of life, both for patients and families. Multi-professional teams provide care in cooperation with physician.This retrospective study analyzed 152 EPC patients from march to december 2017.

Results: In total, 152 patients were evaluable. 97% had solid tumor (mainly breast and digestive cancer, respectively 24% and 37%) and 3% had hematologic malignancies. Median age was 66 years. ECOG PS 0-1 (18%), PS 2 (52%) and PS 3-4 (28%). Most common services used were nutrition (67%), psychological counseling (39%), physical therapy (53%) and social work intervention (30%). Patients were supported to understand their prognosis with clear information about their disease and treatment (45%) and make care decisions (11%). Medical prescriptions included pain control (46%), symptomatic treatment (38%), physiotherapy (27%), psychotropics (6%) and nutritional supplements (12%). Nurses delivered the information allowing 49% to chose their trusted person and 13% both completed advance directives and trusted person. After evaluation, 29% need a second appointment, 66% had oncology consultation, 26% had phone consultation and 21% were hospitalised. Home service was supplied to 63% of them. Out of the 152 patients, 13 (9%) were seen late in our unit, less than 1 month before death, and 83 (55%) were seen more than 1 month before death. Full data about chemotherapy around end of life will be delivered during the meeting.

Conclusions: Professionals should integrate EPC for patients with advanced cancer. Advantages to EPC include improvement in patient's quality of life, reduced aggressive care at the end of life, increased advanced directives. A web-based application for monitoring comfort in patients receiving EPC is currently being evaluated.

Legal entity responsible for the study: Hugues Bourgeois.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1532P Prognostic impact of end-of-life chemotherapy in the last weeks for patients with advanced cancer

S. Hiramoto[1], A. Kikuch[1], T. Hori[2], A. Yoshioka[1], T. Tamaki[3]

[1]Oncology and Palliative Medicine, Mitsubishi Kyoto Hospital, Kyoto, Japan, [2]Respiratory Surgery, Mitsubishi Kyoto Hospital, Kyoto, Japan, [3]Nursing, Mukogawa Woman's University, Nishinomiya, Japan

Background: Appropriately timed cessation of chemotherapy is important for patients with advanced cancer at the end-of-life stage. There are frequent discussions about over-treatment of end-of-life chemotherapy currently, but the definition of end-of-life chemotherapy remains unknown.

Methods: We analyzed patients' data between August 2011 and August 2016. The primary endpoints were prognostic factors (age, sex, primary site, clinical stage, comorbidity, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and Glasgow Prognostic Score (GPS)) following the last administration of chemotherapy within 14 days of death. Patients with either C-reactive protein levels >1.0 mg/dL or albumin levels <3.5 g/dL were classified as GPS1; patients with both were classified as GPS2, and those with neither of the two were classified as GPS0. The secondary endpoints were prognostic factors following the last administration of chemotherapy within 30 days of death. The associations between end-of-life chemotherapy and the frequency of end-of-life symptoms (delirium, cancer pain, dyspnea, nausea and vomiting, and fatigue) and treatment (hydration, continuous sedation, and opioids) were evaluated.

Results: We obtained 300 patients' data including complete information about the last administration of chemotherapy. The number of patients within 14 and 30 days of death from the last administration of chemotherapy were 16 (5.3%) and 50 (16.7%), respectively. In multivariate analysis for end-of-life chemotherapy, ECOG-PS (odds ratio 0.26, $p = 0.046$) and GPS2 (odds ratio 0.19, $p = 0.043$) were significant prognostic factors within 14 days of death, while ECOG-PS (odds ratio 0.34, $p = 0.046$), GPS1 (odds ratio 0.28, $p = 0.010$), and GPS2 (odds ratio 0.22, $p < 0.001$) were significant prognostic factors within 30 days of death. The median survival time from the last administration of chemotherapy of patients with both GPS2 and EGOG-PS (≥2) was 41 days, and that of patients with both GPS0 and EGOG-PS (0-1) was 162.5 days. Prevalence rates at the end-of-life stage for nausea and vomiting (25.0%) within 14 days of death were significantly higher than those (7.4%) over 14 days of death. The mean amounts of hydration (0.50 L/day) at the end-of-life stage within 14 days of death were significantly higher than those (0.20 L/day) over 14 days of death.

Conclusions: GPS and ECOG-PS were significant prognostic factors for over-treatment of end-of-life chemotherapy. Information about these factors can aid clinical decision-making in individual patient risk stratification, especially in palliative care settings, and in the further development of prospective cohort studies about end-of-life chemotherapy.

Legal entity responsible for the study: Mitsubishi Kyoto Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1533P A novel electronic tool to implement palliative sedation (PS) in a department of oncologic medicine

A. Saviola[1], S. Cascinu[2], M. Salati[2], G. Longo[1], C. Fiorani[1], L. Ferrara[1], N. Malavasi[1], R. Postiglione[1], F. Cantile[1], L. Scarabelli[1], M. Rimini[3], F. Ferri[1]

[1]Dipartimento ad Attività Integrata n.4 "Oncologia ed Ematologia", Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [2]Oncology, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [3]Medical Oncology, University Hospital of Modena, Modena, Italy

Background: Palliative sedation (PS) is a medical intervention aimed at relieving suffering in terminally ill cancer patients. Although specific guidelines exist, their application is challenging and varies greatly. We systematically collected relevant data concerning PS, including relatives' perception, in order to inform current practice patterns.

Methods: Electronic medical and nursing records of patients with advanced cancers undergoing PS at the Modena Cancer Centre between December 2016 and February 2018 were retrieved. Data regarding patient demographics, disease characteristics, PS details were collected and organized in items to create a personalized electronic PS record for each patient.

Results: A total of 259 deaths were recorded in our Department during the study period. Among them, 88 patients received PS. The median age was 67.6 years old; 71 (81%) patients had solid tumours, while 17 (19%) had hematologic cancers. At time of PS, 35 (39.8%) patients were receiving chemotherapy, 9 (10,2%) patients radiotherapy and 44 (50%) patients best supportive care alone. Four patients (4.5%) overtly expressed their informed consent to PS. Most frequently treated refractory symptoms were: delirium/agitation (70.5%), dyspnea (34%), intractable pain (16%), and global suffering (4.5%). Midazolam was used in 78 (88.6%) patients and diazepam in 6 (10.4%) patients. Morphine was added to PS in 65 (74%) patients. The Delirium Palliative Prognostic score reported a 30-day survival probability < 30% in 46 (52%) patients, between 30% and 70 % in 31 (35%) patients, >70% in 3 (3.5%) patients. The average duration of PS was 70 hours (range 3-281 hours). Patient's relatives reported peacefulness in 44 (71%) cases, agitation in 10 (16%) cases and concern for suffering in 8 (13%) cases.

Conclusions: The electronic tool permits to have data that provide an auditing of PS practice, facilitate the cooperation among professionals and obtain the standardization of PS. The involvement of patients' family could lead to a more effective communication. We propose this as a user-friendly electronic tool to improve the quality of PS as well as the planning and coordination of end-of-life care in an inpatient setting.

Legal entity responsible for the study: Giuseppe Longo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1534P Congruence between actual place of death and preferences of Egyptian patients with advanced cancer and their family caregivers

S. Alsirafy[1], O. Zaki[2], N.Y. Ibrahim[2], W. Elsherief[2], A. Hammad[1]
[1]Palliative Medicine Unit, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt, [2]Clinical Oncology Department, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt

Background: Identifying the preferred place of death (PPoD) of incurable cancer patients and their family caregivers is important for the delivery of end-of-life care that meets their needs. The PPoD was not studied before in our region where talking with patients about death is largely perceived as unacceptable. Our aim was to study the PPoD of Egyptian patients with incurable cancer and their family caregivers and the actual place of death (APoD) of these patients.

Methods: A prospective observational cohort study that included 92 patient/family caregiver dyads. Patients and family caregivers were asked about their PPoD (home, hospital or other) in the event of patient's death. Patients were followed up until death to know the APoD.

Results: Seventy-nine (86%) dyads answered the question about their PPoD. Home was the PPoD in 74 (93.7%) patients as well as their family caregivers. The congruence in the PPoD between patients and family caregivers was 94.9% (Kappa = 0.573). The APoD was home in 65 (82.3%) patients and hospital in 14 (17.7%). Overall, 78.5% of patients died in their PPoD; however, the kappa value was low (=0.013). Similarly, the congruence between caregivers' PPoD and APoD was poor (Kappa = 0.013). Patients who preferred death at home were more likely to die in their PPoD ($p = 0.001$).

Conclusions: The results suggest that, in the absence of the stand-alone hospice model, home is the PPoD for the vast majority of Egyptian patients with incurable cancer and their caregivers. Although the majority of patients die at home, other patients die in hospital contrary to their home death preference.

Legal entity responsible for the study: Kasr Al-Ainy School of Medicine, Cairo University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1535P Sarawak: Healthcare professionals' perception of palliative care at end of life

C.F. Cheah[1], L.H.Y. Winnie[1], A. Merriman[2], N.I. Mohd Naseri[1], S.W.Y. Chew[3]
[1]Palliative Care Ward, Sarawak General Hospital, Kuching, Malaysia, [2]Palliative Care Ward, Hospice Uganda, Kampala, Uganda, [3]Faculty of Health Science, University of Bristol, Bristol, UK

Background: Palliative care is fundamental to health and a basic human right. Healthcare professional are often the gatekeeper to palliative care for their patients, but there is great disparity in access to palliative care across Malaysia, and little knowledge about healthcare professionals' perception towards palliative care at the end of life in Sarawak.

Methods: We surveyed all healthcare professionals who attended a palliative care seminar and talk by Prof Dr Anne Merriman, founder and director of policy and International program, Hospice Africa when she visited Kuching, Sarawak on 5th and 6th April 2018. Participants were asked to answer a questionnaire designed by Prof Merriman which comprises of 25 questions in trochotomous scale.

Results: A total of 186 responses were obtained, of which 68% (127) were doctors and 25% (46) were nurses. 80% (149) responded that they would like to die at home, while only 5% (9) preferred to pass away in hospital. 96% (179) wished to have family with them and 84% (157) wanted spiritual guidance at the end of life. Only 41% (76) reported that they were afraid to die, yet majority responded that they were afraid of a painful death (86%;160), a prolonged dying process (89%; 164) and troubling others (90%; 167). Less than 50% of healthcare professional surveyed felt that they were able to help patients achieved adequate pain control (43%;80) or support patients emotionally (42%;78), and majority (58%) reported lack of knowledge being the barrier. 95% (176) reported that they would like to attend more palliative care seminars and 92% (171) would like to have palliative care in their unit. 26% (48) responded that they would like it to be lawful to practice euthanasia, but only 15% (28) were prepared to actively practice euthanasia if it is legal.

Conclusions: Home is the preferred place of death even amongst healthcare professional in Sarawak. Lack of knowledge and professional training remains a major barrier to access of palliative care. The survey highlighted the need for palliative care training for local healthcare professional as well the need to develop hospice home care services in our State to provide better palliative care and end of life care for patients and families. Advocacy for advanced directives should be initiated.

Legal entity responsible for the study: Winnie Hui Yee Ling.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1536P Factors associated with length of stay in an acute palliative care unit: A retrospective analysis

D. Hausner[1], A. Pope[1], N. Kevork[1], L.W. Le[2], C. Zimmermann[1]
[1]Department of Supportive Care, Princess Margaret Cancer Centre, Toronto, ON, Canada, [2]Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Acute palliative care units (APCUs) admit patients with cancer for symptom control, transition to community palliative care unit/hospice or end-of-life care. Prognostication is crucial for decision-making. We evaluated factors associated with patients' length of stay (LOS) on an APCU in a cancer centre.

Methods: We analyzed demographic, administrative and clinical data for patients admitted to the APCU in 2015. Clinical data included cancer diagnosis, palliative performance scale (PPS) on admission, delirium screening using the short Confusion Assessment Method (CAM), and Edmonton Symptom Assessment System (ESAS) symptoms. ESAS distress score (EDS; sum of all 9 symptoms) and FDSA sub-score (fatigue, drowsiness, shortness of breath, appetite) were calculated. We conducted univariable (UVA) and multivariable (MVA) regression analyses of factors associated with LOS of patients who died on the APCU and of those who were discharged.

Results: Among 280 patients, 156 (56%) died on the unit and 124 (44%) were discharged. Median LOS was 14 days for discharged patients and 8 days for those who died ($p < 0.001$). Discharged patients were older (median age 68 vs 64, $p = 0.003$) and had higher functional status (median PPS 50 vs 40, $p < 0.001$) than those who died. Patients who died had higher symptom burden (median EDS 44 vs 38, $p < 0.009$), were more likely to be admitted from an inpatient unit ($p < 0.001$) and for terminal care ($p < 0.001$), and were more likely to develop delirium ($p = 0.04$). On MVA of patients who died on the APCU, reason for admission ($p = 0.007$), delirium ($p = 0.02$) and FDSA score ($p = 0.002$) were associated with LOS. Shorter LOS was associated with admission for terminal care ($p = 0.05$) and missing FDSA (patients were too ill to complete) ($p < 0.001$); longer LOS was associated with delirium ($p = 0.02$). For patients who were discharged from the APCU, delirium was associated with longer LOS ($p = 0.02$).

Conclusions: In cancer patients admitted to an APCU, development of delirium was associated with longer LOS in patients who died on the unit as well as in patients who were discharged home or to PCU/hospice.

Legal entity responsible for the study: Camilla Zimmermann.

Funding: Canadian Institutes of Health Research.

Disclosure: All authors have declared no conflicts of interest.

1537P Medical-aid-in-dying use in the US Pacific Northwest

C.D. Blanke[1], M. Leblanc[1], D. Hershman[1], F. Meyskens[1], L. Taylor[2], L.M. Ellis[1]
[1]SWOG, Portland, OR, USA, [2]Neuro-Oncology, University of Washington Medical Center, Seattle, WA, USA

Background: Eight venues in the US allow terminally ill residents to self-administer prescribed oral drugs to end life. The Pacific Northwest states Oregon (OR) and Washington (WA) report number of prescriptions written, pt demographics, and motives underlying the requests. To study reasons for medical-aid-in-dying (MAID) requests and to assess patterns of use, we evaluated a combined 28 years of information from the most extensive database in North America.

Methods: OR and WA Health Authorities monitor MAID compliance. Website data from 1998 –2017 (OR) and 2009-2016 (WA) were collated. Characteristics of those dying from ingested drugs were calculated independently by state and then combined. Time trends for deaths vs. prescriptions written were analyzed using logistic regression.

Results: 3368 prescriptions were writte; 2282 pts took drug and died. The percent ingesting medication per yr ranged from 48-87, with no significant time trend in OR but with an increase over time in WA (2-sided $p = 0.59$ and <0.01, respectively). 77% of pts had cancer; 10% neurologic illness; 5% lung disease (dz); 5% heart dz; 3% other. 4% were sent for psychiatric evaluation. M/F (%): 51/49. 31% were in the largest pt age group represented: 65-74 yrs (overall range 20-102). Race white/other/unknown (%): 95/4/0.8. Eighty-three percent died at home (93 OR, 71 WA); a prescriber was present in 10% of cases (16 OR: 5 WA). Time between drug intake and coma ranged from 1 to 660 min; to death: 1-6240 min. Fewer than 0.5% awoke in OR. Reasons for MAID (%): Poor QOL 87; loss of autonomy 88; loss of dignity 69; inadequate pain control 30 (OR 26; WA 36); financial concerns 6.

Conclusions: Unlike European countries allowing euthanasia, US MAID consists only of terminally ill pts self-administering lethal medication. Up to half the pts requesting prescriptions do not take the drugs. Pts must be legally competent but rarely are referred to psychiatrists for that assessment. Most MAID pts have cancer and most use MAID for conditions that are difficult to palliate (loss of autonomy/dignity/QOL). Of concern, some use it because of inadequate pain control or finances. MAID merits formal study, such as how to develop faster-acting medications, as well as comparing effectiveness and demographics (especially age) with assisted dying data from Canada and Europe.

Legal entity responsible for the study: SWOG Cancer Research Network.
Funding: SWOG Cancer Research Network.
Disclosure: All authors have declared no conflicts of interest.

1538TiP Brain metastases in Norway: A prospective cohort study

O.E. Yri[1], M.L. Smebye[1], M.J. Hjermstad[1], A.T. Karlson[1], N.K. Aass[1], J.H. Loge[1], S. Kaasa[2]
[1]*Department of Oncology, Oslo University Hospital, Oslo, Norway,* [2]*Department of Oncology, Oslo University Hospital and European Palliative Care Research Centre, Oslo, Norway*

Background: Brain metastases (BMs) cause significant morbidity and mortality, and the incidence is increasing. With continuous developments in neurosurgery, radiation techniques such as stereotactic radiotherapy, and novel systemic therapies, treatment decisions have become more challenging. Also, the role of whole brain radiotherapy is being debated due to its marginal survival benefits and potentially significant side-effects. International guidelines on treatment and follow-up exist, but the scientific evidence supporting these guidelines is limited. To improve patient-centered care and promote shared decision-making, systematic, population-based registrations of patient, disease, treatment, and outcome variables are necessary. We have launched a prospective cohort study in the South-East health-care region of Norway (appr. 3 million inhabitants). The study population will consist of consecutive patients newly diagnosed with BMs recruited over a two-year period. Follow-up will be for up to two years or until death. The primary aim is to establish a prospective, clinical registry with data on diagnostics, treatment, and follow-up, including Patient Reported Outcome Measures (PROMs). With this prospective information, evidence-based diagnostic and treatment algorithms and follow-up guidelines can be developed. Study outcomes include: • Detailed description of the study cohort (including patient-, disease-, and treatment characteristics) • Overall survival (from BM diagnosis) • Association between disease, treatment, and patient characteristics and survival • Patient reported symptoms and quality of life.

Trial design: This is a prospective cohort study conducted in the South-East health-care region of Norway. Inclusion criteria: •Radiologically confirmed BMs from solid cancers diagnosed during the study period, regardless of planned treatment for BM. •No previous treatment for BMs •Age $>$ 18 years Timeframe: Two-year consecutive inclusion, started November 2017. Estimated target population: 1,000 cases Data collection: Clinical data are registered every 3 months for up to 24 months. Patient-reported symptoms and quality of life are assessed with standardized questionnaires (EORTC QLQ-C15-PAL, BN-20, and EQ-5D) monthly for up to 12 months.

Clinical trial identification: NCT03346655.

Legal entity responsible for the study: Oslo University Hosptial.

Funding: Norwegian Cancer Society, South-East Health Region in Norway.

Disclosure: All authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii557–viii561, 2018
doi:10.1093/annonc/mdy296

PSYCHO-ONCOLOGY

1539O Post-traumatic growth and death anxiety in caregivers of cancer patients: PHOENIX study

A. Alkan[1], E.B. Köksoy[2], E. Karcı[3], H. Burgaç[1], A. Arıkanoğlu Soğancı[1], D. Yaman[1], F. Çay Şenler[4]

[1]Medical Oncology, Osmaniye Public Hospital, Osmaniye, Turkey, [2]Medical Oncology, Kastamonu Public Hospital, Kastamonu, Turkey, [3]Medical Oncology, Bağcılar Education and Research Hospital, Istanbul, Turkey, [4]Medical Oncology, Ankara University School of Medicine, Istanbul, Turkey

1540PD Health-related quality of life in randomized controlled trials: A systematic review of prognostic significance

J. Mierzynska[1], M. Pe[1], C. Piccinin[1], F. Martinelli[1], C. Coens[1], C. Gotay[2], A.M.M. Eggermont[3], M. Groenvold[4], J. Reijneveld[5], L. Dirven[6], A. Bottomley[1]

[1]QoL, EORTC - European Organisation for Research and Treatment of Cancer, Brussels, Belgium, [2]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada, [3]Oncology, Institut Gustave Roussy, Villejuif, France, [4]Palliative Medicine, Bispebjerg Hospital, Copenhagen, Denmark, [5]Department of Neurology, VU University Medical Center & Brain Tumor Center, Amsterdam, Netherlands, [6]Department of Neurology, Leiden University Medical Center & Haaglanden Medical Center, Leiden, Netherlands

1541P Partners' perceptions of women's body image problems and satisfaction of breast reconstruction long-term after risk-reducing mastectomy

L. Bai[1], B. Arver[1], H. Johansson[1], M. Wickman[2], K. Sandelin[2], Y. Brandberg[1]

[1]Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, [2]Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Background: Knowledge is lacking about partners' perception of women's body image problems and satisfaction of breast reconstruction long-term after risk-reducing mastectomy (RRM) with immediate breast reconstruction (IBR) due to increased risk of hereditary breast cancer.

Methods: Partners' contact information was provided by women participating in a prospective long-term follow-up after going though RRM and IBR 6–18 years ago. They received an information letter about the study and questionnaires to be completed/returned in a prepaid return envelope. The Hospital Anxiety and Depression scale and the Swedish Short Term-36 Health Survey (SF-36) were answered from the partners' perspective, and the Breast Reconstruction Questionnaire (EORTC QLQ-BRR26), the Body Image Scale, and the Sexuality Activity Questionnaire from partners' perception of the women's experience. Partners' responses were compared to the women's responses, and with the SF-36 in the normative Swedish population.

Results: Sixty partners' names were provided by the 146 (73%) women participating in the long-term follow-up study. Thirty-six (60%) partners participated in total. The partners' perception of the women's satisfaction with the IBR was lower than the

women's own perceptions, p = 0.0362. Partners also perceived that the women had more problems with body image than the women themselves, p = 0.0419. Partners scored the sexuality items 'Pleasure', 'Discomfort', and 'Habit' similarly as the women. Both partners and women had in general a higher level of HRQoL compared to the age-standardised normative Swedish population.

Conclusions: This is one of the first studies designed to investigate partners' long-term perception of women's perception of their body image, sexuality, and satisfaction with IBR. The results are important when counselling couples in the decision-making process considering RRM, and to identify areas in need of support where the health care providers can assist the couples in the post-operative setting.

Legal entity responsible for the study: Yvonne Brandberg.

Funding: Swedish Cancer Society, Swedish Research Council, Radiumhemmets forskningsfonder, and Bröstcancerföreningens forskningsfond.

Disclosure: M. Wickman: Employment and leadership role (ended April 2017): Aleris AB. All other authors have declared no conflicts of interest.

1542P The effect of music on the instant anxiety levels of oncologic patients receiving chemotherapy treatment

A. Alacacioglu[1], G. Dissiz[2], S. iriz[2], A. Usluoglu[2], N. Asik[2]

[1]Medical Oncology, Ataturk Training and Research Hospital, Izmir Katip Celebi University, Izmir, Turkey, [2]Medical Oncology, Izmir Katip Celebi University, Izmir, Turkey

Background: This paper aims to determine instant anxiety levels of cancerous patients during treatment, as well as the factors involved, and establish the altering role of music on patients with high levels of anxiety.

Methods: This study was conducted on patients who received treatment at the outpatient chemotherapy unit. The patients were divided into two groups as the study and control group, and those patients who were aged between 18-65, diagnosed with breast cancer, operated and started adjuvant chemotherapy were included in the first course of treatment. In the study group, patients were provided with mp3 players with which they could listen to any music of their taste throughout the first course of chemotherapy treatment, which allowed them to listen to music. The individuals in the control group did not listen to music. The anxiety levels of all patients were determined before and right after chemotherapy by using the state-trait anxiety inventory part of the evaluation scale.

Results: Both groups included 49 patients; the mean age of the study group was 48.8 ± 10.9, and the mean age of the control group was 54.6 ± 11.3. 81.6% of the patients in the study group were married, %18.4 were single, the majority (61.2%) of them were primary school graduates, and 85.7% were housewives. In the control group, 73.5% of the patients were married, 26.5% were single, most of them (65.3%) were primary school graduates, and 87.8% were housewives. Administered prior to treatment, the STAI-I state-trait anxiety inventory score was 52.4 ± 11.3 in the control group and 50.4 ± 11.9 in the study group (p = 0.372). After the treatment, the STAI-I state-trait anxiety inventory score was 45.9 ± 11.2 in the control group, whereas it was 32.7 ± 7.7 in the study group (p = 0.0001).

Conclusions: A comparison of the pre-treatment state-trait anxiety levels of the patients included in the study and control groups revealed no significant difference. However, the patients in the study group who listened to music after the treatment presented significantly decreased anxiety levels.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1543P Ostracism in adolescent cancer patients and predictors (OSTRACA Study): A study of the palliative care working committee of the Turkish Oncology Group (TOG)

A. Alkan[1], Z.G. Güç[2], T. Şakalar[3], G. Zengin[4], A. Yaşar[5], Y. Karakas[6], T. Yavuzsen[7], O.B. Oksuzoglu[8], F. Çay Şenler[9]

[1]Medical Oncology, Osmaniye Public Hospital, Osmaniye, Turkey, [2]Medical Oncology, Dokuz Eylül University School of Medicine, Izmir, Turkey, [3]Medical Oncology, Erciyer University School of Medicine, Kayseri, Turkey, [4]Medical Oncology, Ankara Abdurrahman Yurtaslan Oncology Hospital, Ankara, Turkey, [5]Medical Oncology, Ankara University School of Medicine, Ankara, Turkey, [6]Medical Oncology, Hakkari Public Hospital, Hakkari, Turkey, [7]Medical Oncology, Dokuz Eylul University School of Medicine, Institute of Oncology, Izmir, Turkey, [8]Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Training and Research Hospital, Ankara, Turkey, [9]Medical Oncology, Ankara University School of Medicine, Istanbul, Turkey

Background: Ostracism is defined as being ignored or excluded by others. Being excluded during adolescence can result in various problem behaviors and emotional disturbances. The purpose of the study is to evaluate ostracism in adolescent cancer patients and define the predictors of it.

Methods: The study was conducted as a multicenter survey study. Adolescent cancer patients, who were under remission, were evaluated with structured questionnaires to assess the Ostracism and clinical parameters associated with it. Turkish version of Ostracism Experience Scale for Adolescents (OES-A) and Kutcher adolescent depression scale (KADS) were used.

Results: Between December 2017 and April 2018, 52 patients were evaluated in 4 different cancer centers. Median age was 21 (14-24), 40.4% of them were female and most of them were university student (23, 44.2%). Median OES-A score was 23.5(11.0-41.0). While female sex (28.0 vs 19.0, p = 0.008) and low family income (28.0 vs 21.0, p = 0.02) were associated with more ostracization; patients working full/part time (19.0 vs 25.0, p = 0.01) and university students (19.0 vs 27.0, p = 0.01) were less ostracized. In multivariate analysis, being female was associated with high OES-A scores (OR: 7.8, CI(95%) 1.4-42.9, p = 0.018). Being university student (OR: 0.14, , CI(95%) 0.02- 0.71, p = 0.018) and working (OR: 0.07 , CI(95%) 0.007- 0.7, p = 0.02) were associated with low OES-A scores(Table). Higher OES-A scores were associated with high KADS scores (9.0 vs 7.5, p = 0.16).

Table: 1543P

	High OES-A Score		
Characteristics	OR	CI (95%)	p
Female	7.8	1.4- 42.9	0.018
Low income	3.2	0.6-16.3	0.14
University student	0.14	0.02-0.71	0.018
Working	0.07	0.007- 0.7	0.02

Conclusions: It is the first data about ostracism in adolescent cancer patients. OES-A score was higher than the scores of adolescents without cancer. While female adolescent patients were found to be under risk of ostracism, working and being university student were protective against ostracism. Ostracism in adolescent cancer patients should be studied in larger series.

Legal entity responsible for the study: Ali Alkan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1544P Cognitive functions, coping strategies and psychological distress in patients with resected non-advanced cancer receiving chemotherapy: NEOcoping study data

O. Higuera Gomez[1], C. Calderón[2], I. Ghanem[1], A. Carmona-Bayonas[3], C. Jara[4], R. Hernández[5], B. Castelo[1], M.M. Muñoz[6], C. Beato[7], S. García[8], E. Martínez[9], M. Mut[10], A. Ramchandani Vaswani[11], M. Mangas[12], O. Donnay[13], M.T. García-García[14], M.C. Soriano[6], R. Carrión[15], C. Iglesias Gomez[16], P. Jimenez Fonseca[16]

[1]Medical Oncology, Hospital Universitario La Paz, Madrid, Spain, [2]Clinical Psychology and Psychobiology, University of Barcelona, Barcelona, Spain, [3]Medical Oncology, Hospital Universitario Morales Meseguer, Murcia, Spain, [4]Medical Oncology, Hospital Universitario Fundación Alcorcón, Madrid, Spain, [5]Medical Oncology, Hospital Universitario de Canarias, Tenerife, Spain, [6]Medical Oncology, Hospital Virgen de la Luz, Cuenca, Spain, [7]Medical Oncology, Hospital Universitario Virgen de la Macarena, Seville, Spain, [8]Medical Oncology, Hospital Universitario de la Santa Cruz i Sant Pablo, Barcelona, Spain, [9]Medical Oncology, Hospital Universitario Marqués de Valdecilla, Santander, Spain, [10]Medical Oncology, Hospital Universitario Son Espases, Mallorca, Spain, [11]Medical Oncology, Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain, [12]Medical Oncology, Hospital Galdakao-Usansolo, Galdakao-Usansolo, Spain, [13]Medical Oncology, Hospital Universitario de La Princesa, Madrid, Spain, [14]Medical Oncology, Hospital Universitario Santa Lucia, Cartagena, Spain, [15]Medical Oncology, Hospital Universitario del Sureste, Madrid, Spain, [16]Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain

Background: The loss of cognitive functions is a symptom that impairs the quality of life .The aim of this study is to analyze cognitive functioning in cancer patients who initiate chemotherapy and to study the relationship between coping strategies and psychological distress.

Methods: NEOcoping is a national, multicenter, cross-sectional, prospective study of the Continuous Care Group of the Spanish Society of Medical Oncology conducted between January 2016 and January 2018 in 14 Medical Oncology departments in Spain. The population consisted of patients with histologically confirmed, non-advanced cancer treated with surgery for which international clinical guidelines considered that adjuvant treatment could be an option.The information was collected and updated by medical oncologists through a web-based platform (www.neocoping.es). Questionnaires for doctors and patients were filled out before starting adjuvant chemotherapy and at the end of the treatment. The applied tests were: Mini-Mental Adjustment to Cancer (Mini-MAC), EORTC core quality of life questionnaire (EORTC QLQ-C30, cognitive function scale), and Brief Symptom Inventory (BSI-18).

Results: Seven hundred and ninety-five patients were recruited. The median age was 58 years and 60% were women. Most were married or partnered (77%) and had a primary level of education (56%). The most common employment status was retired (59%). The primary tumor localization was mainly colorectal (41%) and breast (34%) and the stage was I-II (56%) or III (44%).The results indicate that patients who perceived their

physical condition or chemotherapy interfered with their cognitive functions had more anxious coping strategies characterized by constant preoccupation with the type of health, fear of cancer recurrence and this led to a search for frequent reaffirmation ($p = 0.008$). The cognitive function problems were negatively related with somatization ($p < 0.001$), depression ($p < 0.001$) and anxiety ($p < 0.001$).

Conclusions: The perception of impaired cognitive abilities and uncertainty about the prognosis of cancer can make it difficult for patients to adapt to their situation, deteriorate quality of life and increase emotional distress.

Legal entity responsible for the study: Continuous Care Group of the Spanish Society of Medical Oncology (SEOM).

Funding: Sociedad Española de Oncología Médica (SEOM).

Disclosure: All authors have declared no conflicts of interest.

1545P Cancer stigma related to beliefs of patients and care providers

G.S. Bhattacharyya[1], H. Malhotra[2], G. Babu[3], A. Vora[4], S. Bhattacharyya[5]

[1]Medical Oncology, Salt Lake City Medical Centre, Kolkata, India, [2]Division of Medical Oncology, Birla Cancer Center, Jaipur, India, [3]Medical Oncology, HCG Curie Centre of Oncology & Kidwai Memorial Institute of Oncology, Bangalore, India, [4]Medical Oncology, Pratiksha Hospital, Gurugram, Haryana, India, [5]Palliative Care, Salt Lake City Medical Centre, Kolkata, India

Background: Stigma refers to distinctive, discrediting characteristics, rendering its bearer tainted by others and recognises difference and devaluation. Evidence suggests that cancer is a stigmatized disease. Cancer-related stigma is not documented in India, little is known about how it impacts health-seeking behavior, treatment adherence, quality of life and psychosocial wellbeing in cancer patients. Limited study has explored perceptions and cultural representations of cancer. This context specific information is essential for relevant, effective intervention.

Methods: This qualitative study was conducted in two districts Kolkata and North 24 Parganas of West Bengal, India, and included participants from a range of cultural and racial groups. Cancer patients over 18 years ($n = 300$) were recruited through Salt Lake City Medical Centre to participate. Six focus groups and 40 in depth interviews were conducted with cancer patients. Data collection focused on understanding patient experiences of cancer stigma, cognitive, emotional and behavioural responses to this, and inputs on interventions to address this. Six focus groups were also conducted with friends and non-related service providers, ($n = 240$) in order to explore cultural perceptions of cancer and reasons for stigmatization. Data were recorded and were authenticatedly translated and transcribed; and analysed by thematic analysis.

Results: Results indicated very poor knowledge of cancer in patients and care givers. Findings highlight the perception of cancer as a 'death sentence' and a punishment from providence, influencing patients' interactions with others in numerous ways. The influence of cultural beliefs was relevant, exacerbating stigma in some cases. The location of the cancer also played a role in determining level of stigmatization. Certain body parts (associated with masculine and feminine roles) as well as more visible cancers/side-effects were more stigmatised.

Conclusions: Stigmatization is a factor for cancer patients and is related to education and social background, increasing social isolation and negatively impacting quality of life. The implications of the findings for intervention development will be discussed. Education is needed but requires a different focus for different cultural groups.

Legal entity responsible for the study: Gouri Shankar Bhattacharyya.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1546P Relationship between depressive symptoms at social cognitive processing in partners of long term breast cancer survivors

G.S. Bhattacharyya[1], H. Malhotra[2], G. Babu[3], A. Vora[4], T. Shahid[5], S. Misra Ghosh[6]

[1]Medical Oncology, Salt Lake City Medical Centre, Kolkata, India, [2]Division of Medical Oncology, Birla Cancer Center, Jaipur, India, [3]Kidwai Memorial Institute of Oncology, HCG Curie Centre of Oncology, Bangalore, India, [4]Medical Oncology, Pratiksha Hospital, Gurugram, India, [5]Oncology, Apollo Gleneagles Cancer Hospital, Kolkata, India, [6]Psychiatry, Fortis Hospital, Kolkata, India

Background: The number of breast cancer survivors are increasing, so does the number of partners effected by the illness. An estimated 20-40% of spouses suffer from mood disturbance, anxiety and other effective disorders related to the spouses' illness. The survivor usually has a trend of decreasing levels of depression, but about 25% have long term depression. Studies have found relationship between survivor and spousal outcomes. Previous studies have shown decreased quality of life, loss of sleep, fatigue, decline in general health and increase in cardiovasular disease in among partners of survivors. Little is known of the mechanisms of this and there is very little data from developing countries like India.

Methods: 208 partners of breast cancer survivors (post operative, post chemo, and/or radiotherapy) diagnosed between 3 yrs to 10 yrs prior to study, were sampled. Secondary data mediations were conducted to determine, if cognitive processing mediated the relationship between social constraints and depressive symptoms. Age related difference on all stage were tested. Depressive symptoms; secondary variables including social constraints; cognitive processing and potential confounding variables were the main research variables.

Results: Cognitive processing, mediated the relationship between social constraints and depressive syptoms for partners. Partners of younger breast cancer patients and with lower education status had worst outcomes. Younger survivors reported more depressive symptoms, higher scores on intrusive thoughts and more social constraints.

Conclusions: As predicted by the social cognitive processing theory cognitive processing mediated relationship between social constraints and depressive syptoms. In addition, partners of younger breast cancer survors faced worst on social constraints, intrusive thoughts and depressive symptoms more. Results provide support for using social cognitive processing theory in an intervention design with partners of long term breast cancer survivors to decrease depressive symptoms; open communication on social constraints and discsussion of these negative psychological impacts would help. Education of spouse would be important.

Legal entity responsible for the study: Gouri Shankar Bhattacharyya.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1547P Evaluation of the distinction and temporal relationship between prolonged grief disorder and depression in terminally ill cancer patients' caregivers' first two years of bereavement

W-I. Tsai[1,6], S-C. Kuo[2], F-H. Wen[3], J-S. Chen[4], S.T. Tang[5]

[1]Graduate Institute of Clinical Medical Sciences, Chung Gung University, Taoyuan, Taiwan, [2]Nursing Department, Yuanpei University of Medical Technology, Hsinchu, Taiwan, [3]Department of International Business, Soochow University, Taipei, Taiwan, [4]School of Medicine, Chung Gung University, Taoyuan, Taiwan, [5]School of Nursing, Chung Gung University, Taoyuan, Taiwan, [6]Department of Nursing, Meiho University of Medical Technology, Pingtung, Taiwan

Background: Prolonged grief disorder (PGD) and depression are common emotional disorders influencing bereaved caregivers' quality of life (QOL). However, the conceptual distinctiveness and temporal relationship of PGD and depression have been partially and not established, respectively. To fill these knowledge gaps, we conducted this longitudinal study.

Methods: Our convenience sample included 291 caregivers of terminally ill cancer patients. Caregivers' PGD, depression, and psychological QOL were measured 6, 13, 18, and 24 months postloss using the Prolonged Grief-13 scale (PG-13), Center for Epidemiologic Studies-Depression (CESD) scale, and Short Form-36 Health Survey mental health summary, respectively. We examined the associations of PGD and depression with psychological QOL by an incremental validity test, thereby clarifying their conceptual distinctiveness. The temporal relationship between PGD and depression was examined by longitudinal, lower-level mediation analysis with a lagged approach.

Results: After the variance in psychological QOL was significantly explained by CESD scores (pseudo R^2=44.19%, p<.001), PGD significantly, incrementally increased the explained variance in psychological QOL (pseudo R^2=.21%, p<.001), confirming the distinction between PGD and depression. Lower-level mediation analysis showed that CESD scores (depressive symptoms) mediated 90% of the relationship between time and PG-13 scores, whereas PG-13 scores only mediated 76% of the relationship between time and CESD scores. This result indicates that CESD scores assessed at a previous time mediated caregivers' current PGD during bereavement rather than vice versa.

Conclusions: PGD and depression are conceptually distinct disorders, and depression precedes development of PGD. Clinicians must distinguish between the two disorders and appropriately manage bereaved caregivers' depressive symptoms. Alleviating caregivers' depressive symptoms will prevent development of PGD, thus improving QOL.

Clinical trial identification: (NHRI-EX107-10704PI) and Ministry of Science and Technology (MOST 104-2314-B-182-027-MY3), National Science Council (NSC 96-2314-B-182-029-MY2), and Chang Gung Memorial Hospital (BMRP888).

Legal entity responsible for the study: Chang Gung University.

Funding: Ministry of Science and Technology, National Science Council, and Chang Gung Memorial Hospital.

Disclosure: All authors have declared no conflicts of interest.

1548P Patients' and partners' views of treatment and care provided for metastatic castrate resistant prostate cancer (mCRPC) in the UK

S.L. Catt[1], L. Matthews[1], H. Payne[2], M.D. Mason[3], V. Jenkins[4]

[1]Sussex Health Outcomes Research & Education in Cancer (SHORE-C), Brighton and Sussex Medical School, University of Sussex, Brighton, UK, [2]Oncology, University College London Hospital NHS Foundation Trust, London, UK, [3]Velindre Cancer Centre, Velindre Hospital, Cardiff, UK, [4]SHORE-C, BSMS, Brighton, UK

Background: Appraisals of information needs, expectations and experiences of treatment in prostate cancer have highlighted the lack of relevant data in advanced disease. We report interview data from the EXperiences of TREatment and Quality Of Life of men with mCRPC study (EXTREQOL). It aimed to examine factors driving treatment decision-making from the perspectives of patients and healthcare professionals and gather data on the impact of treatments on quality of life (QOL).

Methods: A prospective longitudinal mixed-methods observational design was employed. This included semi-structure interviews conducted with patients and their partners, in-person or by phone, at baseline =within 14 days of starting a systemic treatment (any line) for mCRPC and after 3 months of treatment. Topics explored included experiences of treatment decisions, information provision, what assisted decision-making and how perceived benefits and harms of treatment affected patients' and families' lives.

Results: Thirty three men (56-89yrs) and their female partners (54-79yrs) from 15 UK centres participated. They believed treatment aimed to delay progression (>75%), improve QOL (33%), alleviate pain (≈12%) and extend life (15% -patients, 36% -partners). ≈50% made a joint treatment decision with the doctor and 39% had as long as they needed to decide. The worst symptom most frequently identified was pain (46% -patients, 33% -partners). At baseline and 3 months (50% and 67% respectively) did not need to discuss pain control, those that did received "very/fairly" useful information. At baseline fatigue, nausea/vomiting and diarrhoea were the worst anticipated or experienced side-effects (SEs). The worst SE at 3 months was fatigue, 33% experienced unexpected SEs and 52% sought help for SEs. 75% had helpful SE discussions, 85% received written information and internet searching about SEs was common (33% -patients, 55% -partners). Only 50% had opportunity to talk with a specialist nurse and 50% accessed other supportive services.

Conclusions: More help to manage pain and other symptoms is required. Dedicated clinics maybe warranted, better specialist nurse access and earlier palliative care links would help to optimise symptom control.

Legal entity responsible for the study: Brighton & Sussex Medical School, University of Sussex.

Funding: Sanofi Aventis.

Disclosure: H. Payne: Honoraria for advisory boards, travel expenses, consultant: AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Amgen, Ipsen, Ferring, Sandoz, Novartis; Work support: UCLH/UCL Comprehensive Biomedical Research Centre. M. Mason: Scientific expert: Ellipsis Pharma. All other authors have declared no conflicts of interest.

1549P Exploring the effectiveness of crisis counselling and psycho-education in relation to improving mental wellbeing, quality of life and treatment compliance of breast cancer patients in Qatar

R. Alsulaiman[1], S. Bujassoum[1], A. Bener[2], L. Doodson[3], S. Ghuloum[4], A. Lemaux[1], H. Bugrein[1], R. Alasaam[1], A. Karim[5]

[1]Medical Oncology, National Center for Cancer Care and Research, Doha, Qatar, [2]Department of Biostatistics & Medical Informatics, Istanbul University, Istanbul, Turkey, [3]Psychology and Counseling Studies, Regent's College, London, UK, [4]Department of Psychiatry, Hamad General Hospital, Doha, Qatar, [5]Psychology, National Center for Cancer Care and Research, Doha, Qatar

Background: Insufficient number of studies have been carried out in the Middle East to evaluate the role of structured psychotherapeutic interventions in breast cancer patients. This study has been designed to explore the benefit of two structured interventions 'crisis counselling' and 'psycho-education' in enhancing breast cancer patient's psychological well-being, quality of life and treatment compliance in Qatar.

Methods: A total of 201 women with early stage breast cancer from Qatar were recruited and randomised into either the control group or one of the treatment groups (crisis counseling or psycho-education). Each of the two treatment interventions consisted of a total of six 60-90 minute sessions, which were provided over a period of 12 weeks. The short- and long-term benefits of the crisis counselling and psycho-education interventions were evaluated in terms of improving patients' psychological well-being, quality of life and treatment compliance through DASS21 and QLQ-C30 instruments and by monitoring their compliance to chemotherapy and radiotherapy treatment.

Results: This study revealed that both of the study interventions 'crisis counseling' and 'psycho-education' were effective in improving women's psychological well-being and quality of life over time in comparison to the control group but had no significant impact on patients' compliance with treatment. In addition, the study showed that psycho-education conferred a greater advantage than did the crisis counselling model, especially on improving women's psychological well-being over time.

Conclusions: This study is considered the first of its kind in Qatar to provide evidence on the benefit of crisis counseling and psycho-education interventions in improving the psychological wellbeing and quality of women with early-stage breast cancer. In addition, this study has provided an innovative research that can be used as evidence to propose changes to the psychotherapy services for breast cancer patients in Qatar and which will hopefully lead to a better healthcare system for other cancer patients in the country.

Legal entity responsible for the study: Hamd Medical Corporation.

Funding: Hamd Medical Corporation.

Disclosure: All authors have declared no conflicts of interest.

1550P Pilot study of anxiety, depression, and quality of life in patients with the diagnosis of metastatic uveal melanoma

R. Nshimiyimana[1], C.E. Guzzetta[2], M-M. Brown[3], Q. Zhou[4], J.M. Johnson[1], T. Sato[1], S. Keith[5]

[1]Medical Oncology, Kimmel Cancer Center-Thomas Jefferson University, Philadelphia, PA, USA, [2]School of Nursing, The George Washington University, Washington DC, USA, [3]Nursing, MedStar Health, Columbia, OH, USA, [4]School of Nursing, Virginia Science and Technology Campus, The George Washington University, Ashburn, VA, USA, [5]Biostatistics, Thomas Jefferson University & Jefferson Health, Philadelphia, PA, USA

Background: Awareness of a patient's anxiety, depression, and quality of life (QOL) in those with metastatic uveal melanoma (MUM) can influence care that meets patients' bio-psycho-social-spiritual needs. Objectives: To measure the level of anxiety, depression, and QOL in MUM patients and explore differences by gender, age range, time to metastatic disease, and duration of illness since metastasis.

Methods: We used a descriptive-comparative design. From 9/1/2017 - 12/1/ 2017, a convenience sample of 70 MUM patients aged $\geq$ 18 years, treated at a Mid-Atlantic hospital were invited to complete a combined survey of the Hospital Anxiety and Depression Scale and the World Health Organization Quality of Life-BREF.

Results: There were 65 respondents (93% response rate). 30.8% ($n = 20$) had at least borderline anxiety, 13.8% ($n = 9$) had at least borderline depression, and 32.3% ($n = 21$) had a decrease in global QOL. Patients aged 18 to $\leq$ 60 years had a significantly higher anxiety score (7.52 ± 3.65; $p = 0.003$) and lower QOL in environmental health (32.48 ± 5.23; $p = 0.006$). There was a significant difference in anxiety scores by the duration of illness since metastasis (< 1 year [7.79 ± 3.72], >1 year to < 5 years [5.75 ± 3.45], > 5 years [3.70 ± 2.79]; $p = 0.01$). No differences were found by gender or time to metastatic disease.

Conclusions: Up to 30% of participants had at least borderline anxiety and a decreased global QOL while up to 10% had at least borderline depression. These findings support the integration of bio-psycho-social-spiritual practices in the care of MUM patients.

Editorial acknowledgement: Cathie E Guzzetta, PhD, RN, FAAN Mary-Michael Brown, DNP, RN Qiuping Zhou, PhD, RN Jennifer M. Johnson, MD, PhD, FACP Takami Sato, MD, PhD Scott W. Keith, PhD.

Legal entity responsible for the study: Regine Nshimiyimana.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1551P Making sense of self-conscious and emotion: Linking theory of mind and emotion in women with breast cancer

P.G. Chaudhuri[1], A. Datta[2]

[1]Institute of Psychiatry, Kolkata, India, [2]Psychooncology, Netaji Subhas Chandra Bose Cancer Research Institute, Kolkata, India

Background: During the period of breast cancer's treatment, they had to face many physical and facial changes that make them self-conscious. Self-conscious emotions are just like embarrassment and shame that are correlated with 2 factors of the theory of mind (ToM): 1. the ability to understand that behavior has social consequences in the eyes of others and (b) an understanding of social norms violations. The present study aimed to link ToM with the recognition of self-conscious emotion.

Methods: We compared the performance of patients with breast cancer ($N = 61$) those who were diagnosed and were willing to undergo the psychological assessment, with no history of past psychiatric illness and with age and sex match healthy controls ($N = 19$) who are psychologically and physically stable using the widely used ToM task, Reading the Mind in the Eyes test (RMT). Facial expression, supplemented by clinical examination by experienced researchers.

Results: ToM was assessed with the breast cancer group performed significantly worse than the control group ($p < 0.05$). The present study reports that breast cancer patients have greater impairment in identifying self-conscious emotions compared to healthy control. The degree of impairment is midway in self-conscious emotion between patients with breast cancer and that of normal controls after statistically controlled ToM.

Conclusions: Therefore it can be said that the breast cancer patients suffering from self-conscious emotion may have an additional burden of impaired social cognition, which needs to be addressed urgently for the better quality of life.

Legal entity responsible for the study: Prathama G. Chaudhuri.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1552P Characteristics of the psychosomatic state of patients with lung cancer

G. Zhukova[1], A.I. Shikhlyarova[1], E. Shirnina[1], M. Zinkovich[2], N. Maschenko[1], E. Zlatnik[2], S. Pyltsin[1], P. Anistratov[2], M.I. Bragina[1], A. Zhadobina[1], L.Y. Vladimirova[3]

[1]Testing Laboratory Center, Rostov Research Oncology Institute, Rostov-on-Don, Russian Federation, [2]Medical Oncology, Rostov Research Oncology Institute, Rostov-on-Don, Russian Federation, [3]Medical Department, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Background: The important issue of psychophysiological adaptation to malignant process is poorly studied. The aim of the research was to elucidate characteristics of the psychic, adaptive and hormonal status of patients with lung cancer (LC).

Methods: Studies were performed in 28 LC patients with receiving surgery and chemo-radiotherapy. The patients were divided into 3 groups: 1 - unresectable tumors, 2 - resectable tumors with metastases, 3 - resectable tumors without detected metastases. Personal (PA) and situational anxiety (SA) (Spielberger-Khanin test), depression (Zung test), the types of the mental response to disease (LOBI, Bechterew Institute Personality Inventory) were evaluated. With the help of blood count and the original computer program "Antistress", we calculated the quantitative indicator (QI) of the general nonspecific adaptation reactions of the body (AR) (Garkavi L. H. et al., 1975). Hormone levels of thyroid and pituitary-adrenal (PAS) systems in the blood were determined by electrochemiluminescent method (Cobase 411E).

Results: The studied groups did not differ in PA and SA. The signs of tension of the PAS, elevated thyroxine level and decline in the adaptive status were noted. At the same time, QI of AR in patients of the group 3 was 1.8-2.7 times higher than in patients of other groups ($p < 0.05$). Depression was observed in only one patient. The euphoric type of response to the disease dominated in the groups (39% of cases), the harmonic type was the second most frequent (18% of cases). The patients of group 3 with euphoric reaction (referred to non-rational types of response) were characterized by an uncomplicated postoperative period and the maximal QI of AR in the studied groups, which exceeded by 2 times the indices in the patients of group 3 with harmonic and other reactions ($p < 0.01$).

Conclusions: QI of AR of patients with LC reflected the prevalence of the malignant process. In these patients depression was not expressed, and the euphoric reaction dominated. That could be due to central effects of thyroxin. We assumed that the euphoric reaction in the patients with resectable LC without detected metastases was a favorable diagnostic characteristic. So the questions arise about the clarification of the concept of the euphoric reaction and the ways of its identification.

Legal entity responsible for the study: Ministry of Health of the Russian Federation.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1553P Perception, magnitude and implications of cancer related fatigue in breast cancer survivors: Study from a developing country

A. Gupta[1], S.M. Hussain[1], R. Manaktala[2]

[1]Medical Oncology, Max Institute of Cancer Care, New Delhi, India, [2]Breast Cancer Support Group, Max Institute of Cancer Care, New Delhi, India

Background: Cancer Related Fatigue(CRF) is one of the most common, distressing & incompletely addressed symptom among breast cancer survivors. We have analyzed perceptions, magnitude & overall implications of CRF in breast cancer survivors.

Methods: Breast cancer survivors who attended breast cancer follow-up clinic at our institute between Jan-March 2018 were asked to fill a questionnaire. This questionnaire focused on assessing an individual's perception, severity, potential causes, implications on quality of life and measures taken to deal with CRF.

Results: 65 patients (median age 52 years) completed the CRF questionnaire. Of these 54(83%) had undergone surgery, 59(91%) chemotherapy, 43(66%) radiation therapy and 36(55%) hormonal/targeted therapy. 62(95%) patients experienced any grade CRF. 55(85%) patients experienced moderate to severe CRF affecting work (58%) and activities of daily living (27%). CRF was perceived as generalized weakness by 54(83%), diminished concentration/attention span by 24(37%), decreased motivation and interest in usual activities by 29(45%) and emotional labiality by 16(25%) patients. 56(86%) patients believed that fatigue was due to the effect of cancer treatment on the body, while only 8(12%) attributed it to underlying cancer. 21(32%) also attributed it to psycho-social factors and 5(8%) to genetic/environmental factors. CRF had negative impact on mood, daily activities, interpersonal relationships and professional work in 40(62%), 39(60%), 13(20%) and 10(15%) patients, respectively. Measures taken to overcome CRF were increased physical exercise, psychosocial interventions, mind-body interventions and pharmacological interventions in 32(49%), 8(12%), 28(43) and 17(26%) patients, respectively. 39(60%) patients reported persistence of CRF after completion of treatment while it took upto 6 months, 6-12 months and more than 12 months for resolution of CRF in 13, 10 and 3 patients, respectively.

Conclusions: Development and persistence of moderate to severe intensity CRF impacts multiple aspects of Quality of Life of breast cancer survivors. Current interventions are not able to substantially mitigate this problem and further research in this field is warranted.

Legal entity responsible for the study: Max Institute of Cancer Care, Delhi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1554P Impact of cancer on the quality of life of Tunisian pediatric patients

F. Letaief-Ksontini[1], T. Dorra[1], S. Masmoudi[2], K. Meddeb[2], A. Mokrani[3], Y. Yahyaoui[2], A. Gabsi[1], M. Ayadi[3], N. Chraiet[3], H. Raies[2], A. Mezlini[3]

[1]Medecine, Institut Salah Azaïz, Tunis, Tunisia, [2]Medical Oncology, Salah Azaiez Institute of Cancer, Tunis, Tunisia, [3]Medical Oncology, Institut Salah Azaïz, Tunis, Tunisia

Background: The PedsQL (Pediatric Quality of Life Inventory) is an instrument which measures health-related quality of life (HRQOL) in children and young adults. The PedsQL 4.0 Generic Core Scales (GCS) are child self-report and parent proxy-report scales developed to be integrated with the PedsQL disease specific modules. The PedsQL 3.0 Cancer Module (CM) was designed to measure pediatric cancer specific HRQOL. The aim of this study was to evaluate the impact of their disease and its treatments on their physical, mental and social health.

Methods: This prospective study included 26 patients newly diagnosed and relapsed, on-treatment, from the pediatric ward of Salah Azaiez Institute. Their ages were 5 to 25 years-old. The 23-item PedsQL 4.0 GCS encompass 4 scales: physical, emotional, social, and school functioning. The cancer module scales has 27 items which encompasses 8 scales: pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance and communication. The format instructions, response scale and scoring method are identical for GCS and CM. The scores are between [0-100]. We translated the English version of the GCS and the CM into arabic.

Results: All the children completed their self-report .The mean age was 15.5 years-old.53.8% were boys.27.07% of patients had brain tumors, 19.2% osteosarcoma,19.2% Ewing sarcoma and 11.5%Undifferentiated nasopharyngeal cancer (UCNT). Twenty patients were newly diagnosed. Eight cases had metastatic disease.The child total GCS mean was 60.86 physical score mean 64.06 and social score mean 67.5. For the child total CM score mean, it was 61.53 ; pain score mean 75, nausea score mean 50 which is the lowest and the worry score mean 62.49 . We found that the nausea score is higher for children with intensive chemotherapy (p value=0.026). The parent proxy total GCS mean was lower than the childs score 58.69 as well as the total CM parent score mean which was 60.17. We didn't find significant difference between the age of the patient, staging of his disease and the pedsQL scores.

Conclusions: The HRQL of children is adversely affected as a result of the uncontrolled symptoms from cancer treatment. In Tunisia, we should work more to improve the pediatric HRQL.

Legal entity responsible for the study: Salah Azaiez Intitute.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology 29 (Supplement 8): viii562–viii575, 2018
doi:10.1093/annonc/mdy297

PUBLIC HEALTH POLICY

1556O Potential for value-based prescribing of oral oncology drugs

M.J. Ratain[1], A.S. Lichter[2]
[1]*Medicine, The University of Chicago, Chicago, IL, USA,* [2]*Value in Cancer Care Consortium, Ann Arbor, MI, USA*

1557O Relation between center volumes for pancreatic and esophageal cancer surgeries and outcome in Belgium: A plea for centralization

H. De Schutter[1], G. Silversmit[1], K. Haustermans[2], L. Van Eycken[3]
[1]*Research Department, Belgian Cancer Registry, Brussels, Belgium,* [2]*Department of Radiation Oncology, University Hospitals Leuven, Leuven, Belgium,* [3]*Belgian Cancer Registry, Brussels, Belgium*

1558O Worldwide comparison of colorectal cancer survival by topography and stage at diagnosis (CONCORD-2)

S. Benitez Majano, V. Di Carlo, M. Nikšić, M.P. Coleman, C. Allemani, CONCORD Working Group
Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

1559O Increasing colorectal cancer incidence among young adults in England diagnosed during 2001-2014

A. Exarchakou, L. Donaldson, M.P. Coleman
Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

1560PD **Major determinants of delayed access to innovative medicines for metastatic melanoma: The results of Melanoma World Society and European Association of Dermato-Oncology survey**

L.O. Kandolf Sekulovic[1], S.S. Agarwala[2], A. Hauschild[3], J. Guo[4], G.A. McArthur[5], P. Lorigan[6], G. Cinat[7], C. Caglevich[8], C. Lebbe[9], P.L. Rutkowski[10], H. Gogas[11], R. Dummer[12], B. Neyns[13], L. Bastholt[14], A. Wainstein[15], D. Herceg[16], M. Banjin[17], A. Zhukavets[18], J. Ocvirk[19], C. Garbe[20]

[1]Dermatology, School of Medicine, Military Medical Academy, Belgrade, Serbia, [2]Medical Oncology, St. Luke's Hospital & Health Network, Bethlehem, PA, USA, [3]Dermatology, UK-SH, Campus Kiel, Schleswig-Holstein, Germany, [4]Department of Renal Cancer and Melanoma, Beijing Cancer Hospital, Beijing, China, [5]Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia, [6]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [7]Department of Sarcoma and Melanoma, Instituto Angel H. Roffo, Buenos Aires, Argentina, [8]Medical Oncology, Instituto Oncologico Fundacion Arturo Lopez Perez, Santiago, Chile, [9]Hôpital St. Louis, Paris, France, [10]Surgical Oncology, The Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland, [11]Medical Oncology, Laiko General Hospital of Athens, Athens, Greece, [12]Dermatology, University Hospital Zürich-Dermatology, Zurich, Switzerland, [13]Medical Oncology, Vrije Universiteit Brussel-Campus Jette, Brussels, Belgium, [14]Medical Oncology, Odense University Hospital, Odense, Denmark, [15]Surgical Oncology, ONCAD, Belo Horizonte, Brazil, [16]Medical Oncology, KBC - University Hospital Centre Zagreb, Zagreb, Croatia, [17]Clinic of Oncology, Clinical Centre of Sarajevo University, Sarajevo, Bosnia and Herzegovina, [18]Oncology, N.N. Alexandrov Research Institute, Minsk, Belarus, [19]Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia, [20]Dermatology, University of Tuebingen-Dermatology, Tübingen, Germany

1561PD **Variation in oncology drug approvals in Canada, the United States and Europe**

O.F. Khan[1], N.N. Samuel[2], S. Verma[1]

[1]Department of Oncology, Cumming School of Medicine, Tom Baker Cancer Centre, Calgary, AB, Canada, [2]Department of Medicine, University of Toronto, Toronto, ON, Canada

1562PD **Magnitude of clinical benefit of cancer drugs approved based on single-arm trials (SAT) by the US Food and Drug Administration (FDA)**

C. Molto Valiente[1], M. Borrell[1], A. Ocana Fernandez[2], A.J. Templeton[3], L.P. del Carpio[1], J. Del Paggio[4], A. Barnadas[1], C.M. Booth[5], A. Tibau[1], E. Amir[6]

[1]Oncology Department, Hospital de la Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain, [2]Medical Oncology Department and Translational Research Unit, Albacete University Hospital, Albacete, Spain, [3]Department of Medical Oncology, St. Claraspital and Faculty of Medicine, University of Basel, Basel, Switzerland, [4]Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, Kingston, ON, Canada, [5]Departments of Oncology and Public Health Sciences, Queen's University, Kingston, ON, Canada, [6]Division of Medical Oncology & Hematology, Department of Medicine, Princess Margaret Cancer Centre and the University of Toronto, Toronto, ON, Canada

1563PD **Magnitude of clinical benefit in trials supporting US Food and Drug Administration (FDA) accelerated approval (AA) and European Medicines Agency (EMA) conditional marketing authorisation (CMA) and subsequent trials supporting conversion to full approval**

M. Borrell Puy[1], C. Molto Valiente[1], K. Vokinger[2], T. Hwang[3], A. Ocana Fernandez[4], A.J. Templeton[5], B. Seruga[6], I. Gich Saladich[7], A. Barnadas[1], E. Amir[8], A. Tibau[1]

[1]Oncology Department, Hospital de la Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain, [2]Medicine, University of Zurich Hospital, Zurich, Switzerland, [3]Program on Regulation, Therapeutics, and Law (PORTAL), Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, [4]Medical Oncology, Complejo Hospitalario Universitario de Albacete, Albacete, Spain, [5]Medical Oncology, St. Claraspital AG, Basel, Switzerland, [6]Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia, [7]Epidemiology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [8]Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada

1564PD **Magnitude of clinical benefit of trials supporting US Food and Drug Administration (FDA) approval of breakthrough and non-breakthrough drugs**

C. Molto Valiente[1], M. Borrell[1], T. Hwang[2], I. Gich Saladich[3], A. Barnadas[1], E. Amir[4], A. Kesselheim[2], A. Tibau[1]

[1]Oncology Department, Hospital de la Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain, [2]Program on Regulation, Therapeutics, and Law (PORTAL), Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, [3]Department of Epidemiology, Hospital de la Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain, [4]Division of Medical Oncology & Hematology, Department of Medicine, Princess Margaret Cancer Centre and the University of Toronto, Toronto, ON, Canada

1565PD **Time to access to novel anticancer therapies in Slovenia in view of the ESMO-MCBS scores**

U. Janzic[1], L. Knez[2], A. Janzic[3], T. Cufer[1]

[1]Department of Medical Oncology, University Clinic Golnik, Golnik, Slovenia, [2]Pharmacy, University Clinic Golnik, Golnik, Slovenia, [3]University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

1566PD **Cascade BRCA germline mutation (BGM) testing of women with breast (BC) or epithelial ovarian cancer (EOC) and their families with subsequent risk reducing surgery (RRS): A Canadian economics model**

P. Hoskins[1], A. Ecclestone[2], M. Hurry[3], M. Dyer[4]

[1]Medical Oncology, BC Cancer Agency, Vancouver, BC, Canada, [2]Statistics, DRG Abacus, Manchester, UK, [3]Health Economics, AstraZeneca Canada, Mississauga, ON, Canada, [4]Health Economics, AstraZeneca Academy House, Cambridge, UK

1567PD **Genetic testing of BRCA mutations in breast cancer in six European countries: Barriers and opportunities**

M. Thrift-Perry[1], S. Ahmed[2], S. Wait[2], J. Tate[2]

[1]International Affairs, Pfizer, New York, NY, USA, [2]Research, The Health Policy Partnership, London, UK

1568PD **Public awareness of cancer in the Gaza-Strip: A cross-sectional study**

M.S. Elshami[1], M. Alkhatib[2], A. Elshami[2], K. Abu-Nemer[2], A. Qandeel[2], M. Hana[2], N. Alshorbassi[2], G. Matar[2], O. Baraka[2], M. Elblbessy[2], L. Albarqouni[3], B. Bottcher[2]

[1]Nasser Medical Complex, Ministry of Health, Gaza, Palestinian Self-Rule Area, [2]School of Medicine, Islamic University of Gaza, Gaza, Palestinian Self-Rule Area, [3]Centre for Research in Evidence-Based Practice, Bond University, Queensland, Australia

1569P The impact of primary care access on mortality in lung cancer patients from Bronx, New York

C. Su[1], H. Cheng[2]

[1]Department of Oncology, NYU Langone Medical Center, New York, NY, USA, [2]Microbiology and Immunology, Montefiore Medical Center Albert Einstein College of Medicine, Bronx, NY, USA

Background: Racial and ethnic disparities in cancer care are well described. Lack of access to primary care physicians (PCPs) may be an important contributor to disparities attributed to race and ethnicity. This study examined the effects of primary care access on mortality in lung cancer (LC) patients (pts) in an underserved community.

Methods: Medical records of all pts newly-diagnosed with primary lung cancer between 2012-2016 at a NCI-designated cancer center in the Bronx were reviewed. Demographic data and PCP status were collected. Addresses were correlated with the Health Resources and Services Administration (HRSA) database to identify residences located in primary care shortage areas (PCSAs). Survival data from time of first imaging to death or the end of follow-up on January 1, 2018 were recorded. Data analysis was performed via univariate methods. Survival analysis was performed using Kaplan-Meier and Cox hazards modeling.

Results: Among 1062 pts, 874 (82%) resided in a PCSA, 314 (30%) were Hispanic (H), and 445 (42%) were African-American (AA). Hs and AAs were more likely to reside in PCSAs ($p = 0.0002$ and $p = 0.0008$) and in ZIP codes with lower income (both $p < 0.0001$). Hs and AAs were more likely to depend on public insurance ($p = 0.01$ and $p = 0.02$). Pts who live in PCSAs presented at higher stages at the time of diagnosis ($p = 0.03$) and were diagnosed predominantly in inpatient settings with acute symptoms ($p < 0.0001$) rather than outpatient clinics ($p = 0.0002$). In the overall population, PCSA residence (mean: 24 vs. 30 months, $p = 0.03$, HR = 1.27) and no established PCP (mean: 22 vs. 28 months, $p < 0.0001$, HR = 1.50) were associated with increased all-cause mortality. In Cox modeling adjusting for stage at diagnosis and PCSA residence, lack of established PCP still predicts increased mortality ($p = 0.03$, HR = 1.20).

Conclusions: Among new pts with LC, lack of established PCP is associated with increased mortality. Hs and AAs are more likely to reside in PCSAs, suggesting the link between increased mortality and race/ethnicity may be mediated by lack of access to primary care. Our results demonstrate that effective health policy efforts to reduce lung cancer mortality must include approaches to improve access to primary care.

Legal entity responsible for the study: Albert Einstein School of Medicine, Montefiore Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1570P Are socioeconomic position and region of residence barriers for referral to phase I trials?

K.T. Gad[1], S.O. Dalton[2], A.K. Duun-Henriksen[2], A. Krøyer[2], C. Johansen[1], M. Mau-Sorensen[1], U.N. Lassen[1]

[1]Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Unit of Survivorship, Danish Cancer Society Research Center, Copenhagen, Denmark

Background: Referral pattern to phase 1 oncology trials is a highly relevant topic as the rapid development of new anticancer agents requires increased recruitment to early clinical trials. In this study, we investigated possible recruitment bias. The objective was to compare the socioeconomic position (SEP) and region of residence of patients referred to the Phase 1 Unit at Copenhagen University Hospital to a matched control group. Moreover, we investigated the influence of SEP on the inclusion in trials.

Methods: Data from the Danish registries were compiled based on the civil registration number of patients referred to the Phase I Unit from 2005 to 2016. The association between SEP and referral was examined in a conditional logistic regression analysis based on referred patients and a matched control group. We adjusted for number of cancers, M-stage, comorbidity and psychological disturbances. The association between SEP and enrolment once referred was examined in a Cox regression analysis.

Results: 1255 patients were referred. 1143 of these patients were eligible for this study. Complete data for analyses were available for 1026 patients and 229,788 controls matched on age, gender, type of cancer, year of diagnosis and time from diagnosis to referral. As barriers for referral, we identified short education as compared to long (OR 0.57, 95% CI 0.47-0.69), being outside workforce as compared to being within (OR 0.67, 95% CI 0.56-0.80), living alone as compared to living with a partner (OR 0.85, 95% CI 0.74-0.99) and living far from the Phase 1 Unit 0.34 as compared to living close to (95% CI 0.29-0.40). 252 patients enrolled in trials. Once referred, the socioeconomic parameters did not affect enrolment.

Conclusions: In this single-center study, patients' SEP and region of residence affected referral pattern to phase 1 trials. This suggests inequality in the access to phase 1 trials.

Legal entity responsible for the study: Danish Cancer Society Research Center, Copenhagen, Denmark.

Funding: A.P. Møller Foundation, Knæk Cancer funds, The Health Foundation.

Disclosure: All authors have declared no conflicts of interest.

1571P Breast cancer treatment waiting time, patient and provider contributions: An Egyptian breast cancer centre experience

A.H. Abdelaziz[1], A.M. Abdou[1], C.N. Habeeb[2]

[1]Clinical Oncology, Ain Shams University Hospital, Cairo, Egypt, [2]Medical Oncology, Baheya Foundation for Breast Cancer, Cairo, Egypt

Background: Breast cancer is the most common type of female cancer in Egypt and world wide. Most of the cases present as locally advanced or metastatic rather than early stages in Egypt. There is no data to assess waiting times in the Egyptian breast cancer patient journey from developing first symptom until initiating treatment.

Methods: This is a descriptive study in which the electronic records and paper notes of 200 patients presenting from April until September 2016 to a public non governmental breast cancer centre in Cairo were reviewed for different waiting times. The wait time from developing the first symptom until commencing treatment was divided into stages; Symptom to call (booking an appointment), call to review , review to diagnosis, diagnosis to multidisciplinary team meeting (MDT) and MDT to first therapy.

Results: The average time from developing symptom to booking an appointment (patient factor) was 131 days /4.4 months. The time lag from booking until medical review was 47 days /1.5 months. This is because of the booking system waiting list. The mean time taken from review until getting a final diagnosis was 11 days. All cases were discussed in the MDT and therapy ensued the MDT by 17 days in average. The mean in hospital waiting time (time from review until commencing treatment whether surgery, systemic therapy or radiotherapy) was 37 days while the mean time for the whole journey (symptom to treatment) was 214 days /7.1 months. Patients contributed to 61% of the wait time (131 days / 4.4 months) whereas the provider contributed by 39 % with average of less than 3 months.

Conclusions: Patients contributed to the biggest part of the delay. The second factor was the booking system waiting list. Once reviewed by the medical team the process was accelerated. This indicates a need to improve public awareness of breast cancer symptoms and facilitate patient access to services.

Legal entity responsible for the study: Baheya Research Centre (BRC).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1572P Is age a barrier to chemotherapy? Rates of treatment in older patients with breast, colon or lung cancer in England in 2014: A national registry study

N.M.L. Battisti[1], M. Wallington[2], A. Ring[1], S. Payne[3], R. Birch[4], M. Bomb[5], J. Seligmann[6], T. Kalsi[7], L. Hounsome[2], D. Dodwell[8], S. Underhill[9], L. Mensah[10], E. Morris[4], P.J. Selby[6], J. Mansi[3]

[1]Breast Unit, The Royal Marsden NHS Foundation Trust, Sutton, UK, [2]National Cancer Registration and Analysis Service, Public Health England, London, UK, [3]Medical Oncology, Guy's and St Thomas' NHS Foundation Trust, London, UK, [4]Cancer Epidemiology Group, University of Leeds, Leeds, UK, [5]Data Projects, Public Health England, London, UK, [6]Oncology, St. James's University Hospital Leeds, Leeds, Yorkshire, UK, [7]Guy's and St Thomas' NHS Foundation Trust, London, UK, [8]Institute of Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [9]Regional Programmes, Roche, London, UK, [10]Health Economics and Outcomes Research, Novartis Oncology, London, UK

Background: Survival from cancer in older patients is poorer in the UK than other countries with similar health systems and wealth possibly due to undertreatment and increased toxicities in this specific population. This population-based observational study describes factors affecting systemic anticancer treatment (SACT) use in older patients in England.

Methods: We identified patients aged ≥70 with stage II-III breast cancer, stage III colon cancer and stage IIIB-IV non-small cell lung cancer (NSCLC) diagnosed in 2014 from a dataset collected by the National Health Service in England. We used logistic regression to estimate factors affecting likelihood of receiving SACT and performed separate regression analyses for each disease, adjusting for age, gender, stage at diagnosis, pathological features, performance status, Charlson comorbidity index, ethnicity and socioeconomic group. We assessed 2-year overall survival (OS) using Kaplan-Meier method. Case mix adjusted treatment rates and workload volume were calculated at hospital level and presented using funnel plots, stratified by age groups (<70 and ≥70) to allow for assessment of variation between centres.

Results: 36892 patients were identified: 19879 with stage II-III breast cancer, 5292 with stage III colon cancer and 11721 with stage IIIB-IV NSCLC. Patients over 70 were less likely to receive SACT compared to those aged under 70: breast 11.7% vs 64.6%, $p < 0.001$; colon 37.4% vs 79%, $p < 0.001$; NSCLC 33.5% vs 60.2%, $p < 0.001$. 2-year OS for patients receiving SACT was similar for patients aged ≥70 and <70: breast 91.5% (95% CI: 89.3%-93.2%) vs 96.4% (95% CI: 95.9%-96.7%); colon 84.8% (95% CI: 82.6%-86.8%) vs 88.3% (95% CI: 86.7%-89.8%); NSCLC 16.7% (95% CI: 15.1%-18.4%) vs 19.8% (95%CI: 18.5%-21.1%). Patients receiving SACT had better OS than those untreated. SACT rates varied widely between hospitals after adjusting for case-mix across all ages.

Conclusions: Our study suggests that several factors affect the likelihood of receiving SACT but after adjusting for these, age remains determinant. Identifying hospitals with significantly lower SACT rates should prompt local review of multidisciplinary team practice.

Legal entity responsible for the study: Public Health England.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1573P Awareness and attitude towards breast cancer among Egyptian nurses at university affiliated hospitals: Tanta University Hospitals experience

M.A. Alm El-Din, S.E. Amer, M.A. Elsayed, A.M. Elgohary, A. Ismael, A. Zakzouk, K.M. Emara, F. Elkady, S. Elnahrawy, F. Nada, A. Eissa

Clinical Oncology, Tanta University Hospital, Tanta Faculty of Medicine, Tanta, Egypt

Background: Breast cancer (BC) is the most common cancer among women. In Egypt, BC accounts for 38% of all types of cancer in females with the majority often present at advanced stages. This might be attributed to defective health education programs and poor awareness. The aim of this study is to evaluate the knowledge, attitude and practice of Egyptian nurses at Tanta university hospitals towards BC.

Methods: 421 female nurses from Tanta university hospitals completed a questionnaire that administred through face-to-face interviews by medical students and interns. The questionnaire included five sections: sociodemographic data, knowledge about BC symptoms, risk factors, screenings methods and treatment of BC.

Results: Mean knowledge score was 18.75 ± 5.76 with 57.2% of participants knew the right answers of more than 50% of the questions. The least level of knowledge was in questions related to BC symptoms and risk factors with 60.3% and 52.2% , respectively, of participants had scores of < 50% of the total score. The knowledge for nurses aged 30-39 years-old, those from urban areas and those who have years of work experience ranged between 16 and 25 years had statistically lower levels of knowledge compared to other groups (p value, 0.035, 0.048, 0.005, respectively).

Conclusions: The level of BC knowledge among Tanta university hospitals nursing staff is fair. The Knowledge about BC symptoms and risk factors needs more attention from health care authorities to specifically design educational programs focusing on these areas.

Legal entity responsible for the study: Tanta Faculty of Medicine, Egypt.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1574P Women oncologists participation at the Spanish Society of Medical Oncology (SEOM) annual meetings from 2009 to 2017 and their position in Spanish scientific societies

J. Hidalgo Coloma[1], A. Ruiz Hernández[2]

[1]Medical Oncology, Hospital Lluís Alcanyís, Xàtiva, Spain, [2]Internal Medicine, Hospital Clínico Universitario, Valencia, Spain

Background: Medical Oncology is a feminized profession in Spain. According to SEOM, 57,6% of the medical oncologists in this country are women. This situation will remain unchanged because women occupied 67% of the medical oncology training positions since 2008. However, women are underrepresented in leadership possitions, which may influence their career development.

Methods: We reviewed the participation, role and gender distribution of 2110 professionals at SEOM annual meetings between 2009-2017, the possition of the 237 members of SEOM executive boards (1976-2017) and the 355 members of the current executive boards of 13 of the most important Spanish cooperative groups.

Results: From 2009 to 2017 the 38,4% of the 2110 speakers at SEOM meetings were women. There wasńt a progressing increase over the years. The only year with >40% of female participation was 2017 (42,4%). At educational and clinical sessions, 26% of chairs and 35% of speakers were women. At original presentations sessions, 57% of presenters, 42% of discusors and 30% of chairs were women. At the plenary sessions, 50% of presenters, 17% of discusors and 5% of chairs were women. 31% of members of scientific committees were women; they chaired these panels in 22% of cases. Over the last decade, SEOM awarded 122 research grants, 42% of them to women. The SEOM executive board has been chaired 18 times by a man and 2 by a woman. The first female president was elected in 2011. There were no women at executive boards until 1987. Women occupied 17,3% of the possitions. Currently, 40% of the executive boards members and 2 of the 13 cooperative groups chairs are women.

Conclusions: Spanish women oncologists developed an active cientific activity in their everyday practice and communicated their research data at national meetings. However they were asked to chair or share their expertise in fewer occasions than men. In addition, women were underrepresented at executive boards of the main oncology scientific groups. According to our results, we consider further efforts are required to achieve gender equality. A good example are initiatives like the ESMO Women for Oncology (W4O) network, the Forum of Women in Oncology in Greece or W4O Italy.

Legal entity responsible for the study: Julia Hidalgo Coloma.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1575P Working arrangements after cancer diagnosis: Who, what, when and how?

C. Alleaume, A-D. Bouhnik, M.K. Bendiane, P. Peretti-Watel

Faculté de Médecine, Aix Marseille Univ, INSERM, IRD, Economics and Social Sciences Applied to Health & Analysis of Medical Information (SESSTIM), Marseille, France

Background: Each year, 355,000 new individuals are diagnosed with cancer in France, nearly half of them being in working age and interrupting their professional occupation during treatments. As having working arrangements has been found to facilitate return to work after a long absence, it is provided by French law. This study aims to describe the use of working arrangements and to investigate how it is related to job retention.

Methods: This study combines analyses of quantitative and qualitative data: 1) VICAN5, a national representative survey on living conditions 5 years after cancer diagnosis conducted in 2015-2016 (n = 4,174), and 2) CAREMAJOB, a qualitative longitudinal study carried out in 2017 among patients on sick leave after a cancer diagnosis and interviewed about the impact of the disease on their working lives (n = 21). VICAN5 survey presents an overview about the use of working arrangements in France and the CAREMAJOB survey completes these results by giving the patients' point of view in a more comprehensive manner.

Results: Among the 1,854 cancer survivors aged between 23 and 59 at time of the VICAN survey, and who were employed at diagnosis, 62.7% used working arrangement(s) within the five years following diagnosis. Nearly half of them (45.5%) had a working time arrangement. The other kind of working changes were about working hours (38.8%), working conditions (35.8%), occupation (32.8%), workplace (20.4%), and security at work (19.2%). Moreover, working arrangements are associated with job retention (88.9% of workers with working arrangement were still employed five years after diagnosis versus 69.6% of others). Furthermore, in CAREMAJOB survey, when patient returned to work without any working arrangement, this led to bad experience because of workload. However, some of those who did have an arrangement reported a negative impact on their professional life: they felt discriminated or thought that it has affected their professional credibility.

Conclusions: In the French context, the use of working arrangement seems to be a good factor to enhance job retention. National surveys should however better take into account the context of the implementation of working arrangement to get better understanding of the potential selection bias.

Legal entity responsible for the study: INSERM, UMR_S 1252, « Sciences Economiques & Sociales de la Santé et Traitement de l'Information Médicale » (SESSTIM).

Funding: Canceropole PACA Institut National du Cancer (INCA).

Disclosure: All authors have declared no conflicts of interest.

1577P Financial burden and financial toxicity in patients with colorectal, gastro-oesophageal, and pancreatobiliary cancers: A UK study

N. Flaum[1], G. Papaxoinis[1], K. Hockenhull[1], J. Barriuso[2], W. Mansoor[1]

[1]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK, [2]Division of Cancer Sciences, University of Manchester / The Christie NHS Foundation Trust, Manchester, UK

Background: How cancer affects a patient (pt) in the UK financially and how this changes throughout treatment is unknown. We aimed to assess financial burden (FB) at baseline and financial toxicity (FT) throughout treatment of pts with upper GI (UGI), pancreatobiliary (PB) and colorectal (CR) cancers.

Methods: Pts with UGI, CR and PB cancer enrolled in 5 clinical trials (REAL-3, RAINFALL, ESPAC-4, QoL BIL and CAPITAL) at the Christie, Manchester, were identified. FB at baseline and FT throughout treatment were defined according to answers to the EORTC QLQ-C30 questionnaire (EQ) Q28 to which pts score financial difficulty relating to disease or treatment from 1 (not at all) to 4 (very much).

Results: 141 pts were included, 58 (41.1%) received adjuvant and 83 (58%) palliative treatment. 96 (68.1%) were men; median age was 62 yrs (range 39-84). 15 (10.6%) pts had CR, 85 (60.3%) PB and 41 (29.1%) UGI cancer. 87 (61.7%) had no FB (scored 1 on EQ), 35 (24.8%) scored 2, 12 (8.5%) scored 3 and 7 (5%) scored 4. 97 (68.8%) answered $\geq$2 EQs. Median EQ follow up was 6.3 months (range 0.5-63.1). 63.5% experienced no FT, 19.8% worse FT and 16.7% improving FT. The median index of multiple deprivation (IMD) (the measure of relative deprivation of English regions) was 16,083 (range 3-32,041). Multiple regression analysis showed that younger age, lower IMD and tumor type were independent predictors of FB. Significant covariates included IMD below vs. above median (OR 2.64, 95%CI 1.13-6.15, $p = 0.024$) and age below vs. above median (OR 7.83, 95%CI 3.23-18.94, $P < 0.001$). Of these, no factor predicted FT. Pts who experienced FT were significantly younger compared to those who did not (median age 55 vs. 69, $p < 0.001$) and had significantly lower IMD (median 9,483.5 vs. 19,277, $p = 0.002$). IMD in our series did not show significant interaction with age ($p = 0.270$). Palliative treatment and lower IMD were independent predictors of worse overall survival.

Conclusions: We report the first study of FB and FT in pts with UGI, PB and CR cancers living in UK, identifying independent baseline parameters predicting FB and the prognostic role of IMD. Younger pts and those of lower IMD are at significantly higher risk and should be offered additional support.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1579P Influenza vaccine effectiveness among cancer patients: A population-based study using health administrative and laboratory testing data from Ontario, Canada

P. Blanchette[1], H. Chung[2], K.I. Pritchard[3], C. Earle[2], M. Campitelli[2], N. Crowcroft[4], J. Gubbay[4], T. Karnauchow[5], K. Katz[6], A. McGeer[7], D. McNally[5], D. Richardson[8], S. Richardson[9], L. Rosella[2], A. Simor[10], M. Smieja[11], G. Zahariadis[12], A. Campigotto[13], J. Kwong[2]

[1]Medical Oncology, London Regional Cancer Program, University of Western Ontario, London, ON, Canada, [2]Epidemiology, Institute of Clinical Evaluative Sciences, Toronto, ON, Canada, [3]Medical Oncology, Sunnybrook Odette Cancer Center, Toronto, ON, Canada, [4]Epidemiology, Public Health Ontario, Toronto, ON, Canada, [5]Laboratory Medicine and Pathology, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, [6]Laboratory Medicine and Pathology, North York General Hospital, Toronto, ON, Canada, [7]Laboratory Medicine and Pathology, Mount Sinai Hospital, Toronto, ON, Canada, [8]Infectious Disease, William Osler Heath Centre, Toronto, ON, Canada, [9]Laboratory Medicine and Pathology, The Hospital for Sick Children, Toronto, ON, Canada, [10]Infectious Disease, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [11]Laboratory Medicine and Pathology, McMaster University, Hamilton, ON, Canada, [12]Laboratory Medicine and Pathology, Newfoundland and Labrador Public Health Laboratory, St John's, NL, Canada, [13]Laboratory Medicine and Pathology, London Health Sciences Centre, London, ON, Canada

Background: Seasonal influenza vaccination is recommended for cancer patients despite concerns that disease- or treatment-associated immunosuppression may decrease vaccine effectiveness (VE). The objective of this study was to evaluate VE against laboratory-confirmed influenza among cancer patients.

Methods: We conducted an observational test-negative design study of previously diagnosed cancer patients aged $\geq$18 years who were tested for influenza during the 2010-11 to 2015-16 influenza seasons in Ontario, Canada. We linked individual-level cancer registry, respiratory virus testing, and health administrative data. Vaccination status was determined from physician and pharmacist billing claims. We used multivariable logistic regression to estimate VE, adjusting for age, sex, rurality, neighborhood income, cancer characteristics, chemotherapy exposure, comorbidities, previous healthcare use, influenza season, and calendar time of testing.

Results: We identified 24,668 cancer patients who underwent influenza testing, with 3991 (16%) testing positive and 10,929 (44%) vaccinated. Mean age was 70 years, 52% were male, mean time since cancer diagnosis was 6 years, 79% had a solid tumor malignancy, and 24% were receiving active chemotherapy. The overall adjusted VE (aVE) against laboratory-confirmed influenza was 21% (95%CI, 15%, 27%). The aVE among patients with a solid tumour malignancy was 25% (95%CI, 19%, 31%) as compared with –2% (95%CI, –20%, 14%) amongst patients with a hematologic malignancy (p-value for interaction <0.01). The aVE among patients receiving active chemotherapy was 9% (95%CI, –7%, 23%), compared with 23% (95%CI, 17%, 29%) among patients not on active chemotherapy (p-value for interaction=0.13).

Conclusions: Our results support recommendations for influenza vaccination among cancer patients and survivors. Influenza vaccination appears to be less effective among those undergoing active chemotherapy and we observed uncertain effectiveness among hematologic cancer patients. Strategies to improve VE and influenza vaccine uptake among cancer patients and their families are warranted.

Legal entity responsible for the study: Phillip Blanchette and Jeff Kwong.

Funding: The study was funded by The Canadian Institute for Health Research and Ministry of Health and Long-Term Care in Ontario which provide funding support for Public Health Ontario (PHO) and The Institute of Clinical Evaluative Science (ICES).

Disclosure: K.I. Pritchard: Consultancy: Pfizer, Roche, Amgen, Novartis, Eisai, Genomic Health. A. McGeer: Research funding: Sanofi Pasteur, GlaxoSmithKline. All other authors have declared no conflicts of interest.

1580P How advanced lung cancer patients are really treated at the population level? The Ontario, Canada experience

W.K. Evans[1], W. Flanagan[2], C. Gauvreau[3], P. Manivong[4], S. Memon[3], N. Fitzgerald[3], J. Goffin[5], R. Garner[2], E. Khoo[4], N. Mittmann[4]

[1]Oncology, McMaster University, Hamilton, ON, Canada, [2]Health Analysis, Statistics Canada, Ottawa, ON, Canada, [3]Health Economics, Candian Partnership Against Cancer, Toronto, ON, Canada, [4]Biostatistics, Cancer Care Ontario, Toronto, ON, Canada, [5]Medical Oncology, Juravinski Cancer Centre, Hamilton, ON, Canada

Background: Clinical trials define treatment recommendations but patients in the real world may be unable or unwilling to undergo treatments with demonstrated efficacy in fit patients. The Canadian Partnership Against Cancer has developed a model of lung cancer (LC) management (OncoSim-lung) in 2008 based on clinical trials data and expert advice. To credibly project the future clinical and economic impacts of cancer control measures using OncoSim, the model has been refined using real-world data.

Methods: Treatment data by histology and stage were extracted from the Ontario Cancer Registry for LC cohorts diagnosed in 2010 and 2013. All incident cases that satisfied the IARC rule of a new primary were included. Missing or unknown stage cases were excluded. Clinical pathways were validated by oncologists from different disciplines across Canada.

Results: The 2013 cohort included 8,086 staged LC: NSCLC ($n = 7,143$) Stage I 18.7%, II 8%, III/IIIa 11.4%, IIIb 4.9% IV 56.8%; SCLC ($n = 943$) limited 67.7%, extensive 32.3%. Of 813 stage III/IIIa patients, only 26% underwent surgery, 41% of whom received adjuvant chemotherapy or postoperative radical radiotherapy (16%); 13% received trimodality treatment. Of the 75% of Stage III not receiving surgery, 26% had NAT and 21% had palliative radiotherapy alone. Of those receiving active treatment, 20% received combined chemo +radiotherapy and 13% each had chemotherapy alone or radical radiotherapy alone. Of 356 stage IIIb patients, 17% had NAT, 28% received palliative radiotherapy and only 30% had chemo + radical radiotherapy. 18% had chemo alone. Of 4055 stage IV NSCLC, 47% had NAT, 24% received chemotherapy alone and 23% had palliative radiotherapy only. Of those who received first-line chemotherapy ($n = 1059$), 47% received second line chemotherapy and of those, 37% received third line therapy.

Conclusions: Compared to prior expert opinion, there was a much lower frequency of chemo-radiotherapy in Stage III disease and a higher frequency of NAT across all stages of disease. The updated OncoSim model will now have a credible real-world base from which the impacts of new treatment interventions on survival and budget impact can be better estimated.

Legal entity responsible for the study: Canadian Partnership Against Cancer.

Funding: Canadian Partnership Against Cancer.

Disclosure: All authors have declared no conflicts of interest.

1581P Anticoagulant treatment of patients (pts) with cancer associated thromboembolism (CAT) in Germany: Real world data from a 4 million people sample generated by insurance captured data

A. Kretzschmar[1], M. May[2], A. Heinken[3], H. Riess[4]

[1]Oncology, Klinikum St. Georg gGmbH, Leipzig, Germany, [2]Research, HGC Healthcare Consultants GmbH, Dusseldorf, Germany, [3]Research, Aspen Germany GmbH, Munich, Germany, [4]Oncology, Charite Berlin Mitte, Berlin, Germany

Background: CAT is a common complication of cancer with impact on overall prognosis. After 2003 low molecular weight heparin (LMWH) instead of vitamin K antagonists (VKA) became guideline recommended treatment. Direct oral anticoagulant drugs (DOAC) were investigated in CAT only recently. Little data is available concerning incidence and current treatment situation in Germany.

Methods: Data on drugs and coding of diagnosis for all continuously insured members of SHI were available. An anonymized health claims database (2011-2016) of German SHI was used for a retrospective analysis. With a wash out period of one year patients with preexisting conditions were eliminated. According to our definition pts with CAT had a new a cancer diagnosis and a new VTE diagnosis and a prescrition of any type of anticoagulant. Anticoagulant drug type and duration in CAT pts during the next year was analyzed and then classified according to their dominant (> 51 % of time) anticoagulant drug. Any coded bleeding diagnosis was captured as well. The study has descriptive character.

Results: Out of a sample of > 4 million MSHI which is 5,5 % of the German SHI population 322,600 tumor pts and 13,131 (4%) pts with initial VTE diagnosis were identified. 25% of them had no prescription of any anticoagulant. According to the definition 7,313 were CAT. Dominant anticoagulant was LMWH in 58% VKA in 24%, and DOAC in 18%, respectively. During prescription of anticoagulation approx. 20% of all pts with CAT suffered from bleedings with no significant differences between agents (LMWH, DOAC, VKA). The individual LMWH type (approved for secondary prophylaxis or not) and switch of therapy were analyzed as well.

Conclusions: Out of 7,313 pts with CAT more than half received secondary prophylaxis of VTE with LMWH in accordance with the German guideline. VKA (probably suboptimal choice) as well as DOAC (no data published before 2017) were used in a clinically relevant subset. Bleeding was comparable in different agents of anticoagulation. As compared to available small market research studies our data set offers more reliable information due to its comprehensive character. This has impact on future guidelines and education.

Legal entity responsible for the study: HGC Healthcare Consultants GmbH.

Funding: Aspen Germany GmbH.

Disclosure: A. Kretzschmar: Travel cost compensation: Aspen Pharma. M. May: Research funding: Aspen Pharma GmbH, Germany; Compensation for travel, Employee: HGC. A. Heinken: Employee: Aspen Pharma, Germany. H. Riess: Travel compensation, Honoraria, Advisory board: Aspen Pharma, Bayer Schering, Daiichi Sankyo, Boehringer Ingelheim, Leo-Pharma.

1582P Age distribution for different types of cancer in the United States (1996-2015)

M.A. Gouda

Department of Clinical Oncology, Faculty of Medicine - Menoufia University, Shebin El Kom, Menoufia Governorate, Egypt

Background: There has been an increasing concern about the changing incidence patterns of some types of cancers including age at diagnosis. While there is at least some evidence that some cancers currently occur at age earlier than that expected based on historical data, we still lack evidence about age trends in most types of cancers. This study aims to explore current age distributions for different types of malignancies in the United States based on data from SEER.

Methods: Data were obtained using SEER*Stat version 8.3.5, where (SEER 18 Regs Nov 2017 Submission) database was used as the data source. Only cases diagnosed between 1996-2015 with malignant behavior, known age, and microscopic confirmation were included. Data were exported using the case listing session and were analyzed using SPSS version 21.

Results: Median age at diagnosis was significantly higher in the period between 2006-2015 than in the period 1996-2005 for most types of cancers. GIT malignancies and CML, however, showed an exception with a significantly younger median age of diagnosis. The table shows age distribution as well as median age for some common types of cancers including comparison between cases in the 1996-2005 and 2006-2015 time periods.

Conclusions: Except for GIT malignancies and CML, cancer is still being diagnosed at higher median age. With few exceptions, patients who are over 55 years old are still constituting the vast majority of cases.

Legal entity responsible for the study: Mohamed Alaa Gouda.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1583P Patient reported stressors in the practical domain of a cancer diagnosis: The impact of socioeconomic status and geographic location

C. Ho[1], B. Leung[1], H. Rennie[2], J. Laskin[1], J. Wu[3], A. Bates[2]

[1]Medical Oncology, BC Cancer, Vancouver, BC, Canada, [2]Psychosocial Oncology, BC Cancer, Vancouver, BC, Canada, [3]Radiation Oncology, BC Cancer, Vancouver, BC, Canada

Background: Socioeconomic status (SES) and geographic location may influence access to cancer care. In the Canadian health care system, cancer care is publically funded however, other factors including workplace absences and travel for treatment can be additional stressors. We aimed to assess patient reported distress in the practical aspects of accessing cancer treatment in relation to their SES and community size.

Methods: BC Cancer provides cancer care to a population of 4.6 million dispersed over 944, 735 km^2. All patients referred to BC Cancer from 2011 – 2016 who completed the Psychosocial Screen for Cancer (PSSCAN-R) within 6 months of cancer diagnosis were included in the study. Baseline characteristics were collected from the BC Cancer

Table: 1582P

	Median Age (in years)			Number and Percentage of Cases in Different Age Groups (1996-2015)							
				< 18 years		18-35 years		ears		> 55 years	
	1996-2015	1996-2005	2006-2015	N	%	N	%	N	%	N	%
CML	65	66 *	64	476	1.9%	2310	9.0%	6033	23.6%	16781	65.6%
NHL	67	66	67	4135	1.4%	13792	4.7%	61630	21.1%	212389	72.7%
HD	38	37	39 *	3501	8.6%	15123	37.3%	11242	27.8%	10638	26.3%
Lung Cancer	70	70	70	116	.0%	2571	.3%	100142	12.0%	731999	87.7%
Breast Cancer	61	61	62 *	11	.0%	23824	2.3%	340441	33.4%	655907	64.3%
Bladder Cancer	72	72	72	75	.0%	1705	.6%	30047	10.1%	264547	89.3%
Gonadal Cancer	63	63	63	97	.1%	2887	3.2%	26422	29.1%	61458	67.6%
Cervical and Uterine Cancer	60	59	60 *	22	.0%	13937	5.7%	77435	31.9%	151283	62.3%
Colorectal Cancer	69	71 *	67	338	.0%	10166	1.5%	133171	19.2%	550771	79.3%
Stomach Cancer	70	71 *	69	36	.0%	1952	1.8%	18304	17.3%	85274	80.8%
Liver Cancer	64	65 *	63	208	.2%	1100	1.0%	23862	22.0%	83175	76.8%
Pancreatic Cancer	70	71 *	69	58	.0%	998	.6%	22136	14.1%	134330	85.3%

*Significantly higher median age.

registry. The Canadian Postal Code Conversion File Plus (PCCF+) was used to link the patients' postal codes with standard 2011 census geographic areas and neighbourhood income quintiles. Chi squared test was used for comparisons.

Results: 48,954 patients completed the PSSCAN-R and 45 164 had PCCF+ data available. Baseline characteristics: median age 66, 55% female, 17% presented with metastatic disease. Tumor distribution: 22% breast, 19% GI, 13% GU, 13% lung and 33% other. Income quintiles were grouped into lowest/mid-lower, middle, mid-higher/highest. Community size: >1.5M 53%, 1.5M – 10K 17%, <10K 30%. Patients in lowest/mid-lower compared to mid-higher/highest income groups reported more distress around finances (19% vs 14.1%), getting to appointments (15.3% vs 9.7%) and accommodations during treatment (5.6% vs 3.8%). Concerns regarding school/work were similar (10.5% vs 10.9%). Patients in rural versus large communities (1.5M+) reported more distress around finances (19% vs 15.1%), getting to appointments (15% vs 11.9%), accommodations during treatment (9.7% vs 2.7%) and less distress around school/work (9.7% vs 11.8%).

Conclusions: Lower SES and rural geographic location are associated with higher levels of cancer patient distress in the practical domain, despite a publically funded medical system. Local navigational support services for workplace and income assistance should be developed to alleviate distress for patients in rural areas or with low income.

Legal entity responsible for the study: BC Cancer.

Funding: BC Cancer Foundation.

Disclosure: All authors have declared no conflicts of interest.

1584P Overview on the use of patient reported outcomes in colorectal cancer care

L. Neamtiu[1], S. Deandrea[2], Z. Saz Parkinson[1], L. Pylkkanen[3]

[1]Health in Society, JRC - ISPRA, Ispra, Varese, Italy, [2]Medical Department, ATS Milano, Milan, Italy, [3]Medical Department, Finnish Medicines Agency Fimea, Turku, Finland

Background: The burden of colorectal cancer is high in Europe and still increasing. The disease and treatment can have profound impacts on the patients quality of life (QoL), emphasizing the importance of measuring QoL. An important tool in this process is Patient Reported Outcome Measures (PROMs). The goal of this study is to give an overview on the use of PROMs throughout the colorectal cancer care pathway in Europe.

Methods: Studies were searched via Pubmed until end of April 2018 regarding the development, validation and use of PROMs in colorectal cancer , focusing on the whole care pathway, i.e., screening, diagnosis, treatment, rehabilitation, follow-up, and palliative care. Only studies conducted in Europe, with at least an abstract in English were included.

Results: In total, 49 studies and 7 systematic reviews were analysed. Thirty-six studies evaluated PROMs in clinical trial settings, while 20 focused on screening and patient management. Most of the studies were conducted in the Netherlands (n = 13) and United Kingdom (n = 19). Concerning care processes, most studies focused on treatment – systemic therapy, surgery and radiotherapy - in both trials and patient management. There is a great variation in the PROMs instruments used, as well as in the domains included in them (physical function, symptoms, psychological distress, general QoL, financial aspects, patient satisfaction/experience and decision sharing). The most used standardised instrument was EORTC QoL C30, sometimes in combination with other colorectal cancer specific questionnaires. In almost all studies included, PROMs were assessed at pre-defined key moments: at least before the treatment, during the intervention and at three time points after the intervention (up to 12 months).

Conclusions: In Europe, the use and content of PROMs in colorectal cancer varies, but is still limited. Implementation of a core standardised set of PROMs would allow comparability of patient-perceived quality of care across Europe. Despite some current initiatives (e.g. ICHOM) more work is still needed. Incorporation of a requirement for the use of PROMs in quality assurance measures (e.g. European Initiative on Colorecatal Cancer) may increase patient centredness of the care standards and improve patient experience.

Legal entity responsible for the study: Luciana Neamtiu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1585P Completeness of staging investigation for colorectal cancer: Exploring the role of increasing age and comorbidity using mediation analysis

S. Benitez Majano[1], S. Vansteelandt[2], C. Di Girolamo[1], M. Morris[1], S. Walters[1], B. Rachet[1]

[1]Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK, [2]Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium

Background: Older cancer patients often have fewer staging interventions and inferior treatment than younger patients. Suboptimal cancer management in older patients is frequently attributed to comorbidity, which may contraindicate procedures. We aim to examine how much of the age disparities in completeness of staging investigations for colorectal cancer (CRC) are explained by patients' health status and their diagnostic route.

Methods: Population-based cancer registries provided information on CRC patients diagnosed in England during 2010-2012. Staging investigations and comorbidities in the six years before the cancer diagnosis was derived from the National Bowel Cancer Audit and Hospital Episodes Statistics datasets. A mediation analysis quantified the proportion of the age effect on staging investigations mediated by health status, and by the diagnosis route. Sensitivity analyses for unmeasured confounding tested the robustness of the findings.

Results: Around half of patients had complete staging investigations. There was a U-shape association with more complete investigations among those aged 60-69. The age-investigation association was barely mediated by health status, but was partly mediated by being diagnosed through an emergency route. Overall, an important proportion of the age differential was not mediated by these factors, especially in older patients. These findings were robust to strong assumptions of unmeasured confounding of the relationship between the diagnosis route and having complete staging investigations.

Conclusions: CRC patients' health status and diagnostic route did not fully explain the age differential in the quality of staging investigations, contradicting prevailing beliefs. Findings suggest factors other than patients' health status may play an important role in the age differential. Although some patients may not benefit from aggressive treatment, having a complete investigation is essential to plan optimal management, regardless of age.

Legal entity responsible for the study: London School of Hygiene and Tropical Medicine.

Funding: Cancer Research UK.

Disclosure: All authors have declared no conflicts of interest.

1586P The quality oncology practice initiative program: Experience in Spain

R. Lopez Lopez[1], A. Anton Torres[2], E. Aranda Aguilar[3], A. Carrato Mena[4], M. Constenla Figueiras[5], J.J. Cruz Hernandez[6], E. Diaz Rubio[7], M. Feyjoo[8], J. Garcia Foncillas[9], P.N. Gascon[10], V. Guillem Porta[11], I.S. Lugo Cuan[12], A. Rogado[13], C. Camps[14]

[1]Medical Oncology, Complejo Hospitalario Universitario de Santiago de Compostela SERGAS, Santiago de Compostela, Spain, [2]Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, Spain, [3]Medical Oncology, Hospital Universitario Reina Sofía, Cordoba, Spain, [4]Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, [5]Medical Oncology, Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain, [6]Medical Oncology, Hospital Clínico Universitario de Salamanca, Salamanca, Spain, [7]Real Academia de Medicina, IdISCC, CIBERONC, Madrid, Spain, [8]Medical Oncology, Hospital Universitario La Moraleja, Sanitas, Madrid, Spain, [9]Medical Oncology, Fundación Jiménez Díaz, Madrid, Spain, [10]Medical Oncology, Hospital Universitario Clinic de Barcelona, Barcelona, Spain, [11]Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [12]Quality Project Management, Fundación ECO, Madrid, Spain, [13]Fundación ECO, Madrid, Spain, [14]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain

Background: Patient care quality is a discipline that has acquired enormous relevance in today's healthcare. Quality Oncology Practice Initiative (QOPI) is a referral worldwide in terms of quality for oncology practices. ECO Foundation is a platform of experts representing the major Spanish hospitals involved in the treatment of cancer patients. ECO reached an agreement with QOPI to involve Spanish hospitals in the QOPI program.

Methods: Five rounds of data collection have taken place (Fall 2015 to Fall 2017). Practices had to register online and submit data into the QOPI platform. ECO Foundation offers all centres the necessary support. 16 Spanish hospitals have participated in the five rounds. 7 of them have repeated participation. Core and Lung Cancer modules were completed.

Results: During the five rounds, 1745 charts were submitted by the Spanish practices. In the majority of the rounds, the highest scores were: Pathology report confirming malignancy, Number of chemotherapy cycles documented, Patient consent for chemotherapy and 5 measures of the Lung Cancer module. The lowest scores were: Chemotherapy treatment summary provided to patient within 3 months of chemotherapy end, Chemotherapy treatment summary provided or communicated to practitioner(s) within 3 months of chemotherapy end, Smoking/tobacco use cessation counselling recommended to smokers/tobacco users in past year and Tobacco cessation counselling administered or patient referred in past year. The percentage of participating practices that presented results higher than 70% was successively 64%, 50%, 75% and 100% in the last two rounds. For the 7 hospitals that repeated participation, 3 reported an improvement of their global scores. Regarding QOPI Certification, three Spanish hospitals received this accreditation in September 2017.

Conclusions: These preliminary results are a good starting point for the continued implementation of the QOPI program in Spain, thus providing a well-structured approach to analyse cancer care. ECO Foundation will continue pursuing excellence and quality with further activities like the QOPI Certification program and Quality Training Program, these being performed for the first time in Spain in 2017 and 2018 respectively.

Legal entity responsible for the study: Fundación ECO.

Funding: Mundipharma, Bristol-Myers Squibb, Novartis.

Disclosure: All authors have declared no conflicts of interest.

1587P Can measuring quality lead to improvement? Evidence from international participants of ASCO's quality oncology practice initiative (QOPI®) during 2015-2017

M. Jahanzeb[1], T. Gilmore[2], A. Roach[2], S.S. Grubbs[2], D. Blayney[3], J. Hamm[4], A. Kamal[5], R.J. Kelly[6], E. Martin[7], J.A. Sanchez[8], R. Siegel[9], S.T.S. Crist[2], J. Rosenthal[2], C. Hendricks[10]

[1]Hem/Onc, University of Miami, Sylvester Comprehensive Cancer Center, Deerfield Beach, FL, USA, [2]Clinical Affairs, American Society of Clinical Oncology, Alexandria, VA, USA, [3]Medical Oncology, Stanford Comprehensive Cancer Institute, Stanford, CA, USA, [4]Oncology, Norton Health Care Medical Oncology & Hematology, Louisville, KY, USA, [5]Oncology, Duke University School of Medicine, Durham, NC, USA, [6]Medical Oncology/UAD Program, School of Medicine, Johns Hopkins University, Baltimore, MD, USA, [7]Oncology, Medical Oncology Hematology Consultants, Newark, DE, USA, [8]Oncology, Hospital Escuela, University of Honduras, Tegucigalpa, Honduras, [9]Oncology, St. Francis Hospital, Greenville, SC, USA, [10]Oncology, Associates in Oncology Hematology, Bethesda, MD, USA

Background: Management thinker Peter Drucker had famously said "If you can't measure it, you can't improve it." Similar sentiment among practicing oncologists led to the establishment of QOPI by ASCO in 2006. The availability of guidelines to construct measures should result in measurable and sustained improvement in cancer care. QOPI was launched internationally in 2015. Now several countries are participating and 3 (Brazil, Greece and Spain) have QOPI-Certified practices. For the current analysis, we initiated the proof of concept and hypothesized that measuring quality would not only confirm preconceived benchmarks, but lead to improvement.

Methods: Data for analysis was selected from countries' practices that repeat self-examination. We determined the 5 lowest performing measures excluding the two measures that were deemed not applicable in the Fall (F) and Spring (S) rounds of the years 2015-17. Measure 6 - Pain addressed appropriately (defect-free measures 3, 4a, and 5), Measure 9 - Documented plan for Chemotherapy, including doses, route, and time intervals, Measure 24 - Patient emotional well-being assessed by the second office visit, Measure 33 - Infertility risks discussed prior to chemotherapy with patients of reproductive age and Measure 81-Adjuvant cisplatin-based chemotherapy received within 60 days after curative resection by patients with AJCC Stage II or IIIA NSCLC.

Results:

Table: 1587P

Round	Measure 6	Measure 9	Measure 24	Measure 33	Measure 81
Aggregate Mean %					
F15	75.2	59.5	49.2	10.0	N/A
S16	58.2	67.1	27.3	16.6	66.6
F16	70.3	69.4	40.4	44.1	69.3
S17	74.3	80.3	43.4	27.9	50.0
F17	83.0	82.8	53.8	38.7	80.9

This analysis includes 331 physicians and 22 practices from 5 countries (Brazil, Greece, Romania, Saudi Arabia, and Spain) who participated in QOPI rounds between 2015 and 2017. While the scores fluctuated between rounds, first to last observation invariably showed improvement in mean scores.

Conclusions: Measuring quality led to improvement in the lowest performing quality measures in these participating practices. This bodes well for our patients.

Legal entity responsible for the study: American Society of Clinical Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1588P Treatment algorithm for multiple myeloma: Real-world insights across five European countries

A. Rocci[1], P. Bulger[1], A. Martinez de Pinillos[2], P. Nasuti[2], C. Anger[2], F. Manuguid[2]

[1]Haematology, Manchester University NHS Foundation Trust, Manchester Royal Infirmary, Manchester, UK, [2]Real World & Analytics Solutions, IQVIA, London, UK

Background: Therapy of multiple myeloma (MM) is based on proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs) used alone or in combination. Bortezomib, Thalidomide and Lenalidomide are approved in Europe but national differences in terms of reimbursement policies may determine their diverse use in MM treatment algorithm.

Methods: Anonymized MM patient level data collected through a large cross-sectional survey between April to December 2017 in EU5 (France, Germany, Italy, Spain & UK) was used.

Results: 2472 patients (pts) were included in this study. In pts ≤65 years of age, PIs were largely used in first line across all countries (94% pts) followed by IMiDs (77% pts) with the exclusion of Germany (15% pts) where IMiDs were largely replaced by alkylating agents (78%). In second line, IMiDs were generally the drug of choice across most countries (90% pts) with the exclusion of the UK (36% pts). Opposite picture was observed for PIs: 73% of UK pts received these, whilst only 24% pts in Spain. In pts >65 years in first line, PIs were mostly used (70% pts) whilst IMiDs were only used in 35% pts. The use of alkylating agents varied from 32% (Germany) to 63% pts (France). In second line PIs ranged from 12% in France to 64% in the UK where IMiDs were less used (45%) compared to other countries. Irrespective of age, third line treatment was largely based on IMiDs. In Spain and Germany 1/3 of pts had access to monoclonal antibodies. Interestingly, bone protection treatment (99% bisphosphonate) was administered to 66% of pts in the UK, 52% in Germany and 42% in Spain, but only 24% in Italy and 22% in France.

Conclusions: IMiDs are the most used class of drug to treat MM as single agent or in combination irrespectively from line of treatment even if in Germany their use is less common as first line. PIs are used particularly in first line with the exception of the UK where they are common part of second line treatment. Further analyses to determine the impact on progression-free survival of the different treatment algorithms by country are needed.

Legal entity responsible for the study: IQVIA.

Funding: Has not received any funding.

Disclosure: A. Rocci: Honoraria: Takeda, Sanofi, Celgene, Novartis, Amgen, Janssen; Advisory boards: Novartis, Janssen, Amgen. All other authors have declared no conflicts of interest.

1589P Are treatment recommendations provided by cognitive computing supported by real world data (Watson for Oncology with Cota RWE) concordant with expert opinions?

D.M. Atieh Graham[1], D.M. McNamara[1], S.E. Waintraub[1], S.L. Goldberg[2], A.D. Norden[2], J. Hervey[2], A.L. Pecora[2], C. Landstrom[2], J.L. Snowdon[3], P.M. Francis[3], N. Jungbluth[3], C.K. Wang[3], L. Latts[3]

[1]Breast Oncology, John Theurer Cancer Center, Hackensack, NJ, USA, [2]Cota, Inc, New York, NY, USA, [3]Watson Health, IBM, Cambridge, MA, USA

Background: Treatment selection requires review of patient (pt) and clinical features, medical literature, national guidelines, physician experience, and cost-value issues. The IBM Watson for Oncology with Cota RWE (WfO/Cota) point-of-care decision support tool ingests pt attributes from electronic health records and displays treatment recommendations (TRx) based on Memorial Sloan Kettering Cancer Center training and medical literature. The system has been recently supplemented with real world data curated by Cota listing historical treatments and survival outcomes drawn from the treating physician's institution and a national database. WfO/Cota is undergoing testing at John Theurer Cancer Center (JTCC, Hackensack, NJ, USA). Concordance of WfO/Cota with expert opinions is required to confirm that cognitive computing TRx match best practices.

Methods: 88 early stage post-menopausal breast cancer (BC) cases from the JTCC BC clinic were presented to 3 JTCC BC experts (without using WfO/Cota). The cases were compared against pts with similar demographic and disease characteristics from the Cota database (matched using Cota Nodal Address [CNA] algorithms).

Results: BC experts reviewed 223 cases (not all cases scored by each). WfO/Cota "recommended" option was concordant with selection by BC experts in 175 (78.5%) and "for consideration" option was selected in 21 (9.4%); experts agreed with WfO/Cota in 87.9%. 7 of 88 cases (8%) generated 59% of non-concordant responses with >=2 doctors disagreeing with WfO. The BC expert who worked at MSKCC deviated the least from MSKCC trained WfO. In the Cota database 69.3% of matched historical controls were treated with "recommended," 11.4% "for consideration", 19.3% "not recommended."

Conclusions: WfO/Cota recommendations are largely concordant with disease expert best oncology practices. The observation that nearly a fifth of pts with similar disease (CNA) characteristics received non-recommended options in a real world database highlights a need. WfO/Cota is an innovative decision support tool that derives new insights based on existing real world evidence to reduce variations in practice.

Legal entity responsible for the study: Cota.

Funding: IBM, Cota.

Disclosure: S.L. Goldberg: Cota: Employment, stock ownership. A.D. Norden, J. Hervey, C. Landstrom: Cota: Employment. A.L. Pecora: Cota: Stock ownership. J.L. Snowdon, P.M. Francis, N. Jungbluth, C.K. Wang, L. Latts: IBM: Employment. All other authors have declared no conflicts of interest.

1590P Body shape trajectories and risk of breast cancer: Results from the SUN study project

R. Sanchez Bayona[1], C. Sayon[2], I. Gardeazabal[1], M.A. Martínez-González[2], M. Santisteban Eslava[1], E. Toledo-Atucha[2]

[1]Oncology, Clinica Universidad de Navarra, Pamplona, Spain, [2]Public Health and Preventive Medicine, Universidad de Navarra, Pamplona, Spain

Background: Obesity is a well-known risk factor for some types of cancer including post-menopausal breast cancer. Nevertheless, the influence of adiposity over life course on cancer risk remains poorly understood. The objective of this study was to assess body shape trajectories in early and middle life in relation to subsequent risk of breast cancer in a Mediterranean cohort.

Methods: We used a group-based modelling approach to assess body shape trajectories from age 5 to 40 years, among 10679 women from the SUN cohort study from 1999 to 2014. Four distinct body shape trajectories were identified (lean-heavy increase, medium-stable, medium-heavy increase and heavy-stable). Cox regression models were used to estimate the hazard ratio (HR) for breast cancer according to the assigned body shape trajectory.

Results: Among 106,537 women-years of follow-up a total of 133 probable incident cases of breast cancer were identified (70 of these cases were confirmed). When compared to those in the medium-stable category, women who were lean and had a marked increase (lean-heavy increase category) showed a subsequent higher risk of probable breast cancer (HR = 1.55, 95%CI 1.05-2.29). When stratifying according to menopausal status, there was a higher risk of probable postmenopausal breast cancer for women in the lean-heavy increase category (HR = 2.0, 95%CI 1.06- 3.80) compared to the medium-stable group. The statistical power was reduced and significance was lost when we considered only confirmed cases.

Hazard ratio (HR) and 95% confidence interval (95% CI) of breast cancer according to body shape trajectory in the SUN Project, 1999-2016. Adjusted for potential confounders and age as underlying time variable.

Conclusions: This is the first Mediterranean cohort to suggest that a marked increase in body shape from age 5 to 40 years is associated with a higher risk of breast cancer, especially for postmenopausal women, indicating a role for lifetime adiposity in breast carcinogenesis.

Legal entity responsible for the study: The Seguimiento Universidad de Navarra (SUN) Project.

Funding: Spanish Government-Instituto de Salud Carlos III, the European Regional Development Fund, the Navarra Regional Government and the University of Navarra.

Disclosure: All authors have declared no conflicts of interest.

1591P Total polyphenol intake and breast cancer risk in the SUN project

I. Gardeazabal[1], A. Romanos-Nanclares[2], R. Sanchez Bayona[1], J.J. Graforio[3], M.A. Martínez-González[4], E. Toledo-Atucha[4]

[1]Medical Oncology, Clinica Universitaria de Navarra, Pamplona, Spain, [2]Preventive Medicine and Public Health, Universidad de Navarra, Pamplona, Spain, [3]Ciencias de la Salud, Universidad de Jaén, Jaén, Spain, [4]Public Health and Preventive Medicine, Universidad de Navarra, Pamplona, Spain

Background: Breast cancer (BC) is the most frequently diagnosed cancer in the world. Preventive strategies represent a public health priority. Dietary interventions for preventing BC have been evaluated, mainly using observational designs, with inconsistent results. In this context, polyphenols have shown in vitro and in vivo beneficial properties and anticancer mechanisms. Polyphenols are a wide family of phytochemicals present in diverse foods. Their role in chronic disease prevention including cardiovascular diseases and cancer has been repeatedly suggested. For this reason, we evaluated total polyphenol intake in association with the risk of BC in the SUN Project - a prospective cohort study in a Mediterranean population.

Methods: We included 10,709 middle-aged, Spanish female university graduates. Polyphenol intake was assessed using a validated semi-quantitative 136-item food frequency questionnaire and matching food consumption data with the Phenol-Explorer database. Diagnosis of BC was self-reported or by the next of kin or identified from death certificates. Self-reports of a medically-diagnosed BC were confirmed using medical records. Cox regression models were fitted to estimate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association between terciles of adherence to the total polyphenol intake and BC risk.

Results: After 10.3 years of median follow-up, 83 confirmed and 165 probable incident BC cases were identified. We observed a statistically significant inverse association between total polyphenol intake and BC risk for postmenopausal women when probable BC cases were used as outcome: HR for highest vs lowest tertile of total polyphenol intake 0.47 (95% CI 0.22-0.97; P for trend=0.041). No further significant associations were observed between total polyphenol intake and incident BC when total BC incidence or risk of premenopausal BC were considered.

Conclusions: Despite the small number of incident BC cases observed in this Mediterranean cohort, we observed that the higher total polyphenol intake, the lower risk of BC among postmenopausal women.

Legal entity responsible for the study: Universidad de Navarra.

Funding: The SUN Project has received funding from the Spanish Government-Instituto de Salud Carlos III, and the European Regional Development Fund (FEDER) (RD 06/0045, CIBER-OBN, Grants PI10/02658, PI10/02293, PI13/00615, PI14/01668, PI14/01798, PI14/01764, and G03/140), the Navarra Regional Government (45/2011, 122/2014), and the University of Navarra.

Disclosure: All authors have declared no conflicts of interest.

1592P No effect of length time bias on the genomic risk in ER+ HER2-stage I-IIA breast cancer (BC) patients according to diagnosis in a screening programme: An exploratory analysis

I. Gonzalez Barrallo[1], J.A. Perez Fidalgo[1], J. Ramirez[2], O. Burgues[3], J.V. Sorlí[4], O. Portoles[2], C. Hernando[1], D. Salas[5], A. Lluch[6]

[1]Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain, [2]Department of Public Health, University of Valencia, Valencia, Spain, [3]Pathological Anatomy, Hospital Clínico Universitario de Valencia, Valencia, Spain, [4]Preventive Medicine and CIBER Fisiopatología de la Obesidad y Nutrición, Universitat de València, Valencia, Spain, [5]Area of Cancer and Public Health, Research Center in Public Health - Centro Superior de Investigación en Salud Publica (CSISP), Valencia, Spain, [6]Medical Oncology, Hospital Clinico Universitario de Valencia. INCLIVA.CIBERONC Spain, Valencia, Spain

Background: Length time bias is a form of selection bias that lead to the perception that screened patients have better outcome as more indolent tumors are diagnosed during screening. However, tumors diagnosed in the interval between mammographys or detected by symptom onset are likely more aggressive. The aim was to analyze using a genomic platform if unscreened tumors were more agresive than screened ones in a homogeneous cohort not affected by stage or subtype.

Methods: Since 2014 BC pts with T1-T2 N0-N1mic tumors and/or high ki67 are selected for genomic platform-based risk assessment in order to guide adjuvant treatment. We performed an exploratory retrospective cohort study in a single institution between 2014 and 2018 in operated stage I-IIA BC pts with ER and/or PR + who

Table: 1590P

Probable cases	Overall breast cancer		Premenopausal breast cancer		Postmenopausal breast cancer	
	Cases / woman-years	HR (95% CI)	Cases / woman-years	HR (95% CI)	Cases / woman-years	HR (95% CI)
Lean-heavy increase	43 / 18360	1.55 (1.05-2.29)	13/12456	1.34 (0.69-2.61)	21/5474	2.0 (1.06-3.80)
Medium-stable	65 / 57061	1 (ref.)	28/46602	1 (ref.)	19/9343	1 (ref.)
Medium-heavy increase	22 / 23738	0.81 (0.50-1.32)	12/20048	0.93 (0.46-1.87)	7/3281	1.03 (0.43-2.47)
Heavy -stable	3 / 7378	0.55 (0.17-1.76)				
Confirmed cases						
Lean-heavy increase	20/ 18453	1.22 (0.70-2.13)	8/12456	1.14 (0.49-2.67)	9/5474	1.32 (0.54-3.26)
Medium-stable	37/ 57210	1 (ref.)	18/46602	1 (ref.)	11/9343	1 (ref.)
Medium-heavy increase	13/ 23811	0.86 (0.45-1.62)	8/20048	0.88 (0.37- 2.10)	4/3281	0.24 (0.39-4.0)

underwent an Oncotype risk assessment before deciding adjuvant therapy. Results of the Recurrence score (RS) were compared according to the type of diagnosis of breast cancer as 1) Screened: Diagnosis during screening (when diagnosed occurred during a foreseen mammography visit) and 2) Unscreened: Diagnosis occurred outside screening (in an interval between mammographys or by symptom onset).

Results: 105 pts were included. Median age was 56.4 y (45.2-74.6 y). All patients were ER + (range 50-100%), HER2- and grade was I (12.4%) II (82,9%) or III (4.8%). Median tumor size was 13.7 mm (4-45). 89.5% were N0 and 10.5% N1mic. 68 pts (64.8%) were in the screened and 37 (35.3%) in the unscreened group. Foreseen adjuvant treatment was changed according to Oncotype results in 24.8% patients. Median RS was 18.2 (range 3-46). According to RS risk categories 81% were classified as low , 9.5% as intermediate and 9.5% as high risk. Median RS was 17.6 in the screened vs 19.2 in the unscreened group, these differences were not significant ($p = 0.34$). Differences by RS categories were also not significant (Chi square $p = 0.67$ for two categories low vs intermediate/high risk with a RR 0.92 (0.62-1.38) and $p = 0.2$ for three categories).

Conclusions: No risk differences according to RS was seen between screened vs unscreened patients. These suggest that length time bias in a cohort not affected by stage or subtype might have minimum impact on screening outcomes.

Legal entity responsible for the study: Hospital Clinico Universitario de Valencia. INCLIVA.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1593P Breast cancer screening: Impact on care pathways

D. Lefeuvre[1], N. Catajar[2], C. Le Bihan Benjamin[1], F. De Bels[2], J. Viguier[3], P-J. Bousquet[1]

[1]Survey, Monitoring and Assessment Department, INCa - Institut National du Cancer, Boulogne-Billancourt, France, [2]Screening Department, INCa - Institut National du Cancer, Boulogne-Billancourt, France, [3]Public Health and Healthcare Division, INCa - Institut National du Cancer, Boulogne-Billancourt, France

Background: Breast cancer screening represents a major public health challenge. In France, no evidence has been furnished that women with breast cancer diagnosed following a mammogram carried out within the framework of the screening programme (SP) underwent less aggressive treatment than women diagnosed by other means. The aggressiveness of treatment represents a supplementary indicator for studying the impact of SP.

Methods: To study this indicator, data from the "Cancer Cohort" were used. This consists of a unique cohort including all subjects suffering from cancer since 2010 in France, resulting in care at a hospital or medical practice. All women aged from 50 to 74 years at average risk and treated in 2014 for incident breast cancer were included. Women having undergone a mammogram within the framework of the SP (SP group) were compared to women having undergone a bilateral mammogram outside the SP, because of an opportunistic screening or a clinical symptom (NSP group).

Results: In 2014, 23,788 women aged from 50 to 74 years at average risk treated for incident breast cancer were identified: 13,530 (57%) in the SP group, and 10,258 (43%) in the NSP group. Women in the SP group had a higher rate of in situ or localised invasive breast cancer than in the NSP group. They had a higher rate of breast-conserving surgery (82% vs 70%), and a lower rate of chemotherapy (34% vs 53%). These findings were observed whatever the stage as defined in the study was. Women in the SP group had a higher rate of pathways involving breast-conserving surgery followed by radiotherapy. Finally, among women with metastatic cancer, those in the SP group had a lower proportion of liver, lung, brain and bone metastases, and a higher proportion of lymph node metastases (other than axillary), regardless of the time to onset of metastases.

Conclusions: The women whom cancer was diagnosed following a mammogram carried out within the framework of the SP had less advanced cancer and less aggressive treatments. This study on observational data contributes to illustrate the benefit of the SP in France using another approach than mortality or overall survival.

Legal entity responsible for the study: French National Cancer Institute.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1595P 10-year results of the breast cancer screening program in Khanty-Mansiysk state region Ugra

N.A. Zakharova[1], A.R. Brentnall[2], J. Belaya[1], E. Bilan[3]

[1]Oncology, Radiology and Radiotherapy, Khanty-Mansiysk State Medical Academy, Khanty-Mansiysk, Russian Federation, [2]Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK, [3]Oncology Centre, Khanty-Mansiysk State Clinical Hospital, Khanty-Mansiysk, Russian Federation

Background: Breast cancer is the leading cancer in the female population and one of the most common causes of cancer deaths in women. Improved treatment and the implementation of mammography screening have contributed to substantial reductions in breast cancer mortality over recent decades. The main goal of this study was to evaluate 10-year results of the Breast Cancer Screening Program in Ugra since 2007.

Methods: Biannual mammography screening covers women 40 years old using single reading of two-view mammography. Screening data were obtained from the reports for the State Healthcare Department. Data on female population, breast cancer cases (invasive and in situ) and deaths were provided by the State Cancer Registry and State Information Centre. We studied expected absolute incidence and mortality from breast cancer were calculated over the years 2002-16. Expected absolute number of tumours T1N0M0 and with size over 20 mm detected among women 40+ were calculated over the period in question. Expected number assumed constant rate in pre/post screening epochs and its changes were only due to population size. Rate estimated using pre-screening epoch and were age-adjusted.

Results: During 2007-16 within the Program, 451139 women were screened. The screening coverage rate in the 2015-16 round was 41% (144777 women). 13464 (9.3%) of those screened were referred for further assessment. The screen detection rate was 3.5 per 1000 screened (1582 breast cancer cases). The test sensitivity for the first round was estimated as 80%. The observed T1N0M0 in 2016 was 126 compared with 73 expected (42% increase). The observed number of breast cancers more than 2cm was 231 compared with 292 expected (26% reduction). Breast cancer mortality in 2016 was 119 compared with 187 expected (57.5% reduction) using absolute mortality results.

Conclusions: Trends suggest that mammographic screening in Ugra has contributed to a significant improvement in the early disease diagnosis, and breast cancer mortality has fallen. Improved screening coverage s needed.

Legal entity responsible for the study: Khanty-Mansiysk State Medical Academy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1596P Malignant lymphoma detected by screening program with esophagogastroduodenoscopy of one private screening center in Japan

T. Nakamura[1], M. Ikeda[1], S. Shibata[1], Y. Kon[1], K. Konuma[1], T. Sanada[1], H. Gonda[1], Y. Suto[1], K. Kobayashi[1], H. Tamura[1], M. Kobayashi[1], A. Hasegawa[1], Y. Amagasa[1], A. Suzuki[1], M. Fukuda[1], C. Aoyagi[1], N. Matsuura[1], Y. Kawashima[2], M. Shimura[2], N. Takita[2]

[1]Health Evaluation and Promotion, Ota Memorial Hospital, Ota, Japan, [2]Endoscopy, Ota Memorial Hospital, Ota, Japan

Background: Malignant lymphoma is rarely encountered in health screening program. It is often difficult to recognize it at early stage although the earlier detection would bring the better prognosis like other malignancies.

Methods: Data of screening program with esophagogastroduodenoscopy (EGD) at Ota Memorial Hospital (OMH) in Japan from June 2012 through December 2017 were reviewed and cases of malignant lymphoma detected were analyzed to reveal characteristics.

Results: 26886 individuals participated in EGD screening program of OMH in that term. 91 cases of malignant neoplasm were detected and six of them (6.6%) were diagnoses as malignant lymphoma (detection rate 0.02%). They consisted of three gastric and three duodenal lymphomas. None of them had B symptom. Histopathological exam diagnosed all gastric cases as MALT lymphoma locating at middle part of stomach. Their endoscopic findings were as follows; one was scar-like whitish mucosa without stricture, another was whitish mucosa mixed with erythema, and the other was scar-like lesion surrounded nodular and granular mucosae. Although all gastric lymphoma had no eradication history of Helicobacter pylori (Hp) and serum anti-Hp IgG antibody were less than 3 U/ml, one of them had advanced chronic atrophic gastritis. All gastric MALT lymphoma took irradiation therapy. All duodenal lymphomas were diagnosed as follicular lymphoma. One of them located around duodenal papilla was recurrent lesion that had originated in mesenteric lymph nodes and been treated with chemotherapy six years before. Its endoscopic findings were polypoid and granular lesions. Other two duodenal lymphoma were detected at inferior duodenal angle as nodular and granular appearance. The recurrent follicular lymphoma had the second line chemotherapy. Other two cases were treated by irradiation and molecular targeting therapy with rituximab respectively.

Conclusions: Nearly 7% of malignancy detected by EGD screening program of OMH was malignant lymphoma consisting of gastric MALT lymphoma and duodenal follicular lymphoma although it was rarely encountered. Since it shows non-specific endoscopic findings especially at its early stage, mandate biopsy to any suspicious lesion is strongly recommended.

Legal entity responsible for the study: Ota Memorial Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1597P Worldwide trends in survival from childhood glioma 2000-2014 (CONCORD-3): Preliminary findings and plans for further research

F. Girardi, V. Di Carlo, A. Bonaventure, C. Allemani, M.P. Coleman, CONCORD Working Group

Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

Background: The CONCORD programme was the first to establish global surveillance of cancer survival. The third cycle (CONCORD-3) collected data from 322 cancer registries in 71 countries. Survival from all brain tumours combined varied widely between countries, particularly in children. We propose to examine survival trends by relevant explanatory variables to help explain these disparities.

Methods: We present the numbers of children diagnosed with a glioma (ICD-O-3 morphology codes 938-948) and by each of the main glioma subtypes. Five-year net survival will be estimated by morphology, WHO grade, topography, sex, country and calendar period of diagnosis. Net survival is the probability that patients survive their cancer until a given time since diagnosis (e.g. 5 years), after controlling for competing risks of death (background mortality).

Results: Data were obtained for 56,507 children (aged 0-14 years) diagnosed with a glioma: 19,080 in Europe, 26,751 in North America, 6,111 in Asia, 3,103 in Central and South America, 1,379 in Oceania and 83 in Africa. In Europe, 5% of gliomas were ependymomas, 26% pilocytic astrocytomas, 8% astrocytomas, not otherwise specified (NOS), 5% glioblastomas NOS and 15% medulloblastomas NOS. The distribution was similar in North America. In Africa, Asia, and Central and South America, and in Oceania, pilocytic astrocytoma was less frequent (10%-13%) than in Europe or North America. In Africa, Asia, and Central and South America, astrocytoma NOS was more common (11-32%). The frequency of medulloblastoma was higher in Central and South America (28%) and Asia (23%). The distribution of the morphologic subtypes of childhood glioma varies widely around the world. Survival differs between morphologic groups. We will assess the extent to which the distribution of morphologic subtypes contributes to international variation in childhood glioma survival worldwide.

Conclusions: When comprehensive survival analyses are available for each type of glioma, this project will become the benchmark for future international comparisons of brain tumour survival in children, to inform cancer control plans.

Legal entity responsible for the study: London School of Hygiene and Tropical Medicine.

Funding: Children With Cancer UK.

Disclosure: All authors have declared no conflicts of interest.

1598P Referral patterns and predictors of survival for stage IV pancreatic ductal adenocarcinoma

A.E. Suo, P.A. Tang, D. Tilley, W.Y. Cheung, R. Lee-Ying

Medical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada

Background: We previously found that many patients with a diagnosis of advanced pancreatic ductal adenocarcinoma (PDAC) are not referred for palliative chemotherapy despite recent advances. We sought to investigate referral patterns, chemotherapy eligibility and predictors of overall survival (OS) in a large cohort of advanced PDAC in Alberta, Canada.

Methods: All patients with Stage IV PDAC from 2009 - 2015 in Alberta were identified using the Alberta Cancer Registry. Patients missing laboratory eligibility criteria for chemotherapy were excluded. Demographics, clinical characteristics, cancer centre referral, chemotherapy received, and OS were collected. Primary analysis explored referral patterns and treatment eligibility. Secondary outcomes identified predictors of survival using Kaplan-Meier with log-rank test and multivariable Cox regression analysis.

Results: 1412 patients were identified. ECOG (>1 = 83%; >2 = 72%), age (34%) and bilirubin (>ULN = 30%; >1.5xULN = 22%) were the most common reasons for chemotherapy ineligibility. A proportion of patients who were eligible by trial criteria for FOLFIRINOX (21%) and nab-paclitaxel/gemcitabine (20%) were not referred, yet some patients who were ineligible for any chemotherapy were still referred. Distance to travel to a cancer centre did not have a significant difference on referral patterns. Primary tumor location, any chemotherapy received, referral, ECOG, bilirubin, and ANC were significant predictors of survival in the Cox regression analysis.

Conclusions: More patients who are potentially eligible to receive palliative chemotherapy should be referred to a cancer centre. Patients with obstructive jaundice should have expedited biliary drainage procedures to facilitate systemic treatment eligibility.

Table: 1598P Cox regression analysis of predictors for overall survival

Characteristic		HR	95% CI	p
Tumor	Head/neck	1		.002
	Body	1.37	1.07 - 1.76	.012
	Tail	1.51	1.19 - 1.90	.001
	Overlap or NOS	1.32	1.07 - 1.65	.012
Any chemo		.45	.37 - .55	< .001
Any referral		.54	.45 - .67	< .001
ECOG	0	1		< .001
	1	1.03	.71 - 1.48	.886
	2	1.76	1.20 - 2.58	.004
	3	2.80	1.88 - 4.18	< .001
	4	5.73	3.44 - 9.54	< .001
ANC > 8		2.37	1.97 - 2.84	< .001
Bilirubin	< ULN	1		< .008
	1 - 1.5x ULN	1.35	.99 - 1.83	.057
	> 1.5x ULN	1.41	1.10 - 1.82	.006

Legal entity responsible for the study: Department of Oncology, Tom Baker Cancer Centre, University of Calgary.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1599P Gender difference in cancer survivors' perceived information 5-years after diagnosis: Data from the French national study - VICAN 5

G. Gravis[1], R. Touzani[2], A-D. Bouhnik[3], P. Marino[4], G. Pignot[5], M.K. Bendiane[6]

[1]Medical Oncology, Institut Paoli Calmettes, Centre de Recherche en Cancérologie de Marseille, Aix Marseille Université, Marseille, France, [2]Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, Aix Marseille University, Marseille, France, [3]Aix-Marseille University - Faculté de Médecine Timone, Marseille, France, [4]Institute Paoli-Calmettes, Marseille, France, [5]Chirurgie Oncologique 2, Institute Paoli Calmettes, Marseille, France, [6]Aix Marseille Univ, INSERM, IRD, Economics and Social Sciences Applied to Health & Analysis of Medical Information (SESSTIM), Marseille, France

Background: Information request for cancer patients is high with frequent reported unmet needs. Well informed patients are: more involved in shared decision making, report higher levels of satisfaction with care and better quality of life. The aim of this study is to compare perceived information on cancer evolution between women and men in cancer survivors five years after diagnosis.

Methods: The VICAN survey is a French representative sample of 4174, 5-years cancer survivors. Self-reported data were collected by telephone interviews and self-administrated questionnaires. Only non-gendered cancers were selected (excluded: breast, prostate cancer...). Univariate and multivariate analyzes have been performed using STATA 12.

Results: 2243 out of 4174 patients were selected, 54.2% were male, median age was 58 years and men were significantly older (63 vs 55, $p < 0.001$). Women had a higher level of education ($p = 0{,}011$), reported more attention difficulties ($p = 0.026$) and memory problems ($p < 0{,}001$) while men reported more hearing loss ($p < 0.001$). No difference was found for depression (assessed by HADS scale) and the level of literacy. Women reported being less informed of minor symptoms (28.6% vs. 20.5%, $p < 0.001$) and less informed of severe symptoms of their cancer (18.2% vs. 12.0%, $p = 0.001$) The gender difference was statistically significant for the overall population but not within each localization of cancer, except for kidney cancer: men were feeling not well informed about minor symptoms (21.1% vs 29.1%, $p = 0.020$). Women used more frequently internet to search information (27.6% vs 19.5%, $p < 0.001$). Only 2.7% of patients used internet to look for information about patients' associations and women used it more frequently (3.9% vs. 1.7%, $p = 0.009$).

Conclusions: Cancer survivors have been found to benefit from health care information. In this large prospective analysis in non-gendered cancers, women reported lower levels of information than men and searched online information more frequently. Gender difference and preference for information is an important issue in order to give appropriate information to cancer patients.

Legal entity responsible for the study: SESSTIM (Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale).

Funding: INCA.

Disclosure: All authors have declared no conflicts of interest.

1600P Survival difference between microscopically confirmed and microscopically non-confirmed cancers

M.A. Gouda

Department of Clinical Oncology, Faculty of Medicine - Menoufia University, Shebin El Kom, Menoufia Governorate, Egypt

Background: Cancer is mainly diagnosed by histopathology, but some complex situations may provoke physicians' desire to avoid biopsy. This is particularly important when cancer diagnosis can be made based on other less accurate methods like radiological findings or elevated tumor markers e.g. suspicious ovarian mass with elevated CA125. However, data about these cases treated based on diagnosis "prediction" rather than accurate definition of histopathology are lacking. In this study, survival is compared between cases with microscopic confirmation of diagnosis and those diagnosed with other methods. This is presented for all types of cancer but with particular focus on four main tumors where other modalities for diagnosis may be appealing.

Methods: Data were obtained using SEER*Stat version 8.3.5 (SEER 18 Regs Nov 2017 Submission). Only cases diagnosed between 2001 and 2010 were included. Observed survival was calculated using SEER*Stat where other data analysis including Kaplan Meier analysis was made using SPSS.

Results: Microscopic confirmation (MC) was the mainstay for diagnosis in most of included cases (n = 3594344; 94.2%). In the remaining group (non-microscopically confirmed (NMC) diagnosis, n = 222907; 5.8%), radiography was used in 46% (n = 102401). Clinical diagnosis, positive laboratory test/marker, and direct visualization were used in 11.8%, 5.2%, and 2.7 respectively. There was a significant survival difference between MC and NMC that was consistent in prostate, ovarian, liver, and pancreatic cancer as well as in other types of malignancies ($p < 0.05$). The table shows the 5-years observed survival and 95% CI for different types of cancer in the two groups.

Table: 1600P

	5-years observed survival	
	MC	NMC
Prostate	85.3% (85.2-85.4)	26.6% (25.8-27.5)
Ovary	44.1% (43.6-44.6)	10.9% (9.8-12)
Liver	18.1% (17.7-18.5)	9.6% (9.2-10.1)
Pancreas	6.5% (6.3-6.7)	2.6% (2.3-2.9)
Others	67.4% (57.3-57.4)	14.7% (14.4-14.9)
All	60.5% (60.6-60.6)	13.7% (13.5-13.8)

Conclusions: Microscopic confirmation should be regarded as the only accurate method for diagnosis of cancer. Depending on other diagnosis methods may have a strong detrimental effect on survival. More studies needs to address possible explanations for these findings and potential implications on management.

Legal entity responsible for the study: Mohamed Alaa Gouda.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii576–viii595, 2018
doi:10.1093/annonc/mdy299

SARCOMA

1601O Natural history of sarcomas and impact of reference centers in the nationwide NETSARC study on 35,784 patients (pts) from 2010 to 2017

J-Y. Blay[1], M. Toulmonde[2], N. Penel[3], O. Mir[4], C.M. Chevreau[5], P. Anract[6], E. Bompas[7], M. Rios[8], N. Firmin[9], A. Italiano[10], S. Piperno-Neumann[11], J-E. Kurtz[12], F. Duffaud[13], P. Rosset[14], F. Bertucci[15], C. Perrin[16], C. Chemin[17], F. Ducimetiere[17], F. Gouin[18], A. Le Cesne[19]

[1]Medicine, Centre Léon Bérard, Lyon, France, [2]Medical Oncology, Institute Bergonié, Bordeaux, France, [3]General Oncology Department, Centre Oscar Lambret, Lille, France, [4]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [5]Institut Universitaire du Cancer -Toulouse- Oncopole, Toulouse, France, [6]Orthopedics, Hopital Cochin, Paris, France, [7]Medicine, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [8]Medecine, Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandoeuvre Les Nancy, France, [9]Medecine, Institut de Cancerologie de Montpellier, Montpellier, France, [10]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [11]Medecine, Institut Curie, Paris, France, [12]Gineco & CHRU de Strasbourg Hôpital Civil, Strasbourg, France, [13]Oncology, CHU La Timone Adultes, Marseille, France, [14]Orthopedy, CHU Tours, Tours, France, [15]Medecine, Institute Paoli Calmettes, Marseille, France, [16]Medecine, Centre Eugene - Marquis, Rennes, France, [17]EMS, Centre Léon Bérard, Lyon, France, [18]Orthopedy, CHU Nantes, Nantes, France, [19]Medicine, Gustave Roussy Institut de Cancérologie, Villejuif, France

1602O Outcome following unplanned excision in soft tissue sarcoma: Results of a multicentre study including 728 patients

M.A. Smolle[1], P-U. Tunn[2], E. Goldenitsch[3], F. Posch[4], J. Szkandera[4], M. Bergovec[1], B. Liegl-Atzwanger[5], A. Leithner[1]

[1]Department of Orthopaedics and Trauma, Medical University of Graz, Graz, Austria, [2]Sarcoma Centre, HELIOS Klinikum Berlin-Buch, Berlin, Germany, [3]Sarcoma Care, Orthopaedic Hospital Gersthof, Vienna, Austria, [4]Division of Clinical Oncology, Medical University of Graz, Graz, Austria, [5]Institute of Pathology, Medical University of Graz, Graz, Austria

1603O Initial results of phase I study of DCC-2618, a broad-spectrum KIT and PDGFRa inhibitor, in patients (pts) with gastrointestinal stromal tumor (GIST) by number of prior regimens

S. George[1], M. Heinrich[2], P. Chi[3], A. Razak[4], M. von Mehren[5], M. Gordon[6], K.N. Ganjoo[7], N. Somaiah[8], J.C. Trent[9], J. Rodon Ahnert[10], J. Wolf[11], R. Ruiz-Soto[12], O. Rosen[13], F. Janku[14]

[1]Medical Oncology, Dana Faber Cancer Institute, Boston, MA, USA, [2]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA, [3]Sarcoma Medical Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [4]Medical Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [5]Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [6]Medical Oncology, HonorHealth Virginia G Piper Cancer Care Network, Scottsdale, AZ, USA, [7]Oncology, Stanford Cancer Institute, Stanford, CA, USA, [8]Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [9]Medical Oncology, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA, [10]Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA, [11]Biostatistician, Wolf Consulting Biostatistician, Denver, CO, USA, [12]Clinical Research, Deciphera Pharmaceuticals, Waltham, MA, USA, [13]Clinical, Deciphera Pharmaceuticals, New York, MA, USA, [14]Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA

1604PD **Health-related quality of life in patients with advanced soft tissue sarcoma (ASTS): Results from the TSAR randomized phase III trial of the French Sarcoma Group**

A. Le Cesne[1], R. Kapso Kapnang[2], S. Foulon[2], J. Bonastre[2]

[1]*Department of Medicine, Gustave Roussy, Villejuif, France,* [2]*Biostatistics and Epidemiology, Gustave Roussy, Villejuif, France*

1605PD **Health-related quality of life (HR-QoL) in elderly soft tissue sarcoma (STS) patients from the randomized phase II EPAZ study comparing pazopanib (PAZ) and doxorubicin (DOX) in first line**

V. Grünwald[1], M. Schuler[2], P. Schöffski[3], H-G. Kopp[4], S. Bauer[5], B. Kasper[6], L.H. Lindner[7], J.M. Chemnitz[8], M. Crysandt[9], A. Stein[10], B. Steffen[11], S. Richter[12], M. Kneba[13], G. Egerer[14], S. Zimmermann[15], A. Karch[16], A. Kunitz[17]

[1]*Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany,* [2]*Medical Oncology, Helios Klinikum Emil von Behring, Berlin, Germany,* [3]*General Medical Oncology, University Hospitals Leuven, Leuven, Belgium,* [4]*Molecular Oncology and Pneumatological Oncology, Robert-Bosch-Krankenhaus, Stuttgart, Germany,* [5]*Medical Oncology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany,* [6]*Interdisciplinary Tumor Center Mannheim, Universitätsklinikum Mannheim, Mannheim, Germany,* [7]*Medical Clinic III, Ludwig Maximilians University - Grosshadern, Munich, Germany,* [8]*Hematology, Oncology and Palliative Medicine, Ev. Stift St. Martin, Koblenz, Germany,* [9]*Hematology and Oncology, University Hospital Aachen, Aachen, Germany,* [10]*UCCH, UKE Universitätsklinikum Hamburg-Eppendorf KMTZ, Hamburg, Germany,* [11]*Hematolgoy/ Oncology, University Hospital Frankfurt, Frankfurt, Germany,* [12]*Internal Medicine I, University Hospital Carl Gustav Carus, Dresden, Germany,* [13]*Hematology and Oncology, University Hospital Kiel, Kiel, Germany,* [14]*Hematology, Oncology, Rheumatology, University Hospital Heidelberg, Heidelberg, Germany,* [15]*HCTC, Hannover Clinical Trial Center, Hannover, Germany,* [16]*Institute for Biometry, Hannover Medical School, Hannover, Germany,* [17]*Oncolgoy, Vivantes Netzwerk für Gesundheit GmbH, Berlin, Germany*

1606PD Quality of life in patients with soft tissue sarcoma undergoing palliative treatment: A multicenter, cluster-randomized trial within the Germany Interdisciplinary Sarcoma Group (GISG-12)

L. Hentschel[1], S. Richter[2], H-G. Kopp[3], B. Kasper[4], A. Kunitz[5], V. Grünwald[6], T. Kessler[7], J-M. Chemnitz[8], U. Pelzer[9], U.S. Schuler[10], J. Freitag[2], A. Schilling[11], B. Hornemann[1], K. Arndt[12], G. Ehninger[1], M. Bornhäuser[1], M. Schuler[2]

[1]University Cancer Center, University Hospital Carl Gustav Carus, Dresden, Germany, [2]Internal Medicine I, University Hospital Carl Gustav Carus, Dresden, Germany, [3]Internal Medicine II, Universitätsklinikum Tübingen Medizinische Universitätsklinik, Tübingen, Germany, [4]Interdisciplinary Tumor Center, Universitätsklinikum Mannheim, Mannheim, Germany, [5]Internal Medicine, Vivantes Clinic Spandau, Berlin, Germany, [6]Clinic for Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Medical School Hannover, Hannover, Germany, [7]Hematology Oncology, University Hospital of Münster, Münster, Germany, [8]Internal Medicine, St. Martin Hospital, Koblenz, Germany, [9]Medizinische Klinik Hämatologie, Onkologie und Tumorimmunologie, Universitätsklinik Charité, Campus Virchow Klinikum, Berlin, Germany, [10]Palliative Care, Universitätsklinikum Dresden, Dresden, Germany, [11]Social Work, University Hospital Carl Gustav Carus, Dresden, Germany, [12]Das Lebenshaus e.V., Wölfersheim, Germany

1607PD Immune response, safety, and overall survival of NY-ESO-1+ soft tissue sarcoma patients treated with CMB305 therapy

S.P. Chawla[1], S. Pollack[2], M. Block[3], M. Druta[4], K. Do[5], J.C. Morris[6], J.W. Kim[7], C. Bohac[8], H. Lu[9], S. Gnjatic[10], R.L. Jones[11], P. Hwu[12], N. Somaiah[12]

[1]Medical Oncology, Sarcoma Oncology Center, Santa Monica, CA, USA, [2]Medical Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Department of Oncology, Mayo Clinic, Rochester, NY, USA, [4]Medical Oncology, Moffitt Cancer Center, Tampa, FL, USA, [5]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [6]Medical Oncology, University of Cincinnati, Cincinnati, OH, USA, [7]Medical Oncology, Yale University, New Haven, CT, USA, [8]Clinical Development, Immune Design, South San Francisco, CA, USA, [9]Science, Immune Design, Seattle, WA, USA, [10]Immunology, Mount Sinai, New York, NY, USA, [11]Medical Oncology, Royal Marsden Hospital NHS Foundation Trust, London, WA, UK, [12]Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

1608PD Can we cure patients with abdominal desmoplastic small round cell tumor? Results of a retrospective multicentric study on 100 patients

J-B. Delhorme[1], E. Nassif[2], G. Ferron[3], E. Bompas[4], J. Adam[5], O. Glehen[6], A. Italiano[7], F. Bertucci[8], D. Orbach[9], A. Le Cesne[10], J.Y. Blay[11], C.M. Chevreau[12], O. Mir[13], C. Honoré[14]

[1]General and Digestive Surgery, Hautepierre University Hospital, Strasbourg, France, [2]Medical Oncology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [3]Surgical Department, Centre Claudius-Regaud, Toulouse, France, [4]Medical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France, [5]Pathology, Institut Gustave Roussy, Villejuif, France, [6]Surgical Oncology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, [7]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [8]Medical Oncology, Institute Paoli Calmettes, Marseille, France, [9]Pediatric Oncology, Institut Curie, Paris, France, [10]Department of Medicine, Gustave Roussy, University Paris-Saclay, Villejuif, France, [11]Medical Oncology, Centre Léon Bérard, Lyon, France, [12]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France, [13]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [14]Surgery Department, Institut Gustave Roussy, Villejuif, France

1609PD Preoperative hypofractionated radiotherapy (RT) in patients with locally advanced myxoid liposarcomas: Interim analysis of prospective phase II clinical trial

H.M. Kosela Paterczyk[1], M. Spalek[2], M. Wagrodzki[3], A. Borkowska[2], A. Szumera-Cieckiewicz[3], A. Cieszanowski[4], T. Morysinski[1], J. Palucki[4], P.L. Rutkowski[1]

[1]Department of Soft Tissue/Bone Sarcoma and Melanoma, The Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology (MCMCC), Warsaw, Poland, [2]Department of Radiotherapy, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [3]Department of Pathology, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [4]Radiology, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland

1610PD A phase II study of pazopanib with oral topotecan in patients with metastatic osteosarcoma

B.A. van Tine[1], N. Mohindra[2], M. Milhem[3], S. Attia[4], S.I. Robinson[5], A. Rademaker[6], S.H. Okuno[7], M. Agulnik[2]

[1]Hematology/ Oncology, Siteman Cancer Center at Barnes-Jewish Hospital and Washington University, St. Louis, MO, USA, [2]Hematology/Oncology, Northwestern University, Chicago, IL, USA, [3]Medicine, University of Iowa, Iowa City, IA, USA, [4]Oncology, Mayo Clinic, Jacksonville, FL, USA, [5]Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA, [6]Preventive Medicine, Northwestern University, Chicago, IL, USA, [7]Oncology, Mayo Clinic, Rochester, NY, USA

1611PD A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adults (INI1-negative tumors cohort) (NCT02601950)

S. Stacchiotti[1], J-Y. Blay[2], R.L. Jones[3], G.D.D. Demetri[4], O. Mir[5], A. Italiano[6], D. Thomas[7], T.W-W. Chen[8], P. Schöffski[9], T. Gil[10], T. Jahan[11], G. Cote[12], R. Ratan[13], S. Attia[14], M. Roche[15], S. Daigle[15], I. Sapir[15], A. Clawson[15], M. Gounder[16]

[1]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy, [2]Medicine, Centre Léon Bérard, Lyon, France, [3]Medical Oncology, The Royal Marsden Hospital and Institute for Cancer Research, London, UK, [4]Ludwig Center at Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA, [5]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [6]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [7]Cancer Division, Chris O'Brien Lifehouse, Camperdown, Australia, [8]Medical Oncology, National Taiwan University Hospital, Taipei City, Taiwan, [9]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium, [10]Medical Oncology, Institute Jules Bordet, Brussels, Belgium, [11]Medical Oncology, University of California, San Francisco, CA, USA, [12]Medical Oncology, Massachusetts General Hospital, Boston, MA, USA, [13]Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [14]Oncology, Mayo Clinic, Jacksonville, FL, USA, [15]Clinical, Epizyme, Cambridge, MA, USA, [16]Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

1612PD A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adults (rhabdoid tumor cohort) (NCT02601950)

R.L. Jones[1], J-Y. Blay[2], M. Agulnik[3], R. Chugh[4], O. Mir[5], A. Italiano[6], D. Thomas[7], A. Gupta[8], T. Jahan[9], G. Cote[10], V. Villalobos[11], G.D.D. Demetri[12], M. Roche[13], I. Sapir[13], S. Daigle[13], A. Clawson[13], M. Gounder[14]

[1]Medical Oncology, The Royal Marsden Hospital and Institute for Cancer Research, London, UK, [2]Medicine, Centre Léon Bérard, Lyon, France, [3]Hematology/Oncology, Northwestern Memorial Hospital, Chicago, IL, USA, [4]Medical Oncology, Michigan Medicine Comprehensive Cancer Center, Ann Arbor, MI, USA, [5]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [6]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [7]Cancer Division, Chris O'Brien Lifehouse, Camperdown, Australia, [8]Department of Hematology and Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [9]Medical Oncology, University of California, San Francisco, CA, USA, [10]Medical Oncology, Massachusetts General Hospital, Boston, MA, USA, [11]Medical Oncology, University of Colorado, Denver, CO, USA, [12]Ludwig Center at Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA, [13]Clinical, Epizyme, Cambridge, MA, USA, [14]Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

1613PD **mTOR inhibitors in uterine and extra-uterine malignant PEComas: A multicenter international case series retrospective analysis**

R. Sanfilippo[1], R.L. Jones[2], S. Provenzano[3], G. Antoniou[4], J-Y. Blay[5], E. Fumagalli[3], S. Stacchiotti[6], R.M. Bertulli[3], O. Mir[7], N. Hindi[8], M. Brahmi[9], A. Dufresne[10], A.P. Dei Tos[11], P.G. Casali[12]

[1]Oncologia Medica, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [2]Medical Oncology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [3]Oncologia Medica, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [4]Sarcoma Unit, Royal Marsden Hospital, London, UK, [5]Medicine, Centre Léon Bérard, Lyon, France, [6]Adult Mesenchymal Tumor Medical Oncology Unit, Cancer Medicine Department, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy, [7]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [8]Oncology Unit, Hospital Universitario Virgen del Rocio, Seville, Spain, [9]Department of Medical Oncology, Centre Léon Bérard, Lyon, France, [10]Medical Oncology, Centre Léon Bérard, Lyon, France, [11]Pathology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [12]Medical Oncology Unit 2, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy

1614PD **A phase II study of preoperative chemoradiation plus sorafenib (S) for high-risk extremity soft tissue sarcomas (STS)**

C.W. Ryan, L.E. Davis, Y-C. Doung, J.L. Davis, A.Y. Hung, J.B. Hayden, K.R. Gundle, J.T. Vetto, A. Mansoor, B.R. Beckett, P. Norr, S. Bertolone-Smith, W. Huang

Knight Cancer Institute, Oregon Health Science University, Portland, OR, USA

1615PD **A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adults: Epithelioid sarcoma cohort (NCT02601950)**

M. Gounder[1], P. Schöffski[2], V. Villalobos[3], G. Cote[4], R. Chugh[5], T.W-W. Chen[6], T. Jahan[7], E.T. Loggers[8], A. Italiano[9], A. Gupta[10], M. Agulnik[11], S. Attia[12], R.L. Jones[13], B.A. van Tine[14], G.D.D. Demetri[15], M. Roche[16], I. Sapir[16], S. Daigle[16], A. Clawson[16], S. Stacchiotti[17]

[1]Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium, [3]Medical Oncology, University of Colorado, Denver, CO, USA, [4]Medical Oncology, Massachusetts General Hospital, Boston, MA, USA, [5]Medical Oncology, Michigan Medicine Comprehensive Cancer Center, Ann Arbor, MI, USA, [6]Medical Oncology, National Taiwan University Hospital, Taipei City, Taiwan, [7]Medical Oncology, University of California, San Francisco, CA, USA, [8]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [9]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [10]Department of Hematology and Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [11]Hematology/Oncology, Northwestern Memorial Hospital, Chicago, IL, USA, [12]Oncology, Mayo Clinic, Jacksonville, FL, USA, [13]Medical Oncology, The Royal Marsden Hospital and Institute for Cancer Research, London, UK, [14]School of Medicine, Washington University in St. Louis, St. Louis, MO, USA, [15]Ludwig Center at Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA, [16]Clinical, Epizyme, Cambridge, MA, USA, [17]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

1616P Quantitative multiplexed immune profiling of advanced gastrointestinal stromal tumors (GISTs): Impact of tyrosine kinase inhibitors on immune environment

C. Yoo[1], S-Y. Kim[2], J. Kim[3], Y-M. Ryu[2], M-H. Ryu[1], Y-K. Kang[1]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Convergence Medicine, Asan Institute for Life Sciences, Seoul, Republic of Korea, [3]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Immune microenvironment of GISTs is largely unknown and there is no approved immunotherapeutic agent for the treatment of advanced GISTs. To investigate novel immunotherapeutic strategy in patients with GISTs, immune microenvironment was analyzed in this analysis.

Methods: In this study, 80 surgical specimens of GISTs from 65 patients in different clinical setting (TKI-naïve [n = 20], imatinib-progression [IM-PD, n = 30], and imatinib-progression and sunitinib-treated [IM-PD/SU-treated, n = 30]) were included. CD3, CD8, FoxP3, PD-L1, PD-1 and DOG-1 were simultaneously evaluated in one formalin-fixed paraffin-embedded tissue section using multiplexed immunohistochemistry (IHC) with computational image processing workflows for quantitative assessment.

Results: IM-PD/SU-treated group showed increased FoxP3+CD3+/CD3+, PD-1+CD3+/CD3+, and PD-1+CD8+/CD3+ T cell ratios compared to TKI-naïve ($p = 0.007$, $p = 0.004$, and $p = 0.007$, respectively) and IM-PD ($p = 0.008$, $p = 0.002$, and $p = 0.01$, respectively) groups. PD-1 expression (>1%) on tumor cells (PD-1+DOG-1+/DOG-1+) were also higher in IM/PD-SU-treated group (10%) compared to TKI-naïve (0%) and IM-PD (3%) groups. There were no significant differences in immune microenvironment profiles between TKI-naïve and IM-PD groups ($p > 0.05$).

Conclusions: Anti-angiogenic agents may have immunomodulatory activity in advanced GISTs. Immune exhaustion phenotype (increased Treg, PD-1+ T cells and PD-1+ tumor cells) in IM-PD/SU-treated patients might indicate that this group is a potential candidate for future immunotherapy trials.

Legal entity responsible for the study: Yoon-Koo Kang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1617P Multicentric retrospective analysis of patients with KIT exon 9 mutated GIST

A. Callejo Goena[1], S. Faouzi[2], O. Bouche[3], T. Chevalier[4], N. Isambert[5], F. Duffaud[4], O. Collard[6], O. Mir[2], P. Terrier[7], J-Y. Blay[8], A. Le Cesne[2]

[1]Medical Oncology, Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain, [2]Medical Oncology, Gustave Roussy Institute, Villejuif, France, [3]Digestive Oncology, CHU de Reims - Hôpital Robert Debré, Reims, France, [4]Medical Oncology, CHU La Timone and Aix Marseille Université (AMU), Marseille, France, [5]Departement of Early Clinical Trials, Centre Georges-François Leclerc (Dijon), Dijon, France, [6]Medical Oncology, Institut de Cancérologie de la Loire - Lucien Neuwirth, La Loire, France, [7]Pathology Department, Gustave Roussy Institute, Villejuif, France, [8]Medical Oncology, Centre Léon Bérard, Lyon, France

Background: Patients (pts) with advanced GIST harbouring the KIT exon 9 mutation have a better progression-free survival (PFS) on a higher daily dose level, i.e. 800 mg of imatinib (IM), which is therefore held as standard treatment in this subgroup. This schedule in the adjuvant setting has been subsequently proposed despite the lack of any controlled trials.

Methods: We retrospectively evaluated characteristics of pts with KIT exon 9 mutated GIST in 6 different centers in France and Spain, treated with a daily dose of 400 mg of IM. Pts with localized and advanced GIST were separately analyzed: Kaplan-Meier and Cox proportional hazards model analyses were used to compare median relapse-free survival (mRFS) and OS (mOS) in the adjuvant setting, and overall response rate (ORR), median PFS to IM 400 mg (mPFS), median time to IM failure (mTIF) defined as time to 2nd progression (PD) or death, and mOS in the advanced setting.

Results: We identified 43 pts (44% of males) with a median age of 56 yrs (16-78). 67.4% of GIST was originated in the small bowel and 18.6% in the stomach. In adjuvant situation (31 pts), 42% of pts had a high risk (HR) of relapse (Miettinen classification) and 29% an intermediate risk (IR). 17 out of 31 pts received adjuvant 400 mg/d of IM for a median duration of 21 months (m). The mRFS of pts receiving adjuvant IM was 82 m vs 21 m for those who did not. In the advanced setting, 22 pts were treated with 400 mg of IM. The ORR was 37% (3 CR and 5 PR), with additional 7 stabilizations (benefit in 69% of pts). At PD, 77% of pts received the higher dose IM regimen (800 mg). The mPFS was 12.7 m (CI 95% 6.8-18.6) and the mTIF was 20.6 m (CI 95% 12.2-29). The mOS was 42.9 m. No prognostic variable (gender, age, PS, site of primary disease, diameter of largest lesion, prior surgery of primary) was significantly related with mOS or mTIF.

Conclusions: Despite the limitations of retrospective analysis and the small number of pts, benefit of adjuvant IM (400 mg/d) in pts with localized GIST harbouring KIT exon 9 mutations seems relevant. Pts with advanced GIST initially treated with 400 mg of IM have a similar outcome in terms of mTIF (20 m) than those receiving high-dose IM upfront (19 m in the initial MetaGIST trial, M.V. Glabbeke et al, JCO 2010).

Legal entity responsible for the study: Gustave Roussy Institute.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1618P Prognostic factors for residual lesion surgery following disease control with standard dose imatinib (IM) treatment in patients (pts) with advanced gastrointestinal stromal tumor (GIST)

H. Cho[1], M-H. Ryu[2], H. Chae[2], S.M. Lee[3], Y. Park[3], K-H. Kim[4], C.W. Kim[4], B.S. Kim[4], M-W. Yoo[4], J. Ma[2], M.Y. Beck[2], M. Kim[2], Y-K. Kang[2]

[1]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [4]Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Efficacy of residual lesion surgery in pts with advanced GIST responding to IM has been advocated in several retrospective studies. However, to date, no studies have identified the prognostic factors exclusively for these pts.

Methods: Between September 2002 and December 2015, a total of 107 pts with histologically documented initially metastatic or distant recurrent GIST received residual lesion surgery following disease control with IM 400 mg/day in Asan Medical Center, Seoul, Korea. Among these pts, 89 pts had complete data for potential prognostic factors and were included in the analysis.

Results: Median age was 57 years (range, 12-77) and 56 pts (62.9%) were male. Stomach (n = 41, 46.1%) and small bowel (n = 41, 46.1%) were the most common primary sites followed by peritoneum (n = 4, 4.5%). With a median follow up duration of 47.0 months (range, 16.7-174.7) from residual lesion surgery, the 5-year progression-free survival (PFS) and overall survival rates were 60.6% (95% CI, 47.3-73.9) and 85.7% (95% CI, 76.7-94.7), respectively. In multivariate analysis including potential prognostic factors, male gender ($HR = 3.4$, $p = 0.01$), presence of extra-liver metastasis ($HR = 4.3$, $p < 0.01$), and primary genotype other than KIT exon 11 mutation ($HR = 7.3$, $p < 0.01$) were independently associated with poor PFS. Compared to the good PFS (median 106.7 months) in patients with 0-2 poor prognostic factors, those with 3 factors had very poor PFS (median 8.5 months) ($p < 0.001$).

Conclusions: Our study confirms that long-term survival can be achieved in advanced GIST pts receiving residual lesion surgery following disease control with IM. However, further study is needed to define the role of residual lesion surgery in pts with 3 risk factors considering their poor survival outcomes.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: Y-K. Kang: Consultant: Ono, BMS, Taiho, Roche, Lilly, Blueprint, Taiho, Daehwa, LSK Biopharma. All other authors have declared no conflicts of interest.

1619P Systemic steroid treatment for severe skin rash induced by imatinib in patients with gastrointestinal stromal tumor (GIST): A phase II study

E. Kim[1], M-H. Ryu[2], S.R. Park[2], M.Y. Beck[3], W.J. Lee[4], M.W. Lee[4], Y-K. Kang[2]
[1]Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Department of Oncology, Asan Medical Center, Seoul, Republic of Korea, [4]Department of Dermatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: To achieve optimal clinical outcomes with imatinib in GIST patients, it is crucial to maintain standard imatinib dose. Skin rash is a common and sometimes severe adverse event of imatinib treatment and may affect compliance. Our previous retrospective study suggested that severe skin rash induced by imatinib can be managed by systemic steroid without interruption or dose reduction of imatinib. This phase II study was conducted to evaluate efficacy and safety of systemic steroid in GIST patients with imatinib-associated severe skin rash.

Methods: Between October 2014 and March 2016, 29 patients were enrolled and treated with oral prednisolone for imatinib-associated severe skin rash which was defined as grade 3 skin rash or grade 2 skin rash with pruritus. Prednisolone was started with 30mg daily for 3 weeks, and if skin rash is controlled, steroid was tapered over 12 weeks by determined schedule. The primary endpoint was treatment success rate (TSR). Treatment success was defined as maintaining imatinib without persistence or recurrence of skin rash requiring 1) additional systemic steroid treatment, and 2) interruption or dose reduction of imatinib.

Results: Of 29 patients enrolled, 16 patients (55.2%) received imatinib in adjuvant setting, and 13 (44.8%) in palliative setting. The median age was 61 years (range, 31-77). Eleven patients (37.9%) were male. Twenty-two patients (75.8%, TSR) were treated successfully, 2 (6.9%) were evaluated as treatment failures, and 5 (17.2%) were not evaluable. With a median follow-up of 22 months (range, 16.2-27.8), 71.5% of patients could maintain imatinib dose without recurrence of skin rash for 2 years. Patients aged <65 years showed higher TSR (odds ratio [OR]=4.38, p = 0.192). No one experienced disease progression during follow-up. All toxicities associated with systemic steroid were evaluated. One patient with myelodysplastic syndrome had Pneumocystis pneumonia. Otherwise, systemic steroid was well tolerated.

Conclusions: This study demonstrated that systemic steroid treatment can effectively control severe skin rash and minimize interruption or dose reduction of imatinib in GIST patients with imatinib-associated severe skin rash.

Clinical trial identification: NCT03440515.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1620P Phase II study of paclitaxel in patients with advanced gastrointestinal stromal tumor (GIST) after failure of at least both imatinib and sunitinib

H. Cho[1], M-H. Ryu[2], B.J. Kim[2], Y. Park[3], Y-S. Na[4], J. Ma[2], M.Y. Beck[5], Y-K. Kang[2]
[1]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [4]Asan Institute for Life Science, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [5]Department of Oncology, Asan Medical Center, Seoul, Republic of Korea

Background: Most advanced GISTs are known to be resistant to conventional cytotoxic agents but sensitive to tyrosine kinase inhibitors (TKI) such as imatinib and sunitinib. However, majority of patients eventually develop resistance to TKIs and experience disease progression. Recent preclinical studies suggested that a few conventional cytotoxic agents such as paclitaxel might have antitumor effect on GIST. The current study was conducted to evaluate the efficacy and safety of paclitaxel in patients with advanced GIST after failure of at least imatinib and sunitinib.

Methods: Patients received paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of a 4-week cycle. The primary endpoint was 16-week disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]). Secondary endpoints were progression-free survival (PFS) and overall survival (OS). Translational correlation of PFS with expression of P-glycoprotein (P-gp) was also evaluated. This trial is registered with ClinicalTrials.gov, no. NCT 02607332.

Results: A total of 25 patients were enrolled. Median age was 61 years (range, 38-71), and 16 patients (64.0%) were male. Small bowel was the most common primary site (n = 17, 68.0%), followed by stomach (n = 7, 28.0%). Median 2 cycles (range, 1-12) of paclitaxel were administered per patient. No CR was observed. PR and SD were observed in one patient (4.0%)and 10 patients (40.0%), respectively. The 16-week disease control rate was 20.1%. With a median follow up duration of 20.8 months (range, 17.9-24.0) in surviving patients, median PFS and OS were 1.7 months (95% CI, 0.23-3.13) and 10.9 months (95% CI, 0.0-23.68), respectively. The most frequent grade 3/4 adverse events were neutropenia (20.0%) and leukopenia (8.0%). P-gp expression was evaluable in 19 patients, and a trend toward poor PFS was documented in patients with high P-gp intensity score (3 vs. 1-2; HR 2.3, P = 0.12).

Conclusions: Paclitaxel was well tolerated with modest antitumor efficacy in heavily pretreated patients with advanced GIST. Additionally, P-gp maybe a potential biomarker for selecting patients for paclitaxel treatment.

Clinical trial identification: NCT 02607332.

Legal entity responsible for the study: Asan Medical Center.

Funding: Hanmi.

Disclosure: Y-K. Kang: Consultant: Ono, BMS, Taiho, Roche, Lilly, Blueprint, Taiho, Daehwa, LSK Biopharma. All other authors have declared no conflicts of interest.

1622P Heat shock protein 90 (HSP90) inhibitor as a candidate treatment option for gastrointestinal stromal tumor with acquired resistance for conventional receptor tyrosine kinase inhibitors

M. Yamamura[1], A. Yamauchi[2], N. Katase[3], Y. Katata[1], H. Tanioka[1], M. Okawaki[1], T. Nagasaka[1], Y. Yamaguchi[1]
[1]Medical Oncology, Kawasaki Medical School Hospital, Kurashiki, Japan, [2]Biochemistry, Kawasaki Medical School, Kurashiki, Japan, [3]Oral Pathology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Background: Imatinib functions as a specific inhibitor of a number of tyrosine kinase enzymes, such as KIT and PDGFR, by occupying the TK active site, and thus improves the prognosis of gastrointestinal stromal tumor (GIST) patients. However, resistance to the drug appears with prolonged usage. Mechanisms of acquired resistance are still under elucidation.

Methods: To evaluate mechanisms of acquired resistance for imatinib, we established a imatinib-resistant GIST cell line, so-called T1R, by culturing the GIST cell line, GIST-T1, with increasing concentrations of imatinib. Next, we analyzed receptor tyrosine kinases (RTKs) and intracellular signals strongly expressed in T1R by western blotting and phosphorylated arrays. Finally, we examined the antitumor effect of an agent which was confirmed to inhibit upregulated RTKs in T1R.

Results: Interestingly, imatinib-resistant T1R showed cross resistance to sunitinib, which offers patients with imatinib-resistant GIST a new treatment option to stop further disease progression. By western blotting, T1R showed a suppression of phosphorylation in KIT in contrast to a promotion of phosphorylation in PDGFRA, which never observed before imatinib treatment. A phosphorylation multiplex array also revealed that T1R had additional promotion of phosphorylation in FGFR, Met, Eph, Axl, and Tie2. Therefore we considered activation of PDGFRA owing to one of the candidate machinery of acquired resistance for imatinib as well as sunitinib. HSP90 inhibitors is known to effective against both imatinib-sensitive and resistant GIST models. Therefore, we examined whether HSP90 inhibitors interact with PDGFRA TK kinase activity in T1R. HSP90 inhibitors inhibited the phosphorylation and protein expression of PDGFRA and other RTKs, resulted to inhibit cell proliferation and induce apoptosis in T1R.

Conclusions: Activation of multiple RTKs is an essential for acquired resistance for imatinib in GIST. Inhibition of PDGFRA and other RTKs by HSP90 inhibitors has a potential to the next treatment option for GIST which acquired drug resistance for conventional small-molecule, multi-targeted RTK inhibitors.

Legal entity responsible for the study: Department of Medical Oncology, Kawasaki Medical School Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1623P Correlation of ctDNA and response in patients (pts) with PDGFRα D842 GIST treated with avapritinib

S. George[1], S. Bauer[2], R.L. Jones[3], C. Serrano[4], M. von Mehren[5], Y-K. Kang[6], P. Schöffski[7], P. Cassier[8], F.A. Eskens[9], O. Mir[10], W.D. Tap[11], S.P. Chawla[12], P. Rutkowski[13], H. Shi[14], O. Schmidt-Kittler[15], B. Mar[16], M. Heinrich[17]

[1]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [2]Medical Oncology, University Hospital Essen, Essen, Germany, [3]Sarcoma Unit, Royal Marsden Hospital NHS Foundation Trust, London, UK, [4]Medical Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [5]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [6]Department of General Medical Oncology, Asan Medical Center, Seoul, Republic of Korea, [7]General Medical Oncology, University Hospitals Leuven, Leuven, Belgium, [8]Department of Medical Oncology, Centre Léon Bérard, Lyon, France, [9]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, [10]Sarcoma Group, Institut Gustave Roussy, Villejuif, France, [11]Sarcoma Service, Dept of Medicine, Memorial Sloan Kettering Cancer Centre, New York, NY, USA, [12]Medical Oncology, Sarcoma Oncology Research Center, Santa Monica, CA, USA, [13]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute - Oncology Center, Warszawa, Poland, [14]Biostatistics, Blueprint Medicines Corporation, Cambridge, MA, USA, [15]Translational Medicine, Blueprint Medicines Corporation, Cambridge, MA, USA, [16]Clinical Development, Blueprint Medicines Corporation, Cambridge, MA, USA, [17]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA

Background: Avapritinib (ava) is a potent and selective inhibitor of activated KIT and PDGFRA, which has shown broad activity against GIST in pts in the Phase 1 NAVIGATOR study (NCT02508532), particularly in those with PDGFRα D842 mutations. We investigated whether baseline ctDNA levels and changes in ctDNA during treatment were associated with response.

Methods: Plasma ctDNA was sequenced at baseline and 2 mos after the start of treatment. Pts (n = 20) in dose-escalation were profiled using the Sysmex OncoBEAM™ PDGFRA assay; Pts (n = 12) in dose-expansion were sequenced with a custom Personal Genome Diagnostics PlasmaSELECT™ 60 panel.

Results: As of 11 Jan 2018, response rate was 73% and stable disease rate was 23% per mRECIST v1.1 (modified for GIST). Median progression free survival (PFS) was not reached; estimated 12 mo PFS rate was 78%. Baseline ctDNA mutation allele fraction (MAF) correlated with target lesion size ($p < 0.002$). Lower than median baseline ctDNA MAF identified a group of pts with 100% PFS after a median follow up time of 16 mo (1.8 to 26.6 mo). Ava led to detectable ctDNA declines (median 5.2 fold) in all pts except those near the quantification limit (which changed minimally). Despite this, larger declines, or falling below the limit of quantification (BLQ), did not correlate with greater shrinkage or longer PFS. Instead, declines were barely quantifiable in pts with low baseline ctDNA approaching limit of detection, while larger declines were driven by high baseline MAF. Therefore, pts with the smallest declines in ctDNA had low baseline ctDNA and were least likely to progress.

Conclusions: Large ctDNA declines have been speculated to be a predictor of treatment response. We show in PDGFRα D842 mutant GIST low baseline ctDNA correlates with prolonged PFS yet ctDNA minimally declines due to detection limits. Surprisingly, large fold declines, even falling below the limit of detection, was not predictive of improved outcomes. Our data suggest that although highly effective targeted therapy achieves rapid declines in ctDNA, baseline ctDNA levels may be more prognostic and that declines in ctDNA levels, even to BLQ, may be falsely reassuring in this population.

Clinical trial identification: NCT02508532.

Editorial acknowledgement: Samantha Clark, BSc, from iMed Comms an Ashfield Company, part of UDG Healthcare plc, provided copy editing support funded by Blueprint Medicines.

Legal entity responsible for the study: Blueprint Medicines Corporation.

Funding: Blueprint Medicines Corporation.

Disclosure: S. George: Fees from advisory board membership: Deciphera Pharmaceuticals, Blueprint Medicine; Fees for consulting: AstraZeneca. S. Bauer: Grants and personal fees: Novartis; Personal fees: PharmaMar, Lilly, Deciphera; Grants and personal fees: Blueprint Medicines; Grants: Incyte. R.L. Jones: Fees from consulting: Adaptimmune, Blueprint, Clinigen, Eisai, Epizyme, Daichii, Deciphera, Immunedesign, Lilly, Merck, PharmaMar. C. Serrano: Personal fees: Deciphera Pharmaceuticals for advisory board role; Research grants: Bayer Healthcare, Deciphera Pharmaceuticals, Pfizer. M. von Mehren: Personal fees for advisory board roles: Decipera, Blueprint. Y-K. Kang: Personal fees: BMS, Ono, Blueprint, Daehwa, LSK Biopharma, Novartis, Roche for advisory board participation. P. Schöffski: Consulting or advisory role (institutional support): 6th Element Capital, Adaptimmune, Amcure, AstraZeneca, Bayer, Blueprint Medicines, BMS, Boehringer Ingelheim, Cristal Therapeutics, Daiichi Sankyo, Eisai, Eli Lilly, Epizyme, Genzyme, Ipsen, Loxo Oncology, Medpace, Nektar, Philogen, Piqur Therapeutics, Plexxikon; Research funding (institutional support): Bayer, Blueprint Medicines, Cobiores nv, Exelixis, GSK, Novartis, Plexxikon; Travel, accommodation, expenses (institutional support): 6th Element Capital, Adaptimmune, Amcure, AstraZeneca, Bayer, Blueprint Medicines, BMS, Boehringer Ingelheim, Cristal Therapeutics, Daiichi Sankyo, Eisai, Eli Lilly, Epizyme, Genzyme, GSK, Ipsen, Loxo Oncology, Medpace, Nektar, Novartis, PharmaMar, Philogen. P. Cassier: Personal fees: Amgen, Blueprint Medicines, Novartis, Roche/Genentech for honoraria; Non-financial support from Amgen, Bristol-Myers Squibb, Novartis and Roche for travel accomodation and expenses; Research grants from Abbvie, AstraZeneca, Bayer, Blueprint Medicines, Bristol-Myers Squibb, Celgene, Lilly, Merck Serono, Merck Sharp & Dohme, Novartis, Plexxikon, Roche/Genentech, Taiho Pharmaceutical, Toray Industries, Transgene. O. Mir: Consultancy for Amgen, AstraZeneca, Bayer, Blueprint, Bristol Myers-Squibb, Eli-Lilly, Incyte, Ipsen, Lundbeck, MSD, Novartis, Pfizer, Roche, Servier, Vifor; Speakers bureau for Eli-Lilly, Roche, Servier; Stock ownership: Amplitude Surgical, Transgene. W.D. Tap: Personal fees: Adaptimmune, Blueprint Medicine, Daiichi Sankyo, Eli Lilly, EMD Serono, Esai, Immune Design, Janssen, Loxo, Novartis for Advisory Board participation and consulting. S.P. Chawla: Personal fees: Amgen, Epizyme, Five Prime, Immune design, Janssen, Novartis, PharmaMar, Prachi Pharmaceuticals for advisory and consulting roles; Reserach grants: Amgen, Bayer, Blueprint Medicine, BMS, Cba Pharma, Five Prime, Immune Design, Janssen, Karyopharm, Pharmaron UK, Novartis; Stock ownership: ADI Pharma, Cellestia, Counterpoint Biomedica, Uptick Health. P. Rutkowski: Advisory board: Novartis, Amgen, MSD, Roche, BMS, Bayer and Blueprint Medicine; Honoraria for lectures: Novartis, Pfizer, MSD, BMS, Roche. H. Shi, O. Schmidt-Kittler: Employment and stock ownership with Blueprint Medical. B. Mar: Employment at Blueprint Medical. M. Heinrich: Personal fees: Bayer, Blueprint Medicines, Deciphera, MolecularMD, Novartis for consulting; Personal fees: Novartis for expert testimony; Research funding: Blueprint Medicines, Deciphera; Equity interest: MolecularMD. All other authors have declared no conflicts of interest.

1624P Pathological grade of tumorregression after neoadjuvant chemotherapy with doxorubicin/ifosfamid and regional hyperthermia correlates with survival outcomes in patients with high-risk soft tissue sarcoma

G-E. Schuebbe[1], T. Knösel[2], H.R. Dürr[3], M. Angele[4], F. Röder[5], S. Abdel-Rahman[1], A. Alig[1], R.D. Issels[1], D. Di Gioia[1], L.H. Lindner[1]

[1]Medizinische Klinik und Poliklinik III, LMU Klinikum der Universität München, Munich, Germany, [2]Pathologisches Institut der LMU, Ludwig-Maximilians-Universität München, Munich, Germany, [3]Orthopädische Klinik und Poliklinik, LMU Klinikum der Universität München, Munich, Germany, [4]Klinik f. Allgemein, Viszeral, Gefäß, u. Transpl.-Chirurgie, LMU Klinikum der Universität München, Munich, Germany, [5]Klinik für Strahlentherapie und Radioonkologie, LMU Klinikum der Universität München, Munich, Germany

Background: Anthracycline/ifosfamide-based neoadjuvant chemotherapy (NAC) is considered to improve survival in adult patients (pts) with high-risk soft tissue sarcoma (HR-STS) [Gronchi A et al., Lanacet Oncology 2017; 18(6):812-22]. Regional hyperthermia (RHT) combined with NAC has significantly improved radiological tumor response and survival in pts with HR-STS [Issels RD, Lindner LH et al., JAMA Oncology 2018 2018 Feb 15. doi: 10.1001/jamaoncol.2017.4996]. The purpose of this retrospective analysis was to assess whether the pathological tumor response after NAC with doxorubicin/ifosfamide (AI) combined with RHT can predict survival outcomes in adult pts with HR-STS.

Methods: In our database, we identified 138 pts who underwent NAC with AI in combination with RHT (01/09 – 10/16) followed by resection of the residual tumor. Pathological response after NAC + RHT was assessed in seventy-five pts and correlated with survival outcome. Pathological grade of regression of the resected tumor was evaluated according to Salzer-Kuntschik et al. and survival parameters using Kaplan Meier. In the patient group, we identified 28 pts with L-sarcoma (LS, lipo- and leiomyosarcoma) and 47 pts with non-LS.

Results: All 75 pts (22 – 78y, median age 60y) received perioperative (1 – 8 cycles, median 6 cycles) combined with RHT (2 – 16 RHT, median 8 RHT), 23 pts underwent neoadjuvant radiotherapy (NAR). Overall survival (OS) and disease progression free survival (DFS) was not significantly improved for a higher grade of regression, whereas pts with pathological regression grade ≥ 3 (n = 26) had a significant better local relapse free survival (LRFS) than pts with regression grade < 3 (n = 49) ($p = 0.017$).

Conclusions: Histopathological grade of regression after NAC + RHT seems to be predictive for LRFS in adult patients with HR-STS. Further investigations on molecular markers that can predict histopathological response are needed.

Legal entity responsible for the study: Lars Lindner.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1625P Efficacy of metastasectomy on survival in patients with metachronous soft tissue sarcoma-metastasis: Results of a bi-centre study including 135 patients

A. Leithner[1], V. van Praag[2], F. Posch[3], M. Bergovec[1], L. Leitner[1], J. Friesenbichler[1], R. Heregger[3], F-M. Smolle-Jüttner[4], M. Fiocco[2], M. van de Sande[2], J. Riedl[3], M. Pichler[3], A. Gerger[3], J. Szkandera[3], H. Stöger[3], B. Liegl-Atzwanger[5], M.A. Smolle[1]

[1]Department of Orthopaedics and Trauma, Medical University of Graz, Graz, Austria, [2]Department of Orthopaedic Surgery, Leiden University Medical Centre, Leiden, Netherlands, [3]Division of Clinical Oncology, Medical University of Graz, Graz, Austria, [4]Division of Thoracic and Hyperbaric Surgery, Medical University of Graz, Graz, Austria, [5]Institute of Pathology, Medical University of Graz, Graz, Austria

Background: Metastasectomy is hypothesised to improve overall survival (OS) in patients with metachronous metastasis of STS. Evidence in favour of this approach comes from non-controlled single-arm studies subjected to selection bias. In the

present study, advanced comparative effectiveness methods were used to assess the efficacy of metastasectomy vs. "non-invasive" treatments (i.e. chemotherapy, radiotherapy, best supportive care) in patients with metachronous STS-metastasis.

Methods: 135 patients with metachronous STS metastasis, selected out of a population of over 1000 STS patients, who had primarily undergone surgery for localised STS between 1998 and 2015 at two tertiary tumour centres were retrospectively included. In order to evaluate the efficacy of metastasectomy on OS, a propensity score (PS) was estimated, including variables at time of treatment decision for metastatic disease ("baseline"). Based on the PS, an inverse-probability-of-treatment-weight (IPTW) model was calculated to allow analyses with adjustment for favourable prognostic factors prevailing in patients undergoing metastasectomy (for metastasectomy: IPTW=1/PS; for "non-invasive" treatment: IPTW=1/(1-PS)).

Results: OS was significantly better in those 68 patients (44.4%) who had undergone metastasectomy (10-year OS: 23% vs. 4%; log-rank test: $p < 0.0001$; hazard ratio (HR): 0.34, 95% confidence interval (CI): 0.22-0.53, $p < 0.0001$). This positive association prevailed after recalculation of time-to-event-analyses with IPTW-weighted data ((adjusted 10-year OS: 17% vs. 3%, log-rank-test: $p < 0.0001$; HR: 0.33, 95%CI: 0.20-0.52, $p < 0.0001$), compensating for positive prognostic factors prevailing in patients with metastasectomy (i.e. smaller number of metastases, better ECOG performance status, better haemoglobin- and albumin-levels).

Conclusions: In the present bi-centre study, metastasectomy was associated with a significant benefit on OS, persisting even after adjustment for favourable prognostic factors prevailing in patients undergoing metastasectomy. Our data indicate that metastasectomy should be considered as first choice in patients with metachronous metastasis of STS.

Legal entity responsible for the study: Medical University of Graz.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1626P Trabectedin and radiotherapy in advanced sarcoma: Experience of a reference center

I.C. Carrasco Garcia[1], N. Hindi[2], J. Peinado[3], I. Rincon[3], M. Cordeiro[4], F.J. Jimenez[5], A. Falcon Gonzalez[1], R. Lasso de la Vega[1], M. Noguer Mediavilla[1], P. Sancho Marquez[1], J. Martin-Broto[2]

[1]Medical Oncology Department, Hospital Universitario Virgen del Rocio, Seville, Spain, [2]Medical Oncology, Instituto de Biomedicina de Sevilla (IBIS) CSIC/US, Hospital Univ. Virgen de Rocio, Seville, Spain, [3]Radiation Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain, [4]Medical Oncology, Hospital Universitario Son Espases, Palma de Mallorca, Spain, [5]Medical Oncology, Hospital Universitario Juan Ramon Jimenez, Huelva, Spain

Background: In patients with advanced soft tissue sarcomas (STS) there is low probability to obtain tumor shrinkage with second-line drugs. That means that patients requiring volumetric response to palliative relief have few therapeutic options since active second-line drugs in STS exhibit less than 10% of RECIST response. Trabectedin (T) has shown to be synergistic with radiation therapy (RT) in preclinical experiments. Additionally, a substantial activity of T+RT has recently been reported in a phase I trial with 71% of overall response rate (ORR) in the irradiated nodules.

Methods: Cases with advanced STS treated with T at standard dose of 1.5 mg/m^2 24-h infusion and RT 30-39 Gy (3 Gy per fraction) were collected for this retrospective series from one sarcoma reference center. RT was started 24 h later the trabectedin initiation. ORR according to RECIST 1.1, progression free survival (PFS) and overall survival (OS) were analized.

Results: Twenty patients with median age 51 (27-77) and male/female 9/11 were selected. STS subtypes were uterine and somatic leiomyosarcoma 5(25%) and 4 (20%) respectively, high grade myxoid liposarcoma 4 (20%) and non-L STS 7 (35%). All but one patient received previous systemic lines, 2 (0-6). Response assessment was, 5 (25%) PR, 9 (45%) SD and 6 (30%) PD. Considering only radiated lesions, response evaluation was as follows: PR 5 (25%), SD 13 (65%) and 2 (10%) PD. There were 8/12 minor responses. Patients with non-L sarcomas also had disease control (1 myxofibrosarcoma, 2 sarcoma NOS achieved minor responses, 1 fibrosarcoma, 1 malignant peripheral nerve sleath tumor, 1 synovial sarcoma with SD). There were not toxic deaths and only one G3 SAE (transaminitis). No dose-reductions or interruptions were registered. With a median follow-up of 11.2 mos (4.4-36), there were 11 progression and 6 death events. The median of PFS was 9.9 months (6.5-13.2 months) while the median OS has not been reached.

Conclusions: T + RT have shown relevant clinical activity in advanced STS, whatever the histotype and location. In 70% of cases there was some shrinkage in radiated lesions bringing up the opportunity of better disease control. Both ORR and PFS were clearly superior with T + RT than historical results obtained with T alone.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: N. Hindi: Research funding to institution: Eisai, Novartis, PharmaMar; Travel funding: PharmaMar. J. Martin-Broto: Advisory: PharmaMar; Research funding to institution: Eisai, Novartis, PharmaMar; Travel funding: PharmaMar. All other authors have declared no conflicts of interest.

1627P Single arm prospective study evaluating the role of neoadjuvant chemotherapy in soft tissue sarcoma

A. Tiwari[1], S. Rastogi[2], S.V.S. Deo[3], D.N. Sharma[4], M.C. Sharma[5], S. Bakshi[6]

[1]Department of Medical Oncology, All India Institute of Medical Sciences, Delhi, India, [2]Medical Oncology, Sameer Rastogi, New Delhi, India, [3]Surgical Oncology, All India Institute of Medical Sciences, New Delhi, India, [4]Radiotherapy, AIIMS, New Delhi, India, [5]Pathology, AIIMS, New Delhi, India, [6]Medical Oncology, Sameer Bakshi, New Delhi, India

Background: Surgery is the primary standard of care for localized soft tissue sarcoma (STS). In certain cases, upfront surgery may not be possible, or it may be mutilating and disfiguring. We conducted this study to evaluate the role of neoadjuvant chemotherapy in this setting.

Methods: This single arm prospective study included patients of age $\geq$18 years with chemotherapy naïve STS of size $\geq$ 5 cm and which were grade II/III. These tumors were either upfront unresectable or possibly resectable with undesirable outcomes. Ewings sarcoma, osteosarcoma, rhabdomyosarcoma and other chemoresistant STS were excluded. The patients received three cycles of Ifosfamide (1.8 gm/m^2 d1-d5) and epirubicin (60 mg/m^2 d1-d2) followed by clinical and radiologic reassessment. The primary objective was overall response rate (ORR), and the secondary objective was to assess conversion to limb salvage surgery (LSS). Overall response was defined as complete response (CR) plus partial response (PR).

Results: We included 36 patients in this study with a mean age of 36.9$\pm$14.7 years. The ratio male: female was 1.1. The most common histology in our cohort was synovial sarcoma [16 (44.4%)] followed by MPNST [5 (13.8%)]. Extremity [23 (63.8%)] was the most common site followed by trunk [8 (22.2%)] and head and neck [5 (13.8%)]. PR was seen in 14 (38.8%) patients, 16 (44.4%) patients had stable disease, three patients had progression and none of the patients had CR. The response could not be assessed in three patients. The ORR was 44.4%. LSS could be done for 13 (56.5%) patients with extremity STS. Ten patients with extremity STS required amputation despite neoadjuvant chemotherapy of which 6 (60%) patients did not give consent for amputation. The chemotherapy regimen was well tolerated, febrile neutropenia was seen in 12.5%. There was no treatment-related mortality.

Conclusions: Neoadjuvant chemotherapy is an effective and safe option for unresectable STS or those who are resectable but require mutilating or disfiguring surgery. The acceptance of amputation as a mean of treatment of STS is low in our population.

Clinical trial identification: CTRI/2017/07/008997.

Legal entity responsible for the study: AIIMS.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1628P Preoperative hypofractionated radiotherapy (RT) combined with chemotherapy in primary marginally resectable high grade soft tissue sarcomas (STS) of extremities or trunk wall: Interim analysis of prospective phase II clinical trial

M. Spalek[1], H.M. Kosela Paterczyk[2], A. Borkowska[1], M. Wagrodzki[3], A. Cieszanowski[4], P. Castaneda-Wysocka[4], T. Switaj[2], M.E. Dudzisz-Sledz[2], A.M. Czarnecka[2], E. Dabrowska-Szewczyk[4], P.L. Rutkowski[2]

[1]Radiotherapy, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [2]Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [3]Pathology, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [4]Radiology, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland

Background: The management of marginally resectable STS is challenging. The study aim is to assess the efficacy and safety of preoperative hypofractionated RT combined with chemotherapy in primary locally advanced STS.

Methods: Single-arm clinical trial enrolls patients for one cycle of doxorubicin and ifosfamide (AI) chemotherapy followed by 5x5 Gy RT, and 2 cycles of AI in 7-8 weeks gap between RT end and surgery. Tumor response was assessed in DWI-MR imaging and pathologically by EORTC STBSG criteria. The primary endpoint is rate of limb-sparing surgeries and R0 resections.

Results: 24 patients(pts) met eligibility criteria: 21 finished the whole planned protocol treatment. 3 pts underwent extremity amputation, two after 1st AI cycle due to poor tolerance, one due to extensive tumor invasion without possibility of vessels reconstruction. One toxic death occurred outside our center related to severe bone marrow suppression with septic shock after 2nd AI cycle. Early tolerance of chemotherapy was acceptable. Grade 3+ CTCAE4.03 toxicity developed in 11pts. AI dose was reduced in 8pts who completed therapy (4pts in 2 cycles; 4pts in 1 cycle). Early RT tolerance was satisfactory. EORTC grade 1 radiation dermatitis developed in 13pts and grade 2 in 2pts. Postoperative wound complications occurred in 6pts, including 2 severe wound dehiscence with hospitalization. Very good pathological response (<1% of stainable tumor cells; grade A/B) was reported in 5pts, good pathological response (<50% tumor cells; grade C/D) - in 12pts.

Conclusions: Preoperative AI chemotherapy combined with hypofractionated RT is a feasible method of the management of marginally resectable STS providing a good pathological responses and acceptable treatment toxicity.

Legal entity responsible for the study: Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland.

Funding: Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland.

Disclosure: T. Switaj: Honoraria for lectures: Novartis, Roche, MSD, BMS. A.M. Czarnecka: Honoraria for lectures: Novartis, MSD, BMS. P.L. Rutkowski: Honoraria: Bristol-Myers Squibb, Roche, Novartis, Merck, Sharp & Dohme, GlaxoSmithKline; Paid consulting role: Bristol-Myers Squibb, Roche, Merck, Sharp & Dohme, Blueprint Medicines, Amgen; Speakers' bureau: Novartis, Pfizer, Merck, Sharp & Dohme; Institutional research funding: Bristol-Myers Squibb, Novartis; Travel expenses: Novartis. All other authors have declared no conflicts of interest.

1629P Basket trial in advanced cancers: A clinical observation of apatinib in lung metastases and non-lung metastases

C. Tu, Y. Zhou, K. Yao, Y. Luo, W. Zhang, H. Duan, L. Min

Orthopedics, West China Hospital, Sichuan University, Chengdu, China

Background: Metastatic disease to the lung is one of the most common life-threatening complications of cancer and can be seen with most types of cancer. Apatinib, a tyrosine kinase inhibitor targeting VEGFR-2, has shown efficacy in lung cancer. And the preclinical data also showed plasma concentration of apatinib was high in the lung. This cancer registry study aims to make an exploratory assessment of the efficacy and safety of apabinib in lung metastases.

Methods: Between 2015/05 and 2018/03, this study recorded all patients with advanced cancers in our hospital, with apatinib 500 mg or 250 mg being given. Tumor response assessment and survival analysis were performed.

Results: For a total of 103 patients, 30 had no lung metastases, and 73 had lung metastases, among which most were bone sarcoma (56%) and soft-tissue sarcoma (37%) metastases to lung. Among 57 evaluable patients with lung metastases, 2 achieved CR, 29 achieved PR, and the ORR was 54%. In 11 evaluable patients with no lung metastases, no patient achieved CR, 3 patients achieved PR, and the ORR was 27%. For patients with lung metastases, the mPFS was 12.9 months (95%CI, 8.6-14.9 months), mOS was 21.9 months (95% CI, 15.9-31.3 months). For patients with no lung metastases, the mPFS was 6.0 months (95%CI, 4.6-NE months), the mOS was 10.7 months (95% CI, 5.2-NE months). In lung metastatic patients who received apatinib 500mg, the ORR and DCR were, respectively, 55.1% and 89.8%; when treated with apatinib 250mg, the ORR and DCR were 20% and 80%. When Apatinib was used as first line treatment, the ORR and DCR were respectively 64% and 88%; in second line treatment, the ORR and DCR were respectively 42% and 84%, and when apatinib was used in third line treatment, the ORR and DCR were 33% and 100%. For patients with lung metastases, 89.2% patients experienced adverse events (AEs); the most frequent AEs were hand-foot syndrome (21.6%), diarrhea (20%), hypertension (24.3%) and albuminuria (9.4%).

Conclusions: Based on this exploratory analysis, for bone sarcoma and soft-tissue sarcoma with lung metastases, apatinib 500mg showed promising trends in efficacy and safety profile. An expansion study will be needed.

Legal entity responsible for the study: Chongqi Tu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1630P Efficacy of anlotinib in advanced soft tissue sarcoma by prior lines of therapy, age and dose modification

Y. Yao[1], Y. Chi[2], Z. Fang[3], S. Wang[4], G. Huang[5], Q. Cai[6], G. Shang[7], G. Wang[8], G. Qu[9], Q. Wu[10], Y. Jiang[11], J. Song[12], J. Chen[13], X. Zhu[14], Z. Cai[15], C. Bai[16], Y. Lu[17], Z. Yu[18], J. Shen[19], J. Cai[2]

[1]Medical Oncology, Affiliated Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, China, [2]Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS), Beijing, China, [3]Bone Oncology, Peking University Cancer Hospital, Beijing, China, [4]Oncology, Cancer Centre Sun Yat-sen University, Guangzhou, Guangdong, China, [5]Oncology, Hunan Cancer Hospital, Changsha, China, [6]Bone, Henan Cancer Hospital, Zhengzhou, China, [7]Bone, Liaoning Cancer Hospital and Institute, Shenyang, China, [8]Bone, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China, [9]Bone, Harbin Medical University Cancer Hospital, Harbin, China, [10]Bone, The First Affiliated Hospital of Bengbu Medical College, Bengbu, China, [11]Oncology, West China Hospital, Chengdu, Sichuan, China, [12]Bone, Gansu Provincial Cancer Hospital, Lanzhou, China, [13]Oncology, Wuhan Union Hospital (of Tongji Medical College of HUST), Wuhan, China, [14]Oncology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China, [15]Bone, Shanghai General Hospital, Shanghai, China, [16]Medical Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [17]Oncology, The Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China, [18]Oncology, Jiangxi Cancer Hospital, Nanchang, China, [19]Bone, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: ALTER0203 was a randomized phase IIB trial (NCT02449343) that demonstrated single-agent activity of anlotinib in advanced STS (aSTS). The primary endpoint progression-free survival (PFS) was met and presented as an oral presentation in 2018 ASCO. We evaluated the relationship between age, prior lines of therapy, and dose reductions on the efficacy of anlotinib in aSTS.

Methods: Median PFS (mPFS) was evaluated in subgroups of prior lines of therapy (0 or 1 prior line; 2+ prior lines), age (< 65 y; ≥65 y), and dose reductions (no dose reduction; ≥1 dose reduction). All analyses were descriptive and exploratory and required cautious interpretation.

Results: A total of 158 patients received anlotinib in the ALTER0203 study. Before enrollment, 20 patients of alveolar soft part sarcoma and clear cell sarcoma had no prior line of chemotherapy, 84 patients had received 1 prior line of chemotherapy and 54 patients had received 2+ prior lines of chemotherapy. Median PFS was similar in patients receiving anlotinib who had only 0 or 1 prior line of therapy vs 2+ prior lines of therapy (mPFS, 6.7 vs 6.33 months). In patients receiving anlotinib, mPFS was similar in ages < 65 than ≥65 y (6.33 and 5.9 months, respectively). In patients receiving anlotinib, mPFS was longer in patients requiring ≥ 1 dose reduction vs no reduction (10.43 and 5.73 months, respectively).

Table: 1630P

Subgroups	N	Anlotinib, mPFS, months (95% CI)
Lines of therapy		
0 or 1 prior line	104	6.7 (4.07-9.33)
2+ prior lines	54	6.33 (3.90-8.76)
Age		
< 65 y	152	6.33 (5.06-7.60)
≥65 y	6	5.9 (0.00-14.86)
Dose reduction		
No dose reduction	144	5.73 (3.76-7.7)
≥ 1 dose reduction	14	10.43 (-)

mPFS, median progression-free survival; CI, confidence interval.

Conclusions: In patients receiving anlotinib, longer mPFS was observed in patients requiring ≥ 1 dose reduction. Additionally, mPFS with anlotinib was maintained regardless of lines of therapy or patient age.

Clinical trial identification: NCT02449343.

Legal entity responsible for the study: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Funding: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

1631P Efficacy and safety of apatinib in advanced sarcoma

J. Chen, T. Ye, Z. Zhang, Z. Wang, S. Yang, K. Yang, T. Li

Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Sarcoma constitutes a heterogeneous group of rare solid tumors and has no standard second-line treatment. Anti-angiogenesis tyrosine kinase inhibitors have shown promising efficacy for advanced sarcoma after failure of first-line chemotherapy. Apatinib is a highly selective vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist from China. In the present study, we retrospectively assessed apatinib for safety and activity in advanced sarcoma patients from our cancer center.

Methods: Patients with advanced sarcomas treated with apatinib 250-500mg daily between August 2015 and February 2018 were retrospectively analyzed. Objective response was determined according to RECIST 1.1 criteria, progression-free survival (PFS) was estimated by the Kaplan-Meier curves and safety profile was analyzed.

Results: In total, 52 patients were treated with apatinib and 37 patients (23 males and 14 females) were included for analysis, including 7 alveolar soft part sarcoma (ASPS), 5 PNET/Ewing's sarcoma, 4 osteosarcoma, 4 chondrosarcoma, 3 synovial sarcoma, 4 undifferentiated pleomorphic sarcoma, 4 leiomyosarcoma, 2 angiosarcoma,1 rhabdomyosarcoma, 1 chordoma, 1dedifferentiated liposarcoma and 1 clear cell sarcoma. 5 (13.5%) patients received apatinib as first-line treatment, 17 (45.9%) and 15 (40.5%) were treated with apatinib as second line or later therapy respectively.18 (48.6%) achieved tumor regression, 1 patient with ASPS had complete response, 8 (21.6%) experienced partial response, and disease was stable in 21 (56.8%) patients. The disease control rate was 100% in 5 patients with ASPS. The median PFS for all patients was 12 months, and median PFS of patients except ASPS was 5.9 m. The most frequent treatment-related adverse events included hypothyroidism [11 (29.7%)], Proteinuria [8 (21.6%)], hypertension [11 (29.7%)), hand-foot syndrome [19 (51.4%)], diarrhea [9 (24.3%)], fatigue [5 (13.5%)], hemorrhage [4 (10.8%)], anorexia [5 (13.5%)], oral ulcer [3 (5.4%)], rash [2 (8.1%)], bleaching hair [2 (5.4%)] and aerothorax [2 (5.4%)].

Conclusions: Apatinib may be effective and tolerable in advanced sarcoma, especially in ASPS.

Legal entity responsible for the study: Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Funding: Clinical Research Physician Program of Tongji Medical College, HUST.

Disclosure: All authors have declared no conflicts of interest.

1633P Evaluation of hypertension and hand-foot syndrome as markers of anlotinib efficacy in advanced soft tissue sarcoma

Z. Fang[1], Y. Chi[2], Y. Yao[3], S. Wang[4], G. Huang[5], Q. Cai[6], G. Shang[7], G. Wang[8], G. Qu[9], Q. Wu[10], Y. Jiang[11], J. Song[12], J. Chen[13], X. Zhu[14], Z. Cai[15], C. Bai[16], Y. Lu[17], Z. Yu[18], J. Shen[19], J. Cai[2]

[1]Bone and Soft Tissue Tumors, Peking University Cancer Hospital, Beijing, China, [2]Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS), Beijing, China, [3]Medical Oncology, Affiliated Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, China, [4]Oncology, Cancer Centre Sun Yat-sen University, Guangzhou, China, [5]Oncology, Hunan Cancer Hospital, Changsha, China, [6]Bone, Henan Cancer Hospital, Zhengzhou, China, [7]Bone, Liaoning Cancer Hospital and Institute, Shenyang, China, [8]Bone, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China, [9]Bone, Harbin Medical University Cancer Hospital, Harbin, China, [10]Bone, The First Affiliated Hospital of Bengbu Medical College, Bengbu, China, [11]Oncology, West China Hospital, Chengdu, Sichuan, China, [12]Bone, Gansu Provincial Cancer Hospital, Lanzhou, China, [13]Bone, Wuhan Union Hospital (of Tongji Medical College of HUST), Wuhan, China, [14]Oncology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China, [15]Bone, Shanghai General Hospital, Shanghai, China, [16]Medical Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [17]Oncology, The Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China, [18]Oncology, Jiangxi Cancer Hospital, Nanchang, China, [19]Bone, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: ALTER0203 was a randomized phase IIB trial (NCT02449343) that demonstrated single-agent activity of anlotinib in advanced STS (aSTS). The primary endpoint progression-free survival (PFS) was met and presented as an oral presentation in 2018 ASCO. Similar to other vascular endothelial growth factor pathway-targeted therapies, hypertension and hand-foot syndrome (HFS) have been observed as major adverse events of anlotinib. The goal of our study was to assess if hypertension and hand-foot syndrome induced during treatment with anlotinib were associated with clinical outcome in aSTS patients treated with anlotinib.

Methods: We conducted a review of patients enrolled in ALTER0203. Median PFS was analysed in patients with hypertension and HFS vs patients with no hypertension and HFS. All analyses were exploratory and required cautious interpretation.

Results: A total of 158 patients received anlotinib in the ALTER0203 study. During the study, hypertension was observed in 99 patients (62.66%). HFS was observed in 76 patients (48.1%). Median PFS was longer in patients with hypertension vs patients with no hypertension (7.00 vs 4.37 months, $p = 0.36$). Patients with any grade hypertension while on anlotinib had an adjusted hazard ratio for progression of 0.81 compared to those without hypertension. Also, median PFS was longer in patients with HFS vs patients with no HFS (9.83 vs 4.3 months, $p < 0.01$). Patients with any grade HFS while on anlotinib had an adjusted hazard ratio for progression of 0.47 compared to those without hypertension.

Conclusions: Our data indicate that HFS may represent an interesting prognostic factor for clinical outcome in aSTS patients receiving anlotinib. There is a trend that mPFS of patients with hypertension is longer than those with no hypertension.

Clinical trial identification: NCT02449343.

Legal entity responsible for the study: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Funding: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

1634P Evolution of novel, low cost, sustainable osteosarcoma care over two decades: Reducing inefficiencies & improving outcomes

J. Bajpai[1], T. Mondal[1], V. Simha[1], A. Chandrashekharan[1], S. Hingmire[2], B. Rangarajan[3], N. Shetty[1], K. Shah[1], R. Dusane[4], B. Rekhi[1], T.S. Vora[1], J. Ghosh[1], S. Banavali[1], S. Gupta[1]

[1]Medical Oncology, Tata Memorial Hospital Centre, Mumbai, India, [2]Medical Oncology, Deenanath Mangeshkar Hospital & Research Centre, Pune, Maharashtra, India, [3]Medical Oncology, KMCH Comprehensive Cancer Centre, Coimbatore, India, [4]Biostatistics, Tata Memorial Hospital Centre, Mumbai, India

Background: Osteosarcoma care is challenging especially in lower and middle income countries with limited resources & increasing patient volumes. We need to reduce inefficient practices &reallocate resources to strategies, which can make the greatest &sustainable improvements in patient care.

Methods: We compared the outcomes in non-metastatic osteosarcoma patients treated with 3 sequential non-HDMTX based combination chemotherapy protocols at a single tertiary care center in India over 2 decades. The 1st protocol "OGS-99", involved dose-intense, alternating doublets of, 4 drugs, doxorubicin(Dox),cisplatin(CDDP),ifosfamide(Ifo) & etoposide(Eto); the 2nd protocol, "OGS-99-enhanced", involved OGS-99 drugs with enhanced supportive care including growth factors. The 3 rd dose-dense , "OGS-12" protocol, involved administration of 8 sequential doublets of the 3 most active drugs,(Dox, Cis & Ifo), universal growth factor prophylaxis & targeted nutritional support including IV Iron if required . Event free survival (EFS), overall survivals (OS) and toxicity were estimated using retrospective chart review in OGS-99 & OGS-99-enhanced protocols & prospectively in OGS-12 protocol.

Results: A total of 41, 94 & 385 treatment naive, consecutive, non-metastatic,extremity patients were treated with OGS-99(year 2000-2005), OGS-99-enhanced (2010) & OGS-12 (2011-2016) respectively. At a median follow-up of 19(3-72), 85(2-99) and 36(6-78) months, the 5 year EFS rates are 36%, 50% and 69% in OGS-99, OGS enhanced & in OGS-12 respectively. The corresponding rates of 5 year OS are non-evaluable, 60% & 83% respectively. OGS-12 protocol fared better with respect to grade 3/4 toxicities; febrile neutropenia (40%), thrombocytopenia (36%), anaemia (51%) with 4(1%) chemo toxic deaths & compliance to therapy.

Conclusions: Sequential adaption of more rational chemotherapy regimens, including conception of novel "OGS-12" protocol with, better dose density and elimination of ineffective drugs, enhanced supportive care & thereby reducing the need for dose reductions, resulted in marked improvement in outcomes of non-metastatic osteosarcoma patients. This sustainable, economic efficient strategy is worthy of wide adaption.

Legal entity responsible for the study: Jyoti Bajpai.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1635P HBP-bound doxorubicin: Promising new therapy for bone cancer

E. David, S. Cagnol, J-Y. Goujon, M. Egorov, R. Le Bot

Atlanthera, Saint-Herblain, France

Background: Primary bone cancers and bone metastases derived from advanced cancers have low survival rates. To answer medical need to treat tumors localized in bone environment, we have developed bone-targeted drugs through covalent binding to hydroxybisphosphonates known for their high affinity to bone. Objectives were improvement of efficacy and reduction of systemic toxicity.

Methods: Preclinical proof of concept of lead compound 12b80, an HBP-bound doxorubicin, was carried out on rodents and dogs. 12b80 was administered by IV injection every 3 weeks. Antitumor effects were investigated on various rodent models of bone cancer (orthotopic xenograft models of osteosarcoma or Ewing's sarcoma, models of osteosarcoma-derived lung metastases and models of bone invasion by prostate or mammary adenocarcinoma) and on spontaneous osteosarcoma bearing dogs. Biodistribution was examined by radiolabeling and fluorescence analyses. Toxicity was evaluated by biological and clinical monitoring and histopathological analysis of organs.

Results: 12b80 displayed rapid and sustained targeting of bone tissue and tumor-associated heterotopic bone, and permitted a higher doxorubicin payload in tumor bone environment. Doxorubicin release from 12b80 was dependent on acidic pH associated with active bone tumor environment. 12b80 showed a much lower and reversible toxicity compared with doxorubicin: mild medullar toxicity was recovered within two weeks and no sign of cardiotoxicity or osteonecrosis were observed in rodents and dogs. 12b80 promoted strong antitumor effects on rodent primary bone sarcoma (orthotopic osteosarcoma and Ewing sarcoma), osteosarcoma-derived lung metastasis and on prostate or breast adenocarcinoma bone invasion. 12b80 displayed a dose-response therapeutic effect and was more potent than combination of doxorubicin and zoledronate. First cases of tumor response were also reported in dogs currently under veterinary trial.

Conclusions: HBP-bound doxorubicin 12b80 demonstrated a proof of concept of preclinical bone-targeted doxorubicin delivery. The next step is to complete regulatory phase before starting 12b80 clinical trial (phase I/IIa) as an orphan drug in osteosarcoma salvage therapy.

Legal entity responsible for the study: Atlanthera.

Funding: Atlanthera.

Disclosure: E. David, S. Cagnol, J-Y. Goujon, M. Egorov, R. Le Bot: Employment: Atlanthera.

1636P Perceptions of clinical trial enrollment in patients with bone and soft tissue sarcoma

A. Rosenberg[1], S. Kircher[1], E. Hahn[2], A. Rademaker[3], K. Bilimoria[4], J.D. Wayne[4], M. Agulnik[1]

[1]Hematology/Oncology, Northwestern University, Chicago, IL, USA, [2]Medical Social Sciences, Northwestern University, Chicago, IL, USA, [3]Preventive Medicine, Northwestern University, Chicago, IL, USA, [4]Surgery, Northwestern University, Chicago, IL, USA

Background: Clinical trials represent a critical component in developing effective cancer therapies. Low rates of participation have negatively impacted progress in sarcoma trials. This survey study evaluated patients' attitudes, knowledge, self-efficacy for

decision-making, receptivity, general willingness to participate in trials, and perceptions related to molecular profiling (MP) of tumors.

Methods: IRB approval was obtained. Patients with sarcoma who were evaluated at an academic medical center between 2007 and 2017 were identified through the Enterprise Data Warehouse. A link to an online self-administered survey was emailed to patients. Data were analyzed using Spearman correlations and the Mann-Whitney test.

Results: Surveys were emailed to 750 patients of which 311 patients opened and 206 patients completed a portion of the survey (27.5% of total and 66.2% of opened surveys). Of the 206 patients, median age was 52 years, 57.8% were female, and 24.8% reported metastatic disease. Greater knowledge of trials correlated with increased positive attitudes toward trial participation ($p < 0.001$) and positive attitudes correlated with greater trial self-efficacy ($p < 0.001$). Patients with metastatic disease had more positive attitudes compared with nonmetastatic ($p = 0.033$). Trial enrollment was associated with greater knowledge ($p = 0.002$) and positive attitudes ($p < 0.001$). Among patients who reported knowledge of tumor MP ($n = 46$), 30.4% credit MP with a > 50% chance of isolating a targetable result, and 71.7% assume if an experimental treatment was found based on these results, there is a > 50% likelihood of it being effective. Better attitudes and higher self-efficacy were associated with expectations of lower likelihood of developing side effects from an experimental therapy ($p = 0.0096$; $p = 0.0184$). Of patients who had MP performed ($n = 18$), the most important consideration for this test was its ability to improve their survival and quality of life.

Conclusions: Improving knowledge of trials among sarcoma patients may lead to more positive attitudes and greater self-efficacy regarding trial enrollment. Sarcoma patients tend to overestimate the potential benefit of MP; thus, setting expectations with regards to potential benefit of MP is critically important.

Legal entity responsible for the study: Northwestern University.

Funding: Northwestern University.

Disclosure: All authors have declared no conflicts of interest.

1637P Pneumothorax is a novel sensitivity biomarker for targeting VEGFR2 in lung metastatic sarcoma

Q. Bao[1], Y. Shen[2], W. Zhang[2]

[1]Bone Sarcoma, Shanghai Ruijin Hospital, Shanghai Jiao Tong University, College of Medicine, Shanghai, China, [2]Oncological Orthopaedics, Ruijin Hospital, Shanghai, China

Background: The prognosis of metastatic bone and soft-tissue sarcoma remain distal. VEGFR2 inhibitor (VEGFR2i) has been recently found promising but is limited due to the heterogeneous durability of response.

Methods: From Jan 2016 to Jun 2018, 44 patients with lung metastatic sarcoma, including 32 osteosarcoma, 4 Ewing sarcoma, 3 leiomyosarcoma, 2 chondrosarcoma and 3 other sarcoma, given apatinib treatment were reviewed. Of these patients, extra-pulmonary lesions were noticed in 14 cases including local recurrence (9), bone (3), lymph node (2) and brain (1). A starting 250∼500 mg per day was chosen, with dose adjustment according to the individual tolerability. Progression-free survival (PFS) was accessed by RECIST 1.1 criteria and used to discover the potential predictor of durability of response.

Results: The mean 6 month PFS was 58.9 +/- 8.4%, with the duration of response varying from 1 months to no less than 17 months. 12 of the 44 (27.3%) patients required a long-term dose lowering while the remaining well tolerated or has a dose transient lowering less than 7 days. Adverse effects (AEs) greater than degree 2 was seen in 50.0%, including pneumothorax in 11 cases (25.0%). In 9 of 11 cases with pneumothorax, no or minimal drug discontinuance was conducted, with 5 spontaneous recoveries, 3 recoveries with tube drainage, and 1 thoracic empyema with video-assisted thoracoscopic debridement. Multivariate analysis showed that AEs ($HR = 0.29$ $p = 0.008$) and sarcoma type (osteosarcoma vs other, $HR = 0.17$, $p = 0.001$) were the independent predictors for PFS with VEGFR2i therapy. Surprisingly, pneumothorax was found to be the strongest predictor among all AEs based on the effect size ($HR = 0.29$, $p = 0.036$), indicating that the susceptibility of pneumothorax to VEGFR2i might be a new mechanism-based toxicity biomarker for lung metastatic osteosarcoma.

Conclusions: Our result suggested that pneumothorax is a favorable biomarker for targeting VEGFR2 in lung metastatic sarcoma and we encourage no or minimal drug discontinuation in this circumstance.

Legal entity responsible for the study: Ruijin Hospital, Oncological Orthopaedic Department.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1638P Do Royal Marsden Hospital (RMH) and MD Anderson Cancer Center (MDACC) prognostic scoring systems predict survival in patients with bone sarcoma?

W. Alselwi[1], F. Azam[1], M.F. Latif[1], I.A.E-H. Osman[2], W.A.H. Taha[2], K. Bawazir[2], A. Farooq[3], N. Bukhari[2], F. Ibnshamsah[2]

[1]Medical Oncology, King Fahad Specialist Hospital, Dammam, Saudi Arabia, [2]Adult Medical Oncology, King Fahad Specialist Hospital, Dammam, Saudi Arabia, [3]Internal Medicine, East Lancashire Hospitals NHS Trust, Burnley, UK

Background: There is no specific prognostic scoring system for patients with bone sarcomas. Royal Marsden Hospital (RMH) and MD Anderson Cancer Center (MDACC) prognostic scoring systems are used for prognostic classification of different malignancies. The purpose of this study is to evaluate different clinical factors and their correlation with poor survival in bone sarcomas.

Methods: We retrospectively reviewed clinical files of patients (pts) diagnosed with bone sarcoma at the tertiary Oncology Centre between January 2006 and June 2017. Clinical factors including Serum albumin, serum lactate dehydrogenase (LDH), performance status (PS), number of metastases, (in RMH and MDACC scoring systems), platelet count, hemoglobin (HB), serum creatinine and gender were also evaluated. Data was analyzed using SPSS software.

Results: Total of 87 pts with bone sarcoma were identified of which 33 (38%) pts died. Twenty (61%) pts were males and 13 (39%) pts were females. Median age at the time of diagnosis was 23 (12-83) years. Median overall survival (OS) for the whole group was 12 (1-76) months (mo). Pts presented with metastatic disease had a median OS of 11 mo. Median survival of pts with locoregional disease was 19 mo. On univariate analysis, more than 2 sites of metastases was the only factor associated with poor survival ($p = 0.035$). On regression analysis the co-efficient between all the variables and survival time is high ($R = 0.823$) but this is not statistically significant ($p = 0.112$). There was no statistically significant association between poor survival and low serum albumin, high LDH, poor PS, high platelet count, low HB, high serum creatinine and male gender.

Conclusions: Our study concludes that there is a strong correlation between poor survival and more than 2 metastatic sites in patients with bone sarcomas. Other prognostic factors in RMH and MDACC scoring system were not found to be statistically significant in this study. Further studies are needed to validate these clinical factors.

Legal entity responsible for the study: King Fahad Specialist Hospital, Damman.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1639P The study of molecular and genetic markers of apoptosis and proliferation, their role in the treatment and prevention of osteogenic sarcoma

M.N. Tillyashaykhov[1], D.S. Polatova[2], M-A. Gafur-Akhunov[2], K. Abdikarimov[2], U. Islamov[2], R. Davletov[2]

[1]Urology, National Research Center of Oncology and Radiology, Tashkent, Uzbekistan, [2]Bone and Soft Tissue Sarcomas, National Research Center of Oncology and Radiology, Tashkent, Uzbekistan

Background: The prognostic value of proliferative and apoptotic activity of tumors in patients with osteogenic sarcoma was investigated in order to determine which genes are involved in their pathogenesis and prognosis.

Methods: Immunohistochemical methods (IHC) were used to study the expression of p53, bcl-2, Ki-67 in patients with osteogenic sarcoma in comparison with the effectiveness of treatment. Patients with positive results of chemotherapy (group 1) underwent radiotherapy for a radical program in the total focal dose up to 60-70 Gy. When receiving a good effect from radiation therapy (group 2), patients received another 4-5 courses of chemotherapy. Surgical treatment was performed in 36 patients (41.9%) with a large pulpy component of the tumor and with ineffective chemotherapy or chemoradiotherapy (group 3).

Results: In group 1 patients, who received chemotherapy, the full effect was observed only in patients with negative and weakly positive IHC reactions to the p53 (18%), Ki-67 (16%) and bcl-2 (10%). For partial effect, the phenotype of tumor cells was as follows: negative and weakly positive IHC reaction to the mutant p53 gene was seen in 52% of patients, in Ki-67 - in 62%, and bcl-2 - in 48%. In 6% of patients in this group, the effect of therapy was negative. In the second group, only 10% of the patients had a full effect of the therapy, while in all patients, the tumor cells were mutant p53 negative, 5% had average Ki-67 and bcl2, and 5% were Ki-67 and bcl-2 negative. 25% of patients in this group had partial effects. In 20% of patients in this group, absence or weak expression of mutant p53 gene was detected in tumor cells, expression of Ki67 and bcl 2 genes in 15% was average, the remaining patients were with Ki-67 and bcl-2 negative. In group 3, 56% of patients had positive effect with therapy, among them, those with weak or no, expression of mutant gene p53 were 75% and only 12.5% showed moderate expression of this protein.

Conclusions: Our findings suggest that the study of the expression of the mutated p53 suppressor gene is a more informative prognostic factor in osteogenic sarcoma and contributes to an understanding of the mechanisms of cancer, development of new

diagnostic methods and pathogenetically valid approaches to the therapy of osteogenic sarcoma.

Legal entity responsible for the study: Ministry of Health of Republic of Uzbekistan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1640P Outcome of treatment in giant cell tumors of bones: A single institutional retrospective review

M.A. Elshenawy[1], A.A. Badran[2], M.A. Memon[3], A.M. Elshentenawy[4], T. Elhassan[3]

[1]Oncology, Faculty of Medicine - Menoufia University, Shebin El Kom, Egypt, [2]Oncology, Ain Shams University Hospital, Cairo, Egypt, [3]Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [4]Oncology, Cairo University, Cairo, Egypt

Background: Giant cell tumor of bone (GCTB) is a locally aggressive tumor with 3% incidence of pulmonary metastasis. The standard treatment of GCTB had been surgery until denosumab was approved for these tumors.

Methods: Patients diagnosed to have GCTB in King Faisal Specialist Hospital and Research center, Riyadh, Saudi Arabia were eligible. The aim of this study was to evaluate the clinical outcome of GCTB in our institution in the era before and after denosumab.

Results: We identified 42 patients treated in the period between May 2008 and November 2017. Median follow-up time was 57 months. Median age was 31 years. Twenty-Six (62%) patients were females and 16 (38%) were males. Primary tumor was located in upper limb in 21 (50%) patients - mostly in humerus and radius, in lower limb in 17(43%) patients, and in pelvis/axial skeleton/ribs 3(7%) patients. Thirty patients (71%) had >10 cm. Thirteen patients received neoadjuvant denosumab (median number of cycles 9), all had clinical benefit from therapy.41(98%) had surgery, 27 (64%) patients had enbolic resection and 14 (33%) had intralesional curettage. Fourteen patients (33%) had post-surgical relapse [3(7%) received neoadjuvant denosumab],6(14%) patients with local recurrence and 8(19%) patients with lung metastasis. Denosumab was given to those with metastatic disease (median number of cycles 5). One patient had complete response,2 patients had partial response,3 patients had stable disease and1 patient had progressive disease. Treatment was well tolerated with no incidence of nephrotoxicity, hypocalcemia or osteonecrosis of the jaw.Median recurrence free survival was not reached.

Conclusions: Denosumab is efficient and tolerable in unresectable/metastatic disease as well as in a neoadjuvant setting in locally advanced tumors to facilitate complete surgical resection or avoid mutilating surgery. The risk of recurrences after curettage of GCTB following denosumab raises questions about the optimal management of such cases. Due to rarity of this tumor,larger multicenteric trials should be initiated to clarify the optimal treatment option .

Legal entity responsible for the study: Mahmoud Elshenawy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1641P Adriamycin and ifosfamide-based regimen as induction chemotherapy in desmoplastic small round cell tumors: Results of a retrospective single-center study on 34 patients

T.S. Assi[1], A. Le Cesne[1], E. Nassif[1], A. Cavalcanti[2], M. Faron[2], T. Ibrahim[1], C. Le Pechoux[3], O. Mir[1], J. Adam[4], S. Dumont[1], P. Terrier[4], C. Honore[2]

[1]Medical Oncology, Gustave Roussy Institut de Cancérologie, Villejuif, France, [2]Surgery Department, Institut Gustave Roussy, Villejuif, France, [3]Radiation Oncology Department, Institut Gustave Roussy, Villejuif, France, [4]Pathology Department, Gustave Roussy, Villejuif, France

Background: Desmoplastic small round cell tumours (DSRCT) is a rare disease affecting predominantly children and young adults characterised by a specific translocation t(11:22)(p13;q12) which fuses the ESWR1 gene to the WT1 gene. DSRCT shares characteristics with other small-round blue cell cancers including Ewing's sarcoma. . The best induction chemotherapy (IC) is not yet defined. The aim of this study is to evaluate the role of Adriamycin and Ifosfamide (AI)-based regimen as IC in DSRCT.

Methods: All pts diagnosed in our tertiary care center with DSRCT treated with AI-based regimen as IC between 1991 and 2017 were included in this study. Demographic, clinical and long-term characteristics were obtained from the electronic medical records and retrospectively analyzed.

Results: 34 pts were identified. With a median age of 25 yrs (range 18-56), 25 pts were male (74%). All pts had PS 0-1. 28 pts had symptoms (82%) with pain being the most common (n = 25). 14 pts (41%) had extra-peritoneal metastases (EPM) at diagnosis (liver mets (n = 14) associated with lung mets in 4 pts). Out of 34 pts, 26 pts (77%) received AI as IC. The remaining 8 pts had AI in combination to platinum agents (n = 4) or Etoposide (n = 4). Median number of cycles was 6 ± 1 (range 3-9). Objective response and disease control rates were 71% and 91% respectively. Only 3 pts had progressive disease (PD) (9%). Dose reduction were noted in 2 pts with no treatment discontinuation. 41% had grade 3-4 toxicities. 7 pts (21%) developed febrile neutropenia. 17 pts (50%) underwent surgery (including 2 with EPM). Post-operative chemotherapy was given in 41 pts and radiotherapy in 21 pts. In pts who had surgery, local recurrence free survival was 10 months (95% CI: 7-12) while EPM-free survival was 13 months (95% CI: 7-19). Overall survival (OS) for pts without PD was 25.7 months (95% CI: 20.1-31.3). In pts who had surgery, OS was 28.3 months (95% CI: 13.6-43.1) while those who did not have surgery had an OS of 18.9 months (95% CI: 11.6-26.1).

Conclusions: AI-based regimen is a well-tolerated and active option with good response rate as an IC in DSRCT. Comparative data with currently used Ewing-type regimen are eagerly needed in the future.

Legal entity responsible for the study: Institut Gustave Roussy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1642P Determination of biological behavior of solitary fibrous tumors

L. Krsková[1], M. Kalinova[2], I. Odintsov[2], P. Galgonková[2], R. Kodet[1]

[1]Department of Pathology and Molecular Medicine, 2nd Faculty of Medicine, Motol University Hospital, Prague, Czech Republic, [2]Department of Pathology and Molecular Medicine, Motol University Hospital, Prague, Czech Republic

Background: Solitary fibrous tumor (SFT) is an uncommon neoplasm of pleural and extrapleural site of origin formed by cells with fibroblastic features. This tumor exhibits a spectrum of biological behavior and can occur at any age with the peak in the sixth and seventh decade of life. Most of these tumors grow slowly and their clinical behavior is mostly benign; however, up to 20 % of patients develop local recurrences and/or distant metastases.

Methods: We performed a retrospective study of 54 cases of SFTs. We investigated morphologic characteristics, proliferation activity evaluated using Ki-67 immunostain and existence of NAB2-STAT6 fusion gene together with Ki-67, TPX2, and hTERT mRNA expression levels. The aim was to define relationships between proliferation activity and biological potential and progression of the disease. Recently, several alterations within the TERT gene have been detected in human tumors. The most frequent alteration in the TERT gene, somatic promoter mutation, has been described. We measured Ki-67, TPX2, and hTERT mRNA levels using quantitative real-time reverse transcription PCR (RQ-RT-PCR). Determination of hot spot promoter mutation in TERT was analyzed.

Results: NAB2-STAT6 fusion transcript was found in 46/54 cases (85%) of amplifiable samples. The mRNA expression of Ki-67 correlated with local recurrences ($p = 0.025$) and biological behavior of the tumor ($p = 0.0027$), but did not correlate with the type of the NAB2/STAT6 fusion (0.24). The level of Ki-67 mRNA correlated with IHC established results ($p = 0.02$). The TPX2 mRNA expression did not correlate with local recurrences ($p = 0.26$) nor with biological behavior of the tumor ($p = 0.062$). The mRNA hTERT expression correlated well with biological behavior of the tumor ($p < 0.0001$). The majority of SFTs with benign behavior were without detectable expression of hTERT mRNA. A majority of the patients with hTERT expression had also somatic promoter mutation C228T or less frequently C250T. We observed a significant association between increased Ki-67 and hTERT mRNA levels and the SFTs with malignant potential.

Conclusions: Detection of hTERT mRNA expression and its promoter mutation at routine practice might lead to a better estimation of a biological potential of SFTs.

Legal entity responsible for the study: Ministry of Health, Czech Republic.

Funding: Supported by the Project (Ministry of Health, Czech Republic) for conceptual development of research organization 00064203 (University Hospital Motol, Prague, Czech Republic).

Disclosure: All authors have declared no conflicts of interest.

1643P Pazopanib in advanced or metastatic synovial sarcoma: The Gustave Roussy experience

M. Sroussi[1], S. De Percin[1], A.M. Grecea[1], M.A. Benderra[1], M. Velev[1], S. Akla[1], N. Lezghed[1], S. Dumont[1], C. Le Péchoux[2], C. Honore[3], L. Haddag[4], M. Faron[3], P. Terrier[5], O. Mir[1], A. Le Cesne[1]

[1]Medical Oncology Department, Institut Gustave Roussy, Villejuif, France, [2]Radiation Oncology Department, Institut Gustave Roussy, Villejuif, France, [3]Surgery Department, Institut Gustave Roussy, Villejuif, France, [4]Radiology Department, Institut Gustave Roussy, Villejuif, France, [5]Pathology Department, Institut Gustave Roussy, Villejuif, France

Background: Synovial sarcoma (SS) is a rare malignancy usually considered as sensitive to chemotherapy (CT) based on anthracyclins and ifosfamide. Therapeutic options are limited and prognosis of advanced or metastatic SS (a/mSS) remains dismal. Since approval of pazopanib in advanced soft tissue sarcomas (STS), very few data were reported on the activity of pazopanib in a/mSS.

Methods: We retrospectively reviewed all patients (pts) treated with pazopanib for a/mSS in our institution. The histological diagnosis was confirmed by a referral pathologist within the French Sarcoma Group. Data were obtained from medical records. Radiological response was assessed by CT-scan according to RECIST 1.1. Adverse events were graded according to the Common Terminology Criteria for Adverse Events

of the National Cancer Institute 4.03. The aim of this study was to evaluate the activity of pazopanib in a/mSS.

Results: From December 2006 to April 2018, 16 pts with a/mSS of extremities (10 pts), trunk (5 pts) or head and neck region (1 patient) were treated with pazopanib from 400 mg to 800 mg daily dose. Median age was 40 years old (range: 24-69). Pts received a median of 2 prior lines of doxorubicin-based CT in all but one case. Thirty-one per cent of pts received pazopanib in 2nd line therapy and 69% in subsequent lines. Before treatment, 15 pts (94%) had distant metastases (lung in 94%, bone in 25%, associated with local recurrence in 20%) and 1 patient (6%) had unresectable local recurrence. A clinical benefit was observed in 87.5% of pts: 7 (43%) experienced a partial response and 7 (43%) a stable disease. Two pts progressed rapidly during treatment. Two pts definitively interrupted pazopanib due to grade 3 sepsis or hemoptysia. The dose was reduced for 2 pts due to diarrhea and hematuria. On April 2018, 6 patients were still on treatment. The median progression free survival (mPFS) was 6.5 months (1-17+). After a median follow-up of 8.5 months, the median overall survival was not reached.

Conclusions: Pazopanib showed significant clinical activity in a/mSS along with manageable toxicity profile. We observed a prolonged mPFS compared with other subtypes of STS. These results need to be confirmed in prospective trials dedicated to this histological subtype of STS.

Legal entity responsible for the study: Institut Gustave Roussy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1644P Identification of effective drug combinations with regorafenib (REG) for the treatment of pediatric rhabdomyosarcomas (RMS)

D. Zopf[1], Y. Tsvetkova[1], J. Hoffmann[2]

[1]Drug Discovery, Oncology, Bayer AG, Berlin, Germany,[2]Experimental Pharmacology & Oncology, EPO Berlin-Buch GmbH, Berlin, Germany

Background: REG is a small-molecule multikinase inhibitor involved in normal cellular functions and pathologic processes such as oncogenesis, angiogenesis, and tumor immunity. REG is approved for the treatment of advanced colorectal cancer, gastrointestinal stromal tumors, and hepatocellular carcinoma. REG alone is currently being evaluated for its tolerability and safety in pediatric cancers in a clinical phase 1 study. Preclinically, we investigated a series of drugs, which are established or emerging for the treatment of pediatric patients with RMS, for their combination potential with REG to support its clinical development in pediatric indications.

Methods: Proliferation assays were performed in vitro. In vivo, subcutaneous xenografts derived from pediatric alveolar (RH30) and embryonal (RD) RMS tumor cell lines were treated with REG alone and in combination with 13 different compounds including a combination with irinotecan (IRI) and vincristine (VINC). A study design with one mouse per group and a stepwise dose escalation was applied. The body weight of the mice was closely monitored for tolerability and the tumor growth was determined by caliper measurements. Treatment was for four weeks and the time to tumor regression was followed thereafter.

Results: The pattern of response was heterogeneous, ranging from complete regression (CR) to insensitivity. REG alone at an oral dose of 10mg/kg/d delayed the growth of both RMS xenografts. CRs were observed for IRI (both models), paclitaxel (RH30 model), and VINC (RD model) alone near their maximum tolerated doses in mice. The strong monotherapy effects of IRI and VINC preclude a clear demonstration of a combination benefit with REG in this study. Beneficial combination effects were observed for some other drugs. IRI appeared as the most favorable combination partner of REG of the tested drugs. Surprisingly, the RH30 model was insensitive to VINC in this study. Treatment interruptions were required in some cases of treatment intolerability, but no drug-related deaths were observed.

Conclusions: These results warrant further exploration of a combination of REG with IRI and VINC in pediatric RMS.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: D. Zopf, Y. Tsvetkova: Full-time employment: Bayer AG. J. Hoffmann: CEO and shareholder: EPO GmbH.

1645P KS in the era of HAART: A single institutional retrospective review

K. Sankar[1], K. Foster[2], C. Achenbach[1], M. Agulnik[2]

[1]Medicine, Northwestern University, Chicago, IL, USA, [2]Hematology/Oncology, Northwestern University, Chicago, IL, USA

Background: Kaposi's Sarcoma (KS) is an angioproliferative tumor with 4 sub-types: classic (CKS), endemic, immunosuppression related, and epidemic (AIDS-KS). AIDS-KS prevalence has decreased since the introduction of highly active anti-retroviral therapy (HAART). KS lesions develop in patients (pts) with undetectable viral loads and high CD4 counts. KS is variable across subtypes, disease course, and clinical outcomes. Treatments are individualized.

Methods: IRB approval was obtained. A retrospective cohort was identified of KS pts evaluated and treated between 2005 and 2017 at the Lurie Cancer Center, Northwestern University. Pts were identified through the Enterprise Data Warehouse. Pt data was reviewed for demographics, clinical and pathological features and therapy. Descriptive statistics were used to assess disease severity and treatment.

Results: 130 pts with a diagnosis of KS were identified, of which 95 (73.1%) had AIDS-KS and 31 (23.8%) had CKS. There were 4 patients with immunosuppression therapy-related KS and no endemic cases. Males represented 91.5% of cases. The mean age at diagnosis was 66.8 years ± 14.4 among CKS pts and 42.1 years ± 9.6 in AIDS-KS pts. 18.9% of AIDS-KS pts had metastatic disease vs. 6.5% in the CKS group. At KS diagnosis, 50.5% of AIDS-KS pts had CD4 count >200 cells/mm3 and 33.7% had HIV viral load level < =20 copies/mL. Among the 53 pts who received chemotherapy, 45 were AIDS-KS pts (84.9%). 65% of pts with metastatic disease (lung or GI involvement) at diagnosis, of which 90% had AIDS-KS, received chemotherapy vs 36.3% of pts with skin/mucosa involvement. The most commonly used chemotherapy was liposomal doxorubicin (78.4%) with an average of 10 cycles. Other chemotherapy utilized includes paclitaxel and interferon. 16 pts (12.3%) died, of which only two died of disseminated AIDS-KS.

Conclusions: Our retrospective study confirms that 3/4 of pts diagnosed with KS have AIDS-KS. Despite introduction of HAART and the well-controlled nature HIV/AIDS, KS continues to develop. AIDS-KS pts are younger, more likely to have metastatic disease and more frequently require chemotherapy. Poorly controlled HIV still portends a worse outcome in AIDS-KS. Further investigations are required to better understand the etiology of AIDS-KS in pts with undetectable HIV viral loads.

Legal entity responsible for the study: Northwestern University.

Funding: Lurie Cancer Center.

Disclosure: All authors have declared no conflicts of interest.

1646P Carcinosarcoma: Clinical and epidemiological patterns in the United States

M.A. Gouda

Department of Clinical Oncology, Faculty of Medicine - Menoufia University, Shebin El Kom, Menoufia Governorate, Egypt

Background: Carcinosarcomas are rare tumors that comprise microscopic features of both epithelial tumors (carcinomas) and connective tissue tumors (sarcomas). Data about carcinosarcoma are relatively scarce. In this study, data about carcinosarcoma in the SEER's database were explored and further analyzed and summarized. SEER incorporates clinical and epidemiological data from 18 cancer registries all over the United States and presented data can be extrapolated to generate evidence on this rarely occurring tumor.

Methods: SEER*Stat Version 8.3.5 was used to obtain data from the SEER 18 Regs Nov 2017 Submission database. Cases diagnosed between 2000-2015 with carcinosarcoma (ICD-O-3 8980/3, 8981/3) were included. Both SEER*Stat and SPSS were used for further data analysis.

Results: A total of 8365 patients were diagnosed with carcinosarcoma between 2000 and 2015, with a median age of 68. The disease occurred predominantly in females (n = 7578; 90.6%) and was more common in white race (n = 6231; 74.5%). Incidence rate was 6.2 per million (CI: 6.1-6.3) with a significant increase of incidence over time (annual percent change = 6.1%) The most common sites for occurrence were the corpus uteri (n = 4656; 55.7%) and ovary (n = 1100; 13.2%) followed by other part of the female genital system (n = 886; 10.6%). The disease was the only primary tumor in 5969 (71.4%) of cases, and the first of 2 or more primaries in 493 patients (8.3%). It occurred as a second or later multiple primary in the remaining percentage of patients (n = 1903; 22.7%). Median survival was 20.5 months, with 5-years and 10-years observed survival being 30.6% (CI: 29.3-31.9%) and 22.4% (CI: 21-23.8%) respectively. Relative survival at 5 years and 10 years was 34.5% (CI: 33.1-36%) and 29.5% (CI: 27.7-31.3%) respectively.

Conclusions: Carcinosarcoma is a rare tumor that occurs with an incidence rate of 6.2 per million. It is predominantly a disease of females who represents 90.6% of cases with female genital system being the main site of occurrence. The disease occurred as a second (or later) primary in 22.7% of patients. It has a median survival of 20.5 months and a relative 5-years survival of 34.5%.

Legal entity responsible for the study: Mohamed Alaa Gouda.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1647P First-line treatment of desmoid tumor: Systemic therapy versus upfront surgery

J.C.E.S.O.D. Souza, H.M. Lourenço, G. Mendes

Oncology Department, INCA - Instituto Nacional de Cancer, Rio de Janeiro, Brazil

Background: Desmoid tumor (DT) is a rare and locally invasive proliferative disease. The standard first-line treatment used to be radical surgical resection. However, during recent years it has been debated whether to offer an aggressive and morbidity treatment to a potentially indolent tumor. Desmoid tumor has uncertain behavior, some are aggressive cases, others indolent and there are some reports of spontaneous involution.

Nowadays, the guidelines suggest to watch and wait before offering an aggressive treatment, and avoiding the surgical treatment. But in our experience patients had less morbidity and disease progression with a surgical approach.

Methods: Patients with histological diagnosis of DT and treated at INCA between January 1998 and December 2015 were identified and their medical records were analyzed.

Results: Of 191 patients evaluated, there were 137 females (71.2%). The median age at diagnosis was 34 years (range:17.79-76.96y). Tumor locations were: thoracoabdominal wall (n = 100, 52.3%), extremities (n = 53,27.7%), abdominal cavity (n = 26; 13.6%), and head and neck (n = 12, 6.2%). Tumor sizes were documented in 152 cases (79.5%) and ranged from 1 cm to 37 cm (median, 10 cm). Twenty-seven pts (14.1%) received systemic therapy (ST) (n = 5 vinblastine and methotrexate; n = 22 tamoxifen) and 164 pts (85.8%) were submitted to surgery (4pts received adjuvant tamoxifen) as first-line treatment. There was no difference between gender (p = 0.86), tumor location (p = 0.30), or tumor size (p = 0.53) when choosing first-line treatment. The odds of severe morbidity were 2.13 higher with ST than with upfront surgery. Four pts were submitted to surgery after systemic first-line treatment. After a median follow-up of 71 months, there was significantly more disease progression in the ST group (17pts – 62.9%) than in the surgery group (55 pts – 33.5%) (p = 0.005), and they received more subsequent treatment (p = 0,01). There were 2 deaths in the ST group and 9 deaths in the surgery group, with 10-year survival of 93.2% and 92%, respectively.

Conclusions: DT is an indolent disease but has the propensity for locally invasive growth and recurrence. Although ST is a less aggressive treatment, it was associated with higher severe morbidity, more disease progression, and more subsequent treatment in this trial.

Legal entity responsible for the study: INCA.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1648P Adult rhabdomyosarcoma in Tunisia: Clinical presentation, treatment and outcome

M. Saadi[1], D. Tajina[1], F. Letaief-Ksontini[1], K. Meddeb[1], A. Gabsi[2], Y. Yahyaoui[1], A. Mokrani[1], M. Ayadi[1], N. Chraiet[1], H. Rais[1], A. Mezlini[1]

[1]Medical Oncology, Salah Azaiez Institute, Tunis, Tunisia, [2]Medecine, Salah Azaiez Institute, Tunis, Tunisia

Background: We aimed to describe clinico-pathological features and outcomes of Rahbdomyosarcoma (RMS) in Tunisia.

Methods: We assembled a retrospective cohort of 47 patients aged 18 or older diagnosed with, and treated for RMS at our institute between 1994 and 2013. Patient's characteristics, tumor variables and treatment outcomes were evaluated. Tumors were classified according to the Intergroup RMS Study (IRS) staging.

Results: Median age was 39 and 66% were male. At presentation, 33 had localised disease and 14 metastatic. Metastasis site was lung in 17% of cases. Sixteen patients had node positive disease. Median tumor size was 9 cm. Patients presented with swelling or palpable mass in 63.8% of cases, pain in 17%, exophthalmia in 6.4% and bleeding in 4.3%. Less common clinical presentations were functional impairment, cranial nerve palsies, superior vena cava syndrome and nasal obstruction seen in one case each. Tumor site was extremities in 40.4% of cases, trunk in 23.4%, head and neck in 19.1% and genito-urinary tract in 17%. According to favorable/unfavorable prognostic location, tumor site was unfavorable in 65.9% of cases and favorable in 33.9%. RMS histologic subtype was pleomorphic in 36.2% of patients, embryonic in 25.5%, not mentioned in 23.4%, alveolar in 12.8% and combination of embryonic and alveolar in 2.1%. Among 38 patients who underwent surgery, 40.4% had complete resection (IRS stage I). Chemotherapy was adjuvant in 4 patients, neoadjuvant in 6 and 1st line in 13 with a median number of cycle of 3 in each schedule. Radiotherapy (RT) was adjuvant in 19.1% of cases and symptomatic/palliative in 21.1%. Median dose of adjuvant RT was 55 Gray. Median progression free survival after adjuvant treatment was 4.5 months, 47.1% relapsed locally, 35.3% developed distant metastasis and 17.6% presented local recurrence with distant metastases. Five year overall survival (OS) was 46% for localised RMS and 40% for metastatic disease. Among all studied factors, non operated patients and those under 30 years old had worse OS with p values of 0.005 and 0 respectively.

Conclusions: Adults with RMS have poor prognosis. All patients should therefore undergo multimodality treatment comprising of surgery, radiation, and chemotherapy to achieve better outcomes.

Legal entity responsible for the study: Amel Mezlini.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1649P A pan-cancer landscape analysis reveals a subset of endometrial stromal and pediatric tumors defined by internal tandem duplications of BCOR

L. Juckett[1], D.I. Lin[2], R. Madison[1], C. Patriquin[1], G.M. Frampton[3], V.A. Miller[3], J.S. Ross[3], J. Chung[3], A.B. Schrock[3], S.M. Ali[3], J.A. Elvin[3]

[1]Clinical Bioinformatics Operations, Foundation Medicine, Cambridge, MA, USA, [2]Pathology, Beth Israel Deaconess, Boston, MA, USA, [3]Genetics, Foundation Medicine, Inc., Cambridge, MA, USA

Background: Internal tandem duplications of BCOR (ITD) have been previously observed in pediatric cancers including clear cell sarcoma of the kidney, and rare adult tumors, most recently, in four cases of endometrial stromal sarcoma (ESS) identified by Sanger sequencing (Chiang, 2017; Mariño-Enriquez, 2018). We reviewed the genomic profiles of a large series of advanced cancer patients to identify all cases and diseases harboring BCOR-ITD.

Methods: Tissues from on 140,411 unique advanced cancers were sequenced by hybrid-capture-NGS based comprehensive genomic profiling of 186 to 315 genes plus introns from 14 to 28 genes commonly rearranged in cancer, as well as RNA for 265 genes for a portion of these cases.

Results: BCOR-ITDs were present in 0.024% of all cases (33/140,411), most frequently in sarcomas 63.6% (21/33) either of uterine origin 52.4% (11/21) or in children (non-uterine) 42.8% (9/21). Of the uterine cases, mean age was 42.2 years (range 14-59 years) and referring diagnoses: ESS (6/11), uterine sarcoma (NOS) (2/11), uterine leiomysarcoma (2/11), and undifferentiated uterine sarcoma (1/11). Expert gynecologic pathology central review identified all these cases as having a similar high-grade morphology consistent with ESS, and 90% of cases having a round cell component. The average age of the pediatric sarcoma patients was 3.33 years (range 1-11 years), and most commonly diagnosed as soft tissue sarcoma (NOS) (4/9) and fibrosarcoma (2/9). Cases carrying a BCOR-ITD had a mean Tumor Mutation Burden of 4.12 mut/MB (range 0.8-25.45). The identified BCOR-ITDs occurred most frequently in exon 15, 69.7% (23/33). These exon 15 events had a mean insertion length of 31.7 codons (range 30-38 codons). Of the uterine sarcoma cases harboring exon 15 BCOR-ITDs none simultaneously carried gene fusions typically associated with ESS.

Conclusions: BCOR-ITDs define a rare subset of pediatric and clinically aggressive endometrial stromal sarcoma cases, as defined by NGS for the first time. Our findings along with previous work delineate the pan-cancer landscape of this alteration and suggest the need for focused investigation to delineate the pro-oncogenic function of BCOR, along with any sensitivity to targeted therapies.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: L. Juckett, R. Madison, C. Patriquin, G.M. Frampton, V.A. Miller, J.S. Ross, J. Chung, A.B. Schrock, S.M. Ali, J.A. Elvin: Employee: Foundation Medicine, Inc.; Equity interest: Foundation Medicine, Inc. All other authors have declared no conflicts of interest.

1650P The efficacy of eribulin for patients with taxane-resistant cutaneous angiosarcoma: Interim result of multi-center, prospective observational study

Y. Fujisawa[1], K. Yoshino[2], T. Fujimura[3], S. Matsushita[4], H. Uchi[5], Y. Yamamoto[6], H. Hata[7], A. Otsuka[8], T. Miyagi[9], M. Ishii[10], T. Funakoshi[10]

[1]Dermatology, University of Tsukuba, Tsukuba, Japan, [2]Dermatology, Tokyo Metropolitan Cancer Center, Tokyo, Japan, [3]Dermatology, Tohoku University, Graduate School of Medicine, Sendai, Japan, [4]Dermato-Oncology/Dermatology, Kagoshima University, Kagoshima, Japan, [5]Dermatology, University of Kyushu, Hakata, Japan, [6]Dermatology, Wakayama Medical University, Wakayama, Japan, [7]Dermatology, University of Hokkaido, Sapporo, Japan, [8]Dermatology, Kyoto University-Graduate School of Medicine, Kyoto, Japan, [9]Dermatology, University of Ryukyu, Naha, Japan, [10]Dermatology, Keio University School of Medicine, Shinjyuku, Japan

Background: Taxanes (TAX) are the current first-line treatment for advanced cutaneous angiosarcoma (CAS). On the other hand, eribulin (ERB) is a nontaxane microtubule inhibitor approved for treatment of advanced sarcoma in Japan. However, no study has evaluated ERB in CAS patients. We hypothesized that ERB would be well tolerated and active in patients with TAX-resistant CAS because TAX and ERB have different mechanisms of action to inhibit microtubule formation.

Methods: We designed a single-arm, prospective observational study of ERB administered at dose of 1.4 mg/m^2 on days 1 and 8 in every 21 days. TAX-resistant, advanced CAS patients for whom ERB use was planned were enrolled. The primary endpoint is overall survial (OS), and the secondary endpoint, response ratio (RR), progression-free survival (PFS), and toxicity assessment. The estimated median OS in a previous clinical study (ANGIOTAX), in which patients received TAX as the second-line treatment, was 6 months, so we set this number as the threshold and expected a 6-month OS of 70% with ERB treatment. Based on these numbers, the required number of patients to be enrolled was calculated as 31; thus, we set 35 patients as the target number.

Results: At the time of submissiion, 25 CAS patients, median age 74, were enrolled. All had prior TAX exposure. In all but 1 patient the primary tumor was in the head and neck, and 10 patients had a metastatic tumor. The performance status (PS) was generally good: 22 with PS0 or 1. The median follow-up period was 161 (47-464) days. The

respective Kaplan-Meier estimates for OS and PFS rates at 6 months were 70% and 31%. The respective median OS and PFS were not-reached and 94 days. The respective RR at weeks 7, 13, and 25 were 24%, 12% and 11%. No death related to treatment was observed. Although 9 patients experienced >grade 3 toxicity (7, neutropenia; 2, anemia; 1, retroperitoneal abscess), they all recovered.

Conclusions: ERB is a well-tolerated regimen with promising activity in TAX-resistant CAS. The common toxicity is neutropenia, which requires growth factor support. This study is underway and enrollment is expected to be completed in 2018. This study may provide a new treatment option for patients with PTX-resistant CAS.

Clinical trial identification: UMIN000023331.

Legal entity responsible for the study: University of Tsukuba.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1651P Multicenter, open-label phase II study of daily oral regorafenib for chemotherapy-refractory, metastatic and locally advanced angiosarcoma

M. Agulnik[1], B.A. van Tine[2], S. Attia[3], A. Rademaker[4], M. Milhem[5], S.H. Okuno[6]

[1]Hematology/Oncology, Northwestern University, Chicago, IL, USA, [2]Hematology Oncology, Siteman Cancer Center at Barnes-Jewish Hospital and Washington University, St. Louis, MO, USA, [3]Oncology, Mayo Clinic, Jacksonville, FL, USA, [4]Preventive Medicine, Northwestern University, Chicago, IL, USA, [5]Medicine, University of Iowa, Iowa City, IA, USA, [6]Hematology Oncology, Mayo Clinic, Rochester, NY, USA

Background: Angiosarcoma has a particularly poor prognosis with 5 year overall survival rates of approximately 30-40%. Treatment of locally advanced and metastatic angiosarcoma is inadequate. Data strongly suggest concurrent, potent inhibition of VEGFR and Tie2 represents an attractive therapeutic strategy in angiosarcoma. Regorafenib displays potent VEGFR and Tie2 receptor inhibition and also possesses activity against additional potential targets in angiosarcoma including PDGFRs, RAF, KIT and FGFR.

Methods: A multicenter phase II study of regorafenib in patients with locally advanced or metastatic angiosarcoma was conducted through the Midwest Sarcoma Trials Partnership. Adequate performance status, organ function, measurable disease (RECIST 1.1) and 1-4 prior therapies were required. Regorafenib 160 mg PO daily was given in 28 day cylces (21 days on, 7 days off) until disease progression (PD) or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), assessed at 16 weeks. Secondary endpoints include overall response rate (ORR), clinical benefit rate (CBR), OS, and safety and tolerability. A Simon 2-stage design was used.

Results: A total of 18 pts were enrolled at 5 sites, 14 are evaluable for response. Median age was 55.6 (range 21-82); 61% were female; 72% metastatic disease. PFS at 4 months is 46% with a median PFS and OS of 2.7 and 15 months, median follow-up 7.9 months (0.4-23). 1 confirmed CR and PR, 5 SD and 7 PD were observed. ORR and CBR are 14 and 50%, respectively. Common grade 3-4 adverse events were as expected.

Conclusions: Regorafenib was well tolerated in this study of pretreated patients with angiosarcomas. Median PFS and PFS at 4 months are promising. Regorafenib will continue to be explored in this two-stage optimal Simon design, for a total of 31 patients.

Clinical trial identification: NCT02048722.

Legal entity responsible for the study: Northwestern University.

Funding: Bayer HealthCare.

Disclosure: All authors have declared no conflicts of interest.

1652P Outcomes and prognostic factors for angiosarcoma: A 19-year single institution experience

M.E. Chirila[1], D.T. Eniu[2], N. Todor[3], V.M. Nagy[1], M.L. Galatir[4], D. Coza[5], V. Cernea[1], D.L. Martin[1], Z. Fekete[1]

[1]Radiotherapy, Ion Chiricuta Oncology Institute-IOCN, Cluj-Napoca, Romania, [2]Surgery, University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania, [3]Biostatistics, The Oncology Institute "Prof.Dr.Ion Chiricuta" Cluj-Napoca, Cluj-Napoca, Romania, [4]Pathology, The Oncology Institute "Prof.Dr.Ion Chiricuta" Cluj-Napoca, Cluj-Napoca, Romania, [5]Epidemiology, The Oncology Institute "Prof.Dr.Ion Chiricuta" Cluj-Napoca, Cluj-Napoca, Romania

Background: Angiosarcoma is a rare malignancy, and the data about its clinicopathological features and prognostic factors are limited. The purpose of this study was to present a retrospective analysis of angiosarcoma patients treated at a single institution.

Methods: Clinical and pathological features of 41 patients treated in our institution between 1998 and 2016 were analyzed.

Results: Of the 41 patients included, 53.7% were women and 46,3% were men and median age was 60 (16-81). 34.1% cases were located in the soft tissues (ST) of the limbs or trunk, 24.4% in the viscera (V), 19.5% in the breast (B), 14.6% involved the head and neck (HN) and 7.3% in the bone (B). The overall survival (OS) at 5 years was 26% (IC: 15% - 42%), with a median survival of 14.9 months. For the 17.1% patients that were alive at the time of analysis, the median follow up was 60 months (16.1-222.1).The tumor sites for the 7 surivors involved B(4), ST(1), HN(1) and V(1). Radiation induced angiosarcoma was suspected in 17.1% patients. Chronic lymphedema was described/highly probable for 19.5% of the patients. Surgery(S) was performed in 82.9% cases, chemotherapy(CT) in 41.5% cases, and radiation therapy(RT) for 9.8% of cases. CT was more likely to be given to younger patients, but did not improve OS. The pathology report was uncertain for 39% cases at first examination. Superficial tumors (B, ST and HN) had a better OS than deep tumors (V,B) but not statistically significant (31%vs15%). Women had a significant better OS compared to men (36%vs16%, $p = 0.02$). OS at 5 years for patients under age 67 was 30%, and 17% for patients above 67 ($p = 0.07$). Tumor grade was assesed for 85.4% cases. Grade 1(G1) was found in 12.2%, G2 in 36.6% and G3 in 36.6% patients. Patients having G3 tumors had a lower OS, but not statistically significant. Relapse occured at 58.5% of the patients (from 1 to 4 episodes). Of all relapses, 68.3% occured locally, 7.3% regionally, and 48.8% were distant metastases. The most common metastatic sites were lung (7 cases), bone (4), skin (4) and liver (3).

Conclusions: Angiosarcoma is an agressive tumor that was often underrecognized, occuring in various sites. Women with history of radiotherapy or lymphedema are at higher risk, but have a better prognosis. Younger patients and lower grade seem to have a longer survival.

Legal entity responsible for the study: Chirila Monica-Emilia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1653P Management of locoregional recurrence after radical resection of a primary non-metastatic retroperitoneal soft tissue sarcoma: Results of a retrospective series in a tertiary care center

C. Honoré[1], M. Faron[1], O. Mir[2], L. Haddag[3], S. Dumont[4], P. Terrier[5], J. Adam[5], C. Lepéchoux[6], A. Le Cesne[7]

[1]Surgery Department, Institut Gustave Roussy, Villejuif, France, [2]Cancer Medicine, Institut Gustave Roussy, Villejuif, France, [3]Radiology Department, Institut Gustave Roussy, Villejuif, France, [4]Department of Medicine, Institut Gustave Roussy, Villejuif, France, [5]Pathology Department, Institut Gustave Roussy, Villejuif, France, [6]Radiation Therapy, Gustave Roussy - Cancer Campus, Villejuif, France, [7]Department of Medicine, Gustave Roussy, University Paris-Saclay, Villejuif, France

Background: Retroperitoneal soft tissue sarcomas (RPS) are rare tumors. Despite surgery, 5% to 36% of patients experience locoregional recurrence (LR) the optimum treatment of which is still debated. The aim the study of to report our experience in treating LR.

Methods: All 297 consecutive patients operated for a non-metastatic primary RPS between 1994 and 2017 were retrospectively analyzed to identify patients who developed LR. Demographic data, treatment variables and long-term outcome were recorded to calculate disease free survival (DFS), overall survival (OS) and predictive factors of recurrence.

Results: After a median follow-up of 97 months, 55 patients (19%) developed LR. The first site of recurrence was locoregional in 100% with associated peritoneal metastases in 45% and distant metastases in 5%. The median disease free interval (DFI) was 24 months. After recurrence treatment, the 1-, 3- and 5-year OS rates were 71%, 46% and 33%, and 1-, 3- and 5-year DFS rates were 50%, 22%, and 15%. Low tumor grade, DFI above 24 months, exclusive LR and well-differentiated liposarcoma were predictive of better OS and DFS. Despite finding no statistical difference between treatment strategies, median OS was less than 1 month after best supportive care, 44 months after chemotherapy (including patients who underwent subsequent LR radiotherapy or surgery) and was not reached after upfront surgery or radiotherapy. Fourteen patients underwent initial surveillance for low-grade liposarcoma and eventually required treatment in 86% after a median delay of 20 months during which no patient developed distant metastases.

Conclusions: The management of LR in RPS is complex. An initial surveillance may not alter survival in asymptomatic low-grade and slow-growing LR. A LR decision scheme is proposed.

Legal entity responsible for the study: Gustave Roussy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1654P Soft tissue sarcomas (STS) in elder patients: No impact of age on overall survival (OS) in an unselected cohort

J.A. Perez Fidalgo[1], A. Lopez[2], V. Gambardella[3], S. Navarro[4], A. Iranzo[5], N. Diaz Fernandez[2], P. Tolosa[5], A. Silvestre[6], E. Iriarte Moncho[2], M.C. Garcia Mora[7], A. De la Paz[2], J.J. Soler[8], A. Cervantes[9]

[1]Medical Oncology, Hospital Clinico Universitario de Valencia, INCLIVA, CIBERONC, Valencia, Spain, [2]Medical Oncology, Hospital San Juan, Alicante, Spain, [3]Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, Spain, [4]Pathology, Hospital Clinico Universitario de Valencia, Valencia, Spain, [5]Medical Oncology, Hospital Clinico Universitario de Valencia, INCLIVA, Valencia, Spain, [6]Orthopedic Surgery, Hospital Clinico Universitario de Valencia. INCLIVA, CIBERONC, Valencia, Spain, [7]Radiotherapy, Hospital Clinico Universitario de Valencia, Valencia, Spain, [8]Radiology, Hospital Clinico Universitario de Valencia, Valencia, Spain, [9]Medical Oncology, Hospital Clinico Universitario de Valencia, INCLIVA, CIBERONC Spain, Valencia, Spain

Background: A recent analysis of 12 trials in first line showed similar outcomes for elder vs younger patients. Nevertheless these results might be due to a selection bias. The aim of our study was to assess whether elder patients (pts) (>60 years) had the same outcomes than younger (<60 years) in an unselected population of STS stage I-IV.

Methods: A retrospective analysis of pts diagnosed with STS stages I-IV at two institutions between 2000 and 2015 was performed. GIST and other indolent STS such us low-grade stromal sarcoma tumors, cutaneous Kaposi Sarcoma, Desmoid tumors and dermatofibrosarcoma protuberans were excluded. Demographic, clinical and pathological variables were obtained from the medical charts. Overall survival (OS) was calculated according to the date of death by any cause or lost of follow-up.

Results: 115 pts, men/women 59/56 median age of 54.6 years (16.6-82.62) were included. 71 pts (61.7%) were <60 years (younger) and 44 (38.3%) were >60 years (older). Most frequent subtypes were liposarcoma (16.5%), leiomyosarcoma (14.8%) and undifferentiated sarcoma (9,6%). Most frequent sites were lower extremity (27.8%) , retroperitoneum (13.9%) and thorax (13.0%). TNM Stage (or FIGO in endometrial origin) were stage I-II (53%), III (38%) and IV (19%). 98 pts were operated of the primary tumor (Resection was R0 in 53, R1 in 30 and R2 in 4, in 11 data was missed). 37 pts (32.2%) received anthracyclines in any line (31 in younger and 6 in older pts). 68 pts (59.1%) had a local or systemic relapse. 53 pts died (46.1%). There were no differences by age group on stage, grade and radicality of surgery (chi squares $p = 0.52$, 0.48 and 0.47 respectively). Nevertheless elder patients were less likely to receive anthracycline-based therapy (RR 0.33 95%IC 0.16-0.72, $p = 0.001$). Grade and stage were significant prognostic factors for OS: median OS 104.4 m for Stage I-III vs 14.7 m Stage IV, $p < 0.0001$ and 146 m for low (grade 1-2) vs 49.1 m for high grade (grade 3) $p = 0.0025$, respectively. Age group had no effect on median OS (74.4 months for younger and 78.9 months for older log Rank $p = 0.13$).

Conclusions: Despite significant undertreatment with anthracycline regimens, elderly patients do not have worse survival outcomes in this exploratory analysis of an unselected population.

Legal entity responsible for the study: Hospital Clinico Universitario de Valencia. INCLIVA.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1656P Should we consider altering our patterns of care for elderly sarcoma patients?

S. Vari[1], C. Zoccali[2], V. Anelli[3], A. Annovazzi[4], M.G. Petrongari[5], G. Maggi[6], D. Giannarelli[7], N. Saldducca[2], L. Favale[2], M. Zeuli[1], R. Biagini[2], A. Latini[8], W. Faltyn[1], M.' Anza[1], R. Covello[9], J. Baldi[2], D. Pellegrini[1], E. Checcucci[7], F. Cognetti[1], V. Ferraresi[1]

[1]Oncology, IRCCS-Regina Elena National Cancer Institute, Rome, Italy, [2]Oncological Orthopedics, IRCCS-Regina Elena National Cancer Institute, Rome, Italy, [3]Radiology, IRCCS-Regina Elena National Cancer Institute, Rome, Italy, [4]Nuclear Medicine, IRCCS-Regina Elena National Cancer Institute, Rome, Italy, [5]Radiation Oncology, IRCCS-Regina Elena National Cancer Institute, Rome, Italy, [6]Psychology, IRCCS-Regina Elena National Cancer Institute, Rome, Italy, [7]Biostatistics, IRCCS-Regina Elena National Cancer Institute, Roma, Italy, [8]Dermatology, IRCCS San Gallicano Institute, Rome, Italy, [9]Oncology - Pathology, IRCCS-Regina Elena National Cancer Institute, Rome, Italy

Background: An increasing proportion of elderly patients (pts) are now being seen at cancer centres, with an increasing incidence of sarcoma. This has become a growing challenge for health care providers, because of the worse prognosis of these pts and our poor knowledge from trials, were they are underrepresented or excluded.

Methods: We performed a retrospective review of elderly pts with soft tissue and bone sarcomas treated between 2012 and 2017 at Regina Elena National Cancer Institute. Overall, 124 pts, median age of 77 (range 70-92), were evaluated for: surgery, radiotherapy (RT), medical treatment and related toxicities.

Results: The most common histological subtypes were: pleomorphic sarcoma (32%); liposarcoma (17%); leiomyosarcoma (13%); mixofibrosarcoma (9%); bone sarcoma (7%); and others (22%). A total of 107 pts had localized disease at diagnosis and 98 of them had surgical resection. 10 pts received adjuvant chemotherapy (CT) (8 Adriamicin (ADM), 1 Gemcitabine (Gem) and 1 Imatinib (IM)) and 35 pts adjuvant RT. 2 pts, unsuitable for surgery, were treated with RT, and 7 had best supportive care (BSC) (median age: 80, range: 73-85). Of the 17 metastatic pts, 13 were treated with palliative surgery. After surgery, 3 pts had RT and 3 had single agent CT (1 ADM, 1 Epirubicin (EPI) and 1 patient with GIST received IM followed by 2nd line Sunitinib). The remaining 3 pts had BSC due to age > 80 yr and PS 2. 10 non-metastatic pts had recurrent disease and were treated with 1st line CT (3 EPI, 1 Dacabarzine, 2 Gem, 1 Pazopanib, 1 ADM, 1 Docetaxel/Gem, 1 Bleomicine/Vinblastine). 6 received 2 lines of CT after progression (4 Trabectidin and 2 Gem). 13 of 21 pts treated with CT had no toxicities. The most common toxicities observed in 8 pts left were: haematological (37%); gastrointestinal (12%), and transaminitis (25%).

Conclusions: In our analysis, "fit" elderly pts were treated with the same medical treatments as non-elderly pts. Tolerability was fairly good, without discontinuation or hospitalization. Only 8% were treated with BSC, a relevant result considering the median age of our pts. Future studies designed for elderly pts and rare tumours, such as sarcomas, are needed to improve survival rates and quality of life of this poorly represented group of pts.

Legal entity responsible for the study: Regina Elena Sarcoma Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1657P Return to work and quality of life in disease-free adult sarcoma patients

A. Kollar[1], S. Müller[1], N. Fankhauser[2], I. Briner[1], F. Klenke[3], J. Bernhard[1]

[1]Medical Oncology, University Hospital Bern, Inselspital, Bern, Switzerland, [2]Clinical Trial Unit, University of Bern, Bern, Switzerland, [3]Department of Orthopedic Surgery, University Hospital Bern, Inselspital, Bern, Switzerland

Background: Treatment of extremital sarcoma patients may be associated with significant functional disabilities affecting quality of life (QoL) and therefore the return-to-work (RtW) process. Many studies report on RtW and QoL in childhood, adolescents and young adult cancer survivors of different malignancies. In contrast, studies looking at adult sarcoma patients in particular are limited.

Methods: Patients with the diagnosis of an extremital sarcoma of soft tissue and bone, surgically treated between 2000 and 2015, age at diagnosis of ≥ 18 or < 65 (age of retirement in Switzerland), alive and without evidence of sarcoma disease were invited for an interview. The primary objective was to investigate the employment rate. Secondary aims were to assess biomedical predictors of RtW and investigate the present QoL of adult sarcoma survivors. Health-related QoL measurements including physical, mental, and social domains were investigated with the following questionnaires: TESS (The Toronto Extremity Salvage Score), SF-36 (short-form health survey), CES-D (Center for Epidemiologic Studies-Depression Scale) and FoP-Q-SF (fear of progression).

Results: 5 out of 45 (11.1%) interviewed patients did not return to work. In the univariate analysis no statistically significant parameter predicting RtW could be detected. High educational level and full-time employment before sarcoma diagnosis showed a non-significant tendency towards predicting increased RtW probability. In the multivariate analysis full-time employment before sarcoma diagnosis is a significant predictor of RtW (OR 9.828 (1.318 – 73.303)) whereas high educational level does not show a significant influence. Neither the SF-36 physical and mental summary score nor the scores of the other interviews significantly correlated with RtW outcome. However, the mean difference in the FoP-Q-SF- score between the two groups (no RtW and RtW) was -10.981 (-18.242 to -3.720) in the multivariate model. Age at diagnosis, gender, type of sarcoma, tumor site/grade, amputation rate, Whoops procedure did not correlate with rate of RtW.

Conclusions: Our study reveals a high employment rate and good QoL of adult sarcoma survivors. Part-time employment and fear of progression might hamper the RtW process.

Legal entity responsible for the study: Kollar Attila.

Funding: Swiss Cancer League/Swiss Cancer Research.

Disclosure: All authors have declared no conflicts of interest.

1658P No benefit of preoperative chemotherapy for primary retroperitoneal sarcomas: Results from a single center propensity-matched analysis

M. Faron[1], S. Dumont[2], J. Adam[3], O. Mir[2], L. Haddag[4], C. Le Pechoux[5], P. Terrier[6], A. Le Cesne[7]

[1]Surgery Department, Institut Gustave Roussy, Villejuif, France, [2]Department of Medicine, Institut Gustave Roussy, Villejuif, France, [3]Pathology, Institut Gustave Roussy, Villejuif, France, [4]Radiology Department, Institut Gustave Roussy, Villejuif, France, [5]Radiation Oncology Department, Institut Gustave Roussy, Villejuif, France, [6]Pathology Department, Institut Gustave Roussy, Villejuif, France, [7]Department of Medicine, Gustave Roussy, University Paris-Saclay, Villejuif, France

Background: Surgery for retroperitoneal sarcomas (RPS) is more and more standardized worldwide. Yet, the potential benefits of preoperative chemotherapy remain elusive.

Methods: All consecutive patients operated on for a primary RPS were retrospectively identified. Preoperative chemotherapy was mostly a doxorubicin-based chemotherapy

regimen for 2 to 6 cycles. Surgery was performed according to the "cluster resection" principles. A caliper restricted, propensity score matched analysis was used to balance the groups.

Results: 249 patients were identified, 49(19.7%) of whom had receive preoperative chemotherapy. After matching, 40 pairs of patients were available and well balanced for baseline characteristics. Seven patients had intermediate adipocytic tumors, 30 had malignant adipocytic tumor, 19 had smooth muscle tumors and 24 had other subtypes. The median tumor size at diagnosis was 20 cm (IQR: 12-26 cm). Sixteen tumors (%) were FNCLCC's grade 1, 28 (%) grade 2 and 36 (%) grade 3. Univariate analysis identified the size of the tumor ($p = 0.036$), the histological subtype ($p = 0.0015$), the FNCLCC's grade ($p = 0.0027$) and the postoperative chemotherapy ($p = 0.01$) as prognostic factors. In the multivariate analysis, only the sarcoma histotype ($p = 0.013$) and the FNCLCC's grade ($p = 0.022$) were retained as independent prognostic factor. Preoperative chemotherapy was neither associated with overall survival ($p = 0.41$) nor disease-free survival ($p = 0.11$).

Conclusions: Routine use of chemotherapy should be avoided in the preoperative setting of primary RPS. Targeted treatments and/or accurate selection criteria are needed.

Legal entity responsible for the study: Gustave Roussy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1659P Combination of eribulin plus gemcitabine in L-sarcomas

D.S. Moura, M. Lopez-Alvarez, A. Salinas-Villegas, P. Sanchez-Bustos, N. Hindi, M. Taron Roca, J. Martin-Broto

Advanced Therapies and Biomarkers in Oncology Group, Instituto de Biomedicina de Sevilla, Seville, Spain

Background: Eribulin (Halaven®; Eisai Co., Tokyo, Japan) is a synthetic analogue of halichondrin B that was approved for advanced liposarcoma. Eribulin, besides its well stablished cytotoxic activity, induces vascular remodelling and increased tumor perfusion, as well as inhibits pericyte- and endothelial-driven angiogenesis, which could facilitate the distribution of other drugs within the tumor. Altogether, we hypothesize that eribulin and gemcitabine, acting in different cell cycle phases and modulating distintly tumour microenvironment, could be synergistic, without overlapping toxicity.

Methods: CP0024 human leiomyosarcoma primary cell line, SK-UT-1 human leiomyosarcoma cell line and, 93T449 and 94T778 human liposarcoma cell lines were treated with increased concentrations of eribulin ($1x10^{-7}$M to $1x10^{-11}$M) or gemcitabine ($1x10^{-9}$M to $1x10^{-13}$M) to determine IC50 values. Combination index values of eribulin plus gemcitabine were calculated, after treating L-sarcoma cell lines with both drugs using the following administration sequences: concomitant (E+G), eribulin followed by gemcitabine (E→G) and gemcitabine followed by eribulin (G→E). Cell viability, at 72 hours, was measured by MTS cell proliferation assay.

Results: The IC50 values determined for eribulin ranged between 0.28nM (SK-UT-1) and 1.98nM (94T778), while IC50 values of gemcitabine ranged between 2.10nM (SK-UT-1) and 7.02nM (94T778). The combination index values at ED50 (the effective doses at which 50% of cell killing occurred) ranged: between 0.27 (SK-UT-1) and 0.89 (94T778), when cell lines were treated with E+G; between <0.10 (SK-UT-1) and 0.33 (CP0024) when treated with G→E; and between <0.10 (SK-UT-1) and 0.20 (CP0024) when cells were treated with E→G. All the cell lines showed a higher synergism when treated using the E→G administration sequence.

Conclusions: Eribulin and gemcitabine combination is synergic in L-sarcoma cell lines. The administration of eribulin, followed by gemcitabine is the recommended administration sequence for further studies. The mechanisms underlying eribulin plus gemcitabine synergy, as well as predictive biomarkers of response to the combination, will be evaluated in in vitro and in vivo models of L-sarcoma.

Legal entity responsible for the study: Instituto de Biomedicina de Sevilla.

Funding: Eisai Co., Ltd.

Disclosure: D.S. Moura: Corporate-sponsored research fees: Eisai. Co. Ltd. J. Martin-Broto: Corporate-sponsored research fees: Eisai. Co., Ltd., Novartis, PharmaMar; Honoraria or consultation fees: Lilly, Novartis, PharmaMar; Company sponsored speaker's bureau: PharmaMar. All other authors have declared no conflicts of interest.

1660P The role of chemotherapy in the landscape of liposarcoma

A. De Vita[1], F. Recine[1], L. Mercatali[1], G. Miserocchi[1], C. Liverani[1], C. Spadazzi[1], R. Casadei[2], D. Cavaliere[3], A. Bongiovanni[1], F. Pieri[4], L. Medri[4], N. Riva[1], V. Fausti[1], T. Ibrahim[1]

[1]Osteoncology and Rare Tumors Center, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [2]Department of Orthopedics, Istituto Ortopedico Rizzoli, Bologna, Italy, [3]Unit of Surgery and Advanced Oncologic Therapies, Morgagni-Pierantoni Hospital, Forlì, Italy, [4]Pathology Unit, Morgagni-Pierantoni Hospital, Forlì, Italy

Background: Liposarcoma (LPS) is one of the most common types of soft tissue sarcoma (STS), including four subtypes: well-differentiated/atypical lipomatous tumor (ALT/WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid/round cell liposarcoma (MLPS/RCLPS) and pleomorphic liposarcoma (PLS). The morphological diversity of LPS reflects the heterogeneity in clinical and biological behavior and sensitivity to chemotherapy.

Methods: The study involved six patients affected by low/high grade LPS (1 ALT/WDLPS and DDLPS, 1 DDLPS, 2 MLPS, 1 RCLPS and 1 PLS). Patient-derived primary cultures were established after patient surgery. The cultures were exposed to drugs currently used (e.i. ifosfamide, epirubicin, trabectidin, eribulin) for the treatment of LPS. Drug concentrations were selected according to the human plasma peak in patients with solid tumors. Percentages of cellular survival were assessed by MMT and TUNEL assays.

Results: The results showed the sensitivity of the cultures to chemotherapy. The combination of ifosfamide and epirubicin was the most active regimen and statistically significant among cultures. Ifosfamide did not affect the survival of the cells, except in RCLPS suggesting its role in this LPS subtype. Epirubicin showed a comparable activity of the combination regimen in DDLPS (28%) and RCLPS (14%) while displayed a lesser cytotoxic effect in ALT/WDLPS and DDLPS (83%) and MLPS (65%). Trabectidin had no effect on the cellular survival in DDLPS and an equivalent activity in ALT/WDLPS and DDLPS and MPLS (61% and 65% respectively). In RCLPS exhibited an important activity (28%). Trabectidin showed a higher efficacy in ALT/WDLPS and DDLPS and a similar trend in MLPS compared to epirubicin. Eribulin displayed a comparable activity of trabectidin in ALT/WDLPS and DDLPS (70%), MLPS (68%) and RCLPS (26%) while was more active in DDLPS (83%). Finally, cellular survival of PLS was not affected by all the drugs.

Conclusions: This study provides a rationale for elucidate the role of chemotherapy for all liposarcoma subtypes using patient-derived LPS primary cultures. The improvement in the understanding of the molecular mechanisms in liposarcoma will help in selecting the appropriate treatment with a potential impact in the clinical setting.

Legal entity responsible for the study: Toni Ibrahim.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1661TiP A randomized phase III study of denosumab before curettage for giant cell tumor of bone: Japan Clinical Oncology Group study JCOG1610

H. Urakawa[1], J. Mizusawa[2], K. Tanaka[3], J. Eba[2], H. Hiraga[4], M. Hosaka[5], A. Kawai[6], F. Nakatani[6], E. Kobayashi[6], Y. Nishida[1], T. Okamoto[7], T. Matsunobu[8], Y. Iwamoto[8], H. Fukuda[2], T. Ozaki[9]

[1]Orthopaedic Surgery, Nagoya University, Graduate School of Medicine, Nagoya, Japan, [2]JCOG Data Center/ Operations Office, National Cancer Center, Tokyo, Japan, [3]Endoprosthetic Surgery, Oita University Faculty of Medicine, Yufu, Japan, [4]Orthopaedic Surgery, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan, [5]Orthopaedic Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan, [6]Orthopaedic Surgery, National Cancer Center Hospital, Tokyo, Japan, [7]Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, [8]Orthopaedic Surgery, Kyushu Rosai Hospital, Kitakyushu, Japan, [9]Orthopaedic Surgery, Okayama University Graduate School of Medicine, Okayama, Japan

Background: Giant Cell Tumor of Bone (GCTB) is a rare tumor known to be locally aggressive, but rarely metastasizing. Resectable GCTB without possible postoperative large bone defect has been treated by curettage with local adjuvant treatment, and its recurrence rate is as high as 20-30%. A recent phase II study demonstrated the effects of denosumab for patients with unresectable GCTB and resectable GCTB with possible postoperative large bone defect. However, the efficacy of preoperative denosumab for GCTB without possible postoperative large bone defect is still controversial. Therefore, we have commenced a phase III trial to confirm the superiority of preoperative denosumab for patients with GCTB who can be treated with curettage.

Trial design: Eligibility criteria include histologically proven GCTB, arising in the extremity, primary tumor (Campanacci grade II or III) and first or second local recurrent tumor, tumor which can be treated by curettage, no distant metastases, and aged 20 to 70. Patients are randomized to either arm A (curettage and adjuvant local therapy) or arm B (preoperative denosumab, curettage, and adjuvant local therapy). Preoperative denosumab is administered subcutaneously at a dose of 120 mg on day 1, 8, 15, 29, and 57. Only in a case of insufficient bone formation after 5 times of denosumab, it is allowed to add denosumab 3 times. The primary endpoint is relapse-free survival (RFS). Secondary endpoints include overall survival, joint-preserved survival, local relapse-free survival, metastasis-free survival, adverse events, serious adverse events, surgical and postoperative complications, and discontinuation of denosumab. We assume that the proportion of RFS at 3 years is 80% for arm A and expect a 10% increase in the proportion of RFS at 3 years for arm B. A sample size was calculated as 51 patients per arm to observe 25 total events with a one-sided alpha level of 10%, power of 70%, an accrual period of 5 years, and a follow-up period of 3 years. Thus, the total sample size was defined as 106 patients to account for loss to follow-up. This trial has started in October 2017 and current enrollment is 3 patients in April 2018.

Clinical trial identification: UMIN000029451 (release date: 6. Oct. 2017).

Legal entity responsible for the study: Japan Clinical Oncology Group (JCOG).

Funding: National Cancer Center, Japan.

Disclosure: H. Urakawa: Honoraria: Astellas Pharma, J. Eba: Honoraria: Chugai Pharma (to an immediate family member). H. Hiraga: Honoraria: Taiho

Pharmaceutical, Celgene, Eisai, Hisamitsu Pharmaceutical, Secom Medical System, Astellas Pharma; Research funding to institution: Lilly Japan. A. Kawai: Consulting or advisory role: Novartis, Lilly, Taiho Pharmaceutical, Ignyta; Honoraria: Novartis, Takara Bio, Taiho Pharmaceutical, Eisai, Lilly. Y. Nishida: Consulting or advisory role: Seikagaku; Speakers' bureau: Stryker, Novartis, Eisai, Lilly Pharma; Travel, accommodations, expenses: Taisho Toyama Pharma. H. Fukuda: Honoraria: Taiho Pharmaceutical, Chugai Pharma. All other authors have declared no conflicts of interest.

1662TiP VOYAGER: An open-label, randomised, phase III study of avapritinib vs regorafenib in patients (pts) with locally advanced (adv) metastatic or unresectable gastrointestinal stromal tumour (GIST)

S. Bauer[1], S. George[2], Y-K. Kang[3], W.D. Tap[4], T. Zhou[5], N. Picazio[6], A.L. Boral[6], M. Heinrich[7]

[1]Medical Oncology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany, [2]Medical Oncology, Dana Faber Cancer Institute, Boston, MA, USA, [3]Medical Oncology, Asan Medical Center, Seoul, Republic of Korea, [4]Sarcoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Centre, New York, NY, USA, [5]Biostatistics, Blueprint Medicines Corporation, Boston, MA, USA, [6]Clinical Development, Blueprint Medicines Corporation, Boston, MA, USA, [7]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA

Background: Imatinib is an effective first-line treatment for pts with adv GIST; however, most pts inevitably relapse or progress. Approved second- and third-line agents, sunitinib and regorafenib, have shown limited activity/tolerability, defining an unmet need for pts with imatinib-resistant GIST. Avapritinib is a highly potent and selective oral kinase inhibitor that targets mutant forms of KIT and PDGFRA, including those that confer resistance to approved tyrosine kinase inhibitors. In the Phase 1 NAVIGATOR study (NCT02508532), avapritinib showed substantial clinical activity in pts with both KIT- and PDGFRA-mutant GIST that was resistant to all available therapies. Based on these findings, the VOYAGER study was initiated, comparing avapritinib with regorafenib in pts with adv GIST.

Trial design: VOYAGER (NCT03465722), an international, multicentre, open-label, randomised, Phase 3 study, will include pts (aged $\geq$18; ECOG PS 0–2) with locally adv metastatic or unresectable GIST. The study will evaluate avapritinib vs regorafenib in pts previously treated with imatinib and 1 or 2 other tyrosine kinase inhibitors, who have experienced disease progression, inadequate clinical benefit or intolerance to their prior therapy. Pts with GIST that is wild-type in both KIT and PDGFRA will be excluded. Approximately 460 pts will be enrolled across North America, Europe, Australia and Asia. Pts will be randomised 1:1 to receive avapritinib 300 mg orally, once daily (QD) or regorafenib 160 mg orally, QD (3 wks on/1 wk off), stratified by treatment regimen (third vs fourth), geographic region (Asia vs rest of the world) and mutation status (PDGFRα D842V present vs absent). Pts who experience disease progression on regorafenib, as confirmed by central radiology review, will be allowed to cross over to avapritinib. The primary objective is progression-free survival (PFS), based on central radiological assessment (mRECIST, v1.1). The study is designed to have 90% power to detect a hazard ratio of 0.67 (avapritinib vs regorafenib). Secondary objectives include evaluation of response rate, overall survival, health-related quality of life and safety.

Clinical trial identification: NCT03465722.

Editorial acknowledgement: Samantha Clark from iMed Comms an Ashfield Company, part of UDG Healthcare plc, provided medical writing support funded by Blueprint Medicines Corporation.

Legal entity responsible for the study: Blueprint Medicines Corporation.

Funding: Blueprint Medicines Corporation.

Disclosure: S. Bauer: Grants and personal fees: Novartis, Blueprint Medicines; Personal fees: PharmaMar, Lilly, Deciphera; Grants: Incyte. S. George: Advisory boards: Deciphera Pharmaceuticals, Blueprint Medicines; Consultant: AstraZeneca. Y-K. Kang: Advisory role: BMS, Ono, Blueprint, Daehwa, LSK Biopharma, Novartis, Roche. W.D. Tap: Advisory boards and consultancy: Eli Lilly, EMD Serono, Novartis, Esai, Janssen, Immune Design, Adaptimmune, Daiichi Sankyo, Blueprint Medicines, Loxo. T. Zhou, A.L. Boral: Employee and stock options: Blueprint Medicines Corporation. N. Picazio: Employee of Blueprint Medicines Corporation. M. Heinrich: Consultancy: Novartis, Blueprint Medicines Corporation, Bayer, Deciphera, MolecularMD; Research funding: Blueprint Medicines, Deciphera; Equity interest: MolecularMD; Expert Testimony: Novartis.

Annals of Oncology 29 (Supplement 8): viii596–viii602, 2018
doi:10.1093/annonc/mdy298

SCLC

1664O A randomized non-comparative phase II study of anti–PD-L1 ATEZOLIZUMAB or chemotherapy as second-line therapy in patients with small cell lung cancer: Results from the IFCT-1603 trial

J-L. Pujol[1], L. Greillier[2], C. Audigier Valette[3], D. Moro-Sibilot[4], L. Uwer[5], J. Hureaux[6], L. Thiberville[7], D. Carmier[8], J. Madelaine[9], J. Otto[10], V. Gounant[11], P. Merle[12], P. Mourlanette[13], O. Molinier[14], P.A. Renault[15], J. Mazieres[16], M. Antoine[17], A. Langlais[18], F. Morin[18], P-J. Souquet[19]

[1]Pneumologie, Hopital Arnaud de Villeneuve, Montpellier, France, [2]Department of Multidisciplinary Oncology and Therapeutic Innovations, Assistance Publique Hopitaux de Marseille, Marseille, France, [3]Pneumologie, Hospital Sainte Musse, Toulon, France, [4]Pneumologie, CHU Grenoble-Alpes, Grenoble, France, [5]Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandoeuvre Les Nancy, France, [6]Pneumologie, CHU Angers, Angers, France, [7]Pneumologie, CHU Hôpitaux de Rouen-Charles Nicolle, Rouen, France, [8]Pneumologie, CHRU Bretonneau, Tours, France, [9]Pneumologie, CHU de Caen, Caen, France, [10]Centre Antoine Lacassagne, Nice, France, [11]Pneumologie, Hopital Bichat Claude Bernard, Paris, France, [12]Pneumologie, CHU, Clermont-Ferrand, France, [13]Pneumologie, Clinique des Cedres, Cornebarrieu, France, [14]Pneumologie, Centre Hospitalier du Mans, Le Mans, France, [15]Pneumologie, Centre Hospitalier, Pau, France, [16]Thoracic Oncology, Hospital Larrey, Toulouse, France, [17]Pathology, APHP, CancerEst, Tenon University Hospital, Paris, France, [18]Clinical Research Unit, French Cooperative Thoracic Intergroup, Paris, France, [19]Pneumologie, Centre Hospitalier Lyon Sud, Pierre Bénite, France

1665PD Preliminary efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant ED-SCLC from arm A of the phase II BALTIC study

I. Bondarenko[1], O. Juan-Vidal[2], G. Pajkos[3], A. Kryzhanivska[4], Z. Pápai Székely[5], D. Vicente[6], I.O. Vynnychenko[7], S. Jones[8], Y. Wang[8], H. Jiang[8], N. Reinmuth[9]

[1]Oncology, Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine, [2]Medical Oncology, La Fe University Hospital, Valencia, Spain, [3]Medical Oncology, Bacs-Kiskun County Hospital, Kecskemét, Hungary, [4]Department of Oncology, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine, [5]Medical Oncology, St George Hospital of Fejér County, Szekesfehervar, Hungary, [6]Medical Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, [7]Medical Oncology, Sumy State University, Sumy, Ukraine, [8]Medical Oncology, AstraZeneca, Gaithersburg, MD, USA, [9]Medical Oncology, Asklepios Lung Clinic, Munich-Gauting, Germany

1666PD Trilaciclib (T) decreases multi-lineage myelosuppression in extensive-stage small cell lung cancer (ES-SCLC) patients receiving first-line chemotherapy

K.H. Dragnev[1], T.K. Owonikoko[2], T. Csoszi[3], M. Maglakelidze[4], J.T. Beck[5], M. Domine Gomez[6], A. Lowczak[7], A. Fulop[8], R.J. Hoyer[9], W. Hanna[10], P. Lowry[11], R. Aljumaily[12], V.K. Chiu[13], I. Bulat[14], Z. Yang[15], P.J. Roberts[16], J.M. Antal[17], R.K. Malik[17], S.R. Morris[17], J.M. Weiss[18]

[1]Hematology/Oncology, Norris Cotton Cancer Center Dartmouth-Hitchcock Medical Center, Lebanon, PA, USA, [2]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA, [3]Oncology, Hetenyi Geza Korhaz, Onkologiai Kozpont, Szolnok, Hungary, [4]Oncology, Research Institute of Clinical Medicine, Tbilisi, Georgia, [5]Medical Oncology and Hematology, Highlands Oncology Group, Fayetteville, AZ, USA, [6]Oncology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [7]Oncology, Samodzielny Publiczny Zespol Gruzlicy i Chorob Pluc, Olsztyn, Poland, [8]Oncology, OKTPI-Korányi National Institute for Tuberculosis and Pulmonology, Budapest, Hungary, [9]Oncology, Memorial Hospital, University of Colorado Health, Colorado Springs, CO, USA, [10]Hematology/Oncology, University of Tennessee Medical Center, Knoxville, TN, USA, [11]Oncology, Guthrie Medical Group, Sayre, PA, USA, [12]Oncology, Oklahoma University Medical Center, Oklahoma City, OK, USA, [13]Hematology/Oncology, University of New Mexico Comprehensive Cancer Center, Albuquerque, NM, USA, [14]Oncology, ICS ARENSIA Exploratory Medicine SRL, Chisinau, Moldova, [15]Biostatistics, G1 Therapeutics, Inc., Research Triangle Park, NC, USA, [16]Translational Medicine, G1 Therapeutics, Inc, Research Triangle Park, NC, USA, [17]Clinical Development, G1 Therapeutics, Inc., Research Triangle Park, NC, USA, [18]Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

1667PD Impact of early prophylactic cranial irradiation with hippocampal avoidance on neurocognitive function in patients with limited disease small cell lung cancer: A multicenter phase II trial (SAKK 15/12)

H. Vees[1], F. Caparrotti[2], A. Xyrafas[3], A.C. Fuhrer[4], U.R. Meier[5], M.T. Mark[6], O. Elicin[7], D.M. Aebersold[7], D.C. Betticher[8], C. Biaggi Rudolf[4], K. Ribi[9], T. Finazzi[10], D.R. Zwahlen[11]

[1]Radiation Oncology, Hirslanden Klinik Zürich, Zurich, Switzerland, [2]Radiation Oncology, Hôpitaux Universitaires de Genève - HUG, Geneva, Switzerland, [3]Research, SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland, [4]Clinical Trial Management, SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland, [5]Radiation Oncology, Kantonsspital Winterthur, Winterthur, Switzerland, [6]Medical Oncology, Kantonsspital Graubünden, Chur, Switzerland, [7]Radiation Oncology, Inselspital - Universitätsspital Bern, Bern, Switzerland, [8]Department of Medicine, Medical Oncology, Fribourg, Switzerland, [9]Quality of Life Office, Swiss Group for Clinical Cancer Research Study Group, Bern, Switzerland, [10]Radiation Oncology, Universitaetsspital Basel, Basel, Switzerland, [11]Radiation Oncology, Kantonsspital Graubünden, Chur, Switzerland

1668P A pooled analysis of individual patient data (IPD) of concurrent chemoradiotherapy for limited-stage small cell lung cancer (LS-SCLC) in elderly compared to younger patients (pts) who participated in US National Cancer Institute cooperative group studies

T.E. Stinchcombe[1], W. Fan[2], S.E. Schild[3], E.E. Vokes[4], J. Bogart[5], Q-T.X. Le[6], C.R. Thomas Jr.[7], M. Edelman[8], L. Horn[9], R. Komaki[10], H.J. Cohen[1], A.K. Ganti[11], H. Pang[12], X. Wang[13]

[1]Medical Oncology, Duke Cancer Center, Durham, NC, USA, [2]Biostatistics and Bioinformatics, Duke University, Durham, NC, USA, [3]Radiation Oncology, Mayo Clinic Arizona, Scottsdale, AZ, USA, [4]Medical Oncology, The University of Chicago Medical Centre, Chicago, IL, USA, [5]Radiation Oncology, SUNY Upstate Medical University, Syracuse, NY, USA, [6]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA, USA, [7]Department of Radiation Medicine, Oregon Health & Science University, Portland, OR, USA, [8]Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [9]Medical Oncology, Vanderbilt Ingram Cancer Center, Nashville, TN, USA, [10]Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA, [11]Medical Oncology, University of Nebraska Medical Center, Omaha, NE, USA, [12]School of Public Health, Hong Kong University Li Ka Shing Faculty of Medicine, Hong Kong, China, [13]Biostatistics, Alliance Statistics and Data Center, Durham, NC, USA

Background: Platinum and etoposide with concurrent thoracic radiation is the standard treatment for LS-SCLC. Elderly pts are common, and may experience higher rates of adverse events (AEs) and have a worse outcome from this treatment.

Methods: IPD were collected from 11 phase 2 or 3 trials for LS-SCLC conducted by the US National Cancer Institute-supported cooperative groups activated from 1990 to 2010. Overall survival (OS), progression-free survival (PFS) and AEs were compared between pts age $\geq$ 70 years (elderly) and for pts $<$ 70 years (younger). Unadjusted and adjusted hazard ratios (HRs) for survival time and CIs were estimated by univariate and multivariable frailty Cox models.

Results: IPD from 1049 younger and 254 elderly pts were analyzed. In the univariate and multivariable models, elderly pts compared with younger pts had worse OS (HR of 1.40; 95% CI, 1.20 to 1.65 and 1.36; 95% CI, 1.15 to 1.59). Median OS in elderly and younger pts was 17.8 months and 23.5 months, respectively. In the univariate and multivariable models, elderly pts had worse PFS (HR of 1.23; 95% CI, 1.06 to 1.43 and 1.19; 95% CI, 1.03 to 1.39). Median PFS in elderly and younger pts was 10.6 and 12.3 months, respectively. Elderly and younger pts had a similar rates of all grade $\geq$ 3 AEs, but elderly pts had a statistically significantly higher rate of all grade $\geq$ 4 AEs ($p < 0.01$), hematologic $\geq$ 4 AEs ($p < 0.01$), and grade 5 AEs (8% vs 3%, $p < 0.001$). When specific AEs were analyzed, elderly pts experienced a higher rate of grade $\geq$ 3 dyspnea ($p = 0.03$), but a lower rate of grade $\geq$ 3 vomiting ($p = 0.01$) and esophagitis ($p = 0.03$). Elderly pts compared with younger pts completed treatment at a lower rate ($p = 0.02$), stopped treatment at higher rates due to adverse events ($p = 0.02$), patient refusal ($p < 0.01$), and death during treatment ($p < 0.01$).

Conclusions: Elderly pts with LS-SCLC experienced a worse PFS and OS, and experienced a statistically higher rate of grade 4 and 5 adverse events. Future trials should investigate methods to identify vulnerable elderly pts and reduce the toxicity of treatment.

Legal entity responsible for the study: Tom Stinchcombe and Xiaofei Wang.

Funding: NIH grant: R21-AG042894.

Disclosure: All authors have declared no conflicts of interest.

1669P Treatment beyond four cycles of first line platinum and etoposide chemotherapy in real-life patients with stage IV small cell lung cancer: A retrospective study of the Merseyside and Cheshire cancer network

M. Sallam[1], H. Wong[2], C. Escriu[3]

[1]School of Medicine, University of Liverpool, Liverpool, UK, [2]Department of Clinical Governance, Clatterbridge Cancer Centre, Merseyside, UK, [3]Medical Oncology, Clatterbridge Cancer Center, Merseyside, UK

Background: Dose intensity and dose density of first line Platinum and Etoposide (PE) chemotherapy does not influence Overall Survival (OS) of Small Cell Lung Cancer (SCLC) patients. The effect of treatment length, however, remains unclear. Current guidelines recommend treating beyond four cycles – and up to six - in patients that respond to and tolerate systemic treatment. This has led to variable practice both in real-life and clinical research. Here we aimed to quantify the possible clinical benefit of the extended regimen in our real-life patients treated with PE doublet.

Methods: Of all patients with SCLC treated in our network with non-concurrent first line PE chemotherapy between 2008 and 2015, we retrospectively identified patients that received four cycles (4c) or more (>4c), and compared clinical outcomes between both groups.

Results: We identified 671 patients overall; 578 (86%) received 4c and 93 (14%) received >4c. 74% of patients in the >4c group had stage IV disease. Of 310 patients with stage IV disease, 241 (78%) had 4c and 69 (22%) had >4c. Performance status, comorbidities and radiological responses were similarly distributed between the latter treatment groups. >4c patients were more likely to have sequential thoracic radiotherapy, which may indicate a lower metastatic burden in this group. Nevertheless, there were no statistically significant differences when comparing clinical outcomes. The median Duration of Response (time from last chemotherapy cycle to progression) was 5 months in both groups (HR 1.22; 95% CI 0.93-1.61). Median PFS (Progression-free Survival; time from diagnosis to progression) was 8 months (4c) versus 9 months (>4c) (HR 0.86; 0.66-1.13), and median OS (time from diagnosis to death) was 11 (4c) versus 12 (>4c) months (HR 0.86; 0.66-1.14).

Conclusions: Our results highlight a lack of clinical benefit by extending first line platinum combination treatment beyond four cycles in selected patients. This supports limiting the number of cycles to four until the superiority of a longer regimen is identified in a randomised study.

Legal entity responsible for the study: Department of Clinical Governance, Clatterbridge Cancer Centre.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1670P Timing of treatment in small cell lung cancer

S. Bhandari[1], D. Pham[1], C. Pinkston[2], M. Oechsli[1], G. Kloecker[1]

[1]Hematology/Medical Oncology, Brown Cancer Center University of Louisville, Louisville, KY, USA, [2]Department of Bioinformatics and Biostatistics, School of Public Health, University of Louisville, Louisville, KY, USA

Background: Small cell lung cancer (SCLC) is an aggressive disease with 5-year survival rate of 31% in stage I and 2% in stage IV. Current general practice is to treat SCLC patients as soon as possible after diagnosis given its rapid doubling time and high growth fraction. There is no good evidence for appropriate timing of treatment from diagnosis (TTD) for SCLC. This study evaluates TTD in SCLC and its effect on survival.

Methods: SCLC patients were abstracted from 2012 to 2015 Kentucky Cancer Registry as a part of Lung Cancer Education Awareness Detection Survival (LEADS) Collaborative and included 2992 patients. Data collected included age at diagnosis, stage, gender, race, insurance and treatment. Factors associated with TTD were identified with logistic regression analyses adjusted for age, gender, race, stage, and insurance status. Derived odds ratios (OR) and 95% confidence intervals (CIs) are reported. Survival of patients by TTD ($\leq$4 weeks vs $>$ 4 weeks) was assessed with Cox proportional hazards models, adjusted for age, gender, race, stage, and insurance status. Hazard ratios (HR) and 95% CIs were reported.

Results: Among the 2992 SCLC patients, 67% were stage 4 and 27% were stage 3 diseases. 2371(79%) of SCLC patients were treated with one or more treatment modalities and 621(21%) received no treatment after diagnosis. Among treated patients 93% patient received chemotherapy $\pm$ radiation with mean time of treatment from diagnosis of 18 days. Most patients (80%) have TTD of $\leq$ 4 weeks with 33% treated within 1 week, 20% 1-2 weeks, and 27% 2-4 weeks from diagnosis. Delay in treatment (TTD >4 weeks) was less in stage III and IV disease (OR: 0.34 & 0.27 respectively, $p < 0.01$) but not significantly associated with age, race, gender and insurance. One and two-year survival of patients with TTD $\leq$4weeks was significantly worse when compared to $>$ 4 weeks (HR = 1.43, 95% CI 1.2-1.6, $p < 0.01$; HR = 1.45, 95% CI 1.3-1.6, $p < 0.01$ respectively). This is true even when stratified by stage.

Conclusions: These results show a trend towards poor survival with early treatment in SCLC which refutes current belief of better survival with early treatment. It is unclear why this trend exists, and further studies are needed to better clarify appropriate timing of treatment from diagnosis in SCLC and who will benefit from early vs late treatment.

Legal entity responsible for the study: Brown Cancer Center, University of Louisville.

Funding: LEADS Collaborative supported by Bristol-Myers Squibb foundation.

Disclosure: All authors have declared no conflicts of interest.

1671P Trilaciclib (trila) preserves and enhances immune system function in extensive-stage small cell lung cancer (ES-SCLC) patients receiving first-line chemotherapy

J.A. Sorrentino[1], A. Lai[1], J.M. Weiss[2], K.H. Dragnev[3], T.K. Owonikoko[4], S. Adler[5], J.M. Antal[5], R.K. Malik[5], P.J. Roberts[1]

[1]Translational Medicine, G1 Therapeutics, Inc, Research Triangle Park, NC, USA, [2]Hematology/Oncology, University of North Carolina, Chapel Hill, NC, USA, [3]Hematology/Oncology, Norris Cotton Cancer Center Dartmouth-Hitchcock Medical Center, Lebanon, PA, USA, [4]Medical Oncology, Emory University Winship Cancer Institute, Atlanta, GA, USA, [5]Clinical Development, G1 Therapeutics, Inc, Research Triangle Park, NC, USA

Background: Chemotherapy (chemo) efficacy may be limited due to damage to hematopoietic stem and progenitor cells (HSPCs) leading to multi-lineage myelosuppression. Trila is an iv CDK4/6 inhibitor in development to preserve HSPC and immune system function during chemo (myelopreservation). Preclinically, transient trila-induced G1 arrest renders HSPCs resistant to chemo cytotoxicity, leading to faster hematopoietic recovery and enhanced anti-tumor immunity. In a randomized, placebo-controlled, double-blind Phase 2 trial (NCT02499770), the addition of trila to etoposide/carboplatin (EP) in ES-SCLC patients showed multi-lineage myelopreservation, fewer supportive care interventions and dose reductions, and encouraging duration of response and progression free survival. Peripheral blood immunophenotyping was performed to characterize the effects of trila on the immune system.

Methods: Whole blood from patients in the EP + trila or EP + placebo arms was collected at baseline, during, and after treatment for flow cytometry analyses of monocytes, T, B, NK, dendritic, and myeloid-derived suppressor cells. T cells were also stimulated ex vivo to evaluate their ability to produce cytokines upon activation.

Results: Preliminary analyses indicate that B cells were significantly depleted during treatment with EP + placebo, but not with EP + trila. In addition to an increase in total CD8+ cells during treatment, EP + trila resulted in a larger population of activated $CD8^+$ T cells, and fewer regulatory T cells which is consistent with a more robust immune response. Further analyses of trila's effect on other immune cell types is ongoing.

Conclusions: These clinical trial findings demonstrate that in addition to preserving neutrophil and red blood cell lineages, adding trila to EP treatment can preserve B cells and enhance T lymphocyte function. In preclinical models, trila similarly enhanced activity of intra-tumor T cells, leading to superior anti-tumor efficacy when combined with chemo + anti-PDL1. A Phase 2 study to assess safety and efficacy of trila or placebo with EP and atezolizumab in first-line ES-SCLC has completed enrollment (NCT03041311).

Clinical trial identification: NCT02499770.

Legal entity responsible for the study: Delaware.

Funding: G1 Therapeutics.

Disclosure: J.A. Sorrentino, A. Lai, R.K. Malik, P.J. Roberts, S. Adler, J.M. Antal: Employee: G1 Therapeutics. J.M. Weiss: Financial support to institution: AstraZeneca, Celgene, Merck; Advisory board: AstraZeneca, Celgene, Boston Biomedical. All other authors have declared no conflicts of interest.

1672P Maintenance treatment with the TLR9 agonist lefitolimod in extensive-stage small-cell lung cancer (ES-SCLC): Final results from the randomized phase II IMPULSE study

M. Thomas[1], S. Ponce Aix[2], A. Navarro Mendivil[3], J. Riera Knorrenschild[4], M. Schmidt[5], E. Wiegert[6], K. Kapp[7], C. Mauri[8], M. Domine Gomez[9], J. Kollmeier[10], P. Sadjadian[11], K-P. Fröhling[12], R.M. Huber[13], M. Wolf[14]

[1]Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital, Translational Lung Research Center Heidelberg (TLRC-H), German Center for Lung Research (DZL), Heidelberg, Germany, [2]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [3]Vall d'Hebron Institute of Research (VHIR), Vall d'Hebron University Hospital, Barcelona, Spain, [4]Klinik für Hämatologie, Onkologie und Immunologie, Uniklinikum Giessen und Marburg, Marburg, Germany, [5]Early & Translational R&D, Mologen AG, Berlin, Germany, [6]Clinical Development, Mologen AG, Berlin, Germany, [7]Translational R&D, Mologen AG, Berlin, Germany, [8]Divison of Medicine, University College London, London, UK, [9]Medical Oncology Department, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [10]Lungenklinik Heckeshorn, Helios Klinikum Emil von Behring GmbH, Berlin, Germany, [11]Klinik für Hämatologie, Onkologie und Palliativmedizin, Johannes Weseling Klinikum, Minden, Germany, [12]Klinik für Innere Medizin/ Pneumologie, Kath. Klinikum Koblenz-Montabaur, Koblenz, Germany, [13]Thoracic Oncology Centre Munich, LMU Klinikum der Universität München, Munich, Germany, [14]Medizinische Klinik IV, Klinik Kassel, Kassel, Germany

Background: The immune surveillance reactivator lefitolimod (MGN1703), a DNA-based TLR9 agonist, is currently in a comprehensive clinical development program including a phase 3 trial in mCRC. The phase 2 IMPULSE study was designed to evaluate efficacy and safety of lefitolimod in ES-SCLC, an indication with high unmet medical need and stagnant treatment improvement in the last decades.

Methods: IMPULSE is a randomized, international, multicenter, open-label trial to assess the effect of lefitolimod on overall survival (OS) in ES-SCLC. 103 patients with objective tumor response following 4 cycles of platinum-based first-line induction therapy were randomized 3:2 to receive either lefitolimod maintenance therapy or local standard of care until progression or unacceptable toxicity.

Results: From 103 patients, 62 were randomized to lefitolimod, 41 to the control arm. Patient demographics and response patterns to first-line therapy were balanced. Lefitolimod exhibited a favorable safety profile in this vulnerable population and pharmacodynamic assessment confirmed the mode-of-action showing clear activation of monocytes and production of interferon-gamma-induced protein 10. While in the ITT population no relevant effect of lefitolimod on OS could be observed, two pre-defined patient subgroups indicated promising results, favoring lefitolimod with respect to OS: Patients with a low frequency of activated $CD86^+$ B cells (HR 0.53, 95%CI 0.26-1.08; n = 38 of 88 analyzed) and patients with reported chronic obstructive pulmonary disease (COPD) (HR 0.48, 95%CI 0.20-1.17, n = 25 of 103). Notably, a post-hoc analysis revealed that a strong lefitolimod-induced immune activation translated into an OS benefit when analysed after 4 weeks of treatment. Two patients from the lefitolimod arm exhibited long-term disease control.

Conclusions: The IMPULSE study showed (1) the expected pharmacodynamic response, (2) positive efficacy signals in two pre-defined subgroups regarding OS and (3) a favorable safety profile. This data provides significant guidance for defining patient populations most likely to benefit from lefitolimod treatment.

Clinical trial identification: NCT02200081.

Legal entity responsible for the study: Mologen AG.

Funding: Mologen AG.

Disclosure: M. Schmidt, K. Kapp, E. Wiegert, C. Mauri: Employee: Mologen AG. All other authors have declared no conflicts of interest.

1673P Phase II study of NAB-paclitaxel in sensitive and refractory relapsed SCLC (NABSTER TRIAL)

F. Gelsomino[1], M. Tiseo[2], F. Barbieri[3], F. Riccardi[4], L. Cavanna[5], A. Frassoldati[6], A. Delmonte[7], L. Longo[8], C. Dazzi[9], S. Cinieri[10], I. Colantonio[11], M. Tognetto[12], D. Baldari[13], L. Tofani[13], A. Ardizzoni[14]

[1]Medical Oncology, AOU Policlinico S. Orsola-Malpighi, Bologna, Italy, [2]Medical Oncology, AOU di Parma, Parma, Italy, [3]Medical Oncology, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [4]Medical Oncology, Azienda Ospedaliera Cardarelli, Naples, Italy, [5]Oncology Department, Azienda Ospedaliera Piacenza, Piacenza, Italy, [6]Medical Oncology, Azienda Ospedaliera di Ferrara St. Anna, Ferrara, Italy, [7]Scientific Institute of Romagna for the Study and Treatment of Cancer, Meldola, Italy, [8]Medical Oncology, AUSL of Modena, Carpi, Italy, [9]Medical Oncology, AUSL of Romagna, Ravenna, Italy, [10]Medical Oncology, Perrino Hospital, Brindisi, Italy, [11]Medical Oncology, Hospital of Cuneo, Cuneo, Italy, [12]Medical Oncology, Policlinico S.Orsola-Malpighi, Bologna, Italy, [13]Clinical Trial Center, Istituto Toscano Tumori, Florence, Italy, [14]Division of Oncology, S.Orsola-Malpighi Hospital, Bologna, Italy

Background: Despite high sensitivity to first-line chemotherapy (CT), most small-cell lung cancer (SCLC) patients relapse. Efficacy of 2nd-line CT is modest and influenced by treatment-free-interval (TFI). Topotecan demonstrated modest activity and significant haematological toxicity. Paclitaxel-based regimens showed to be active in this setting. Nab-paclitaxel, compared to paclitaxel, has a reduced incidence of hypersensitivity reactions and of neutropenia. Safety and efficacy in relapsed SCLC have not been prospectively studied.

Methods: This open-label phase II study enrolled patients with extensive- (ED) or limited-disease (LD) SCLC progressed during or after etoposide/platinum-based 1st-line CT with the aim to assess the activity and safety of Nab-paclitaxel. Patients were classified as refractory (TFI $<$ 60 days) or sensitive (TFI $\geq$ 60 days). Eligible patients received Nab-paclitaxel 100 mg/mq on days 1,8,15 every 28 days for 6 cycles, progressive disease or intolerable toxicity. Computed tomography scan was performed every 2 cycles. Treatment could be continued beyond the 6^{th} cycle in presence of prolonged response, clinical benefit and good tolerance to drug. The primary endpoint was objective response, evaluated according to RECIST v1.1 criteria. The secondary endpoints were toxicity, measured according to NCI-CTCAE v4.03, progression-free and overall survival.

Results: From January 2017 to March 2018, 68 patients (25 refractory and 43 sensitive) were enrolled in the modified intentiontotreat population. Median age was 68.5 years (range 44-80). 44 patients were males and 57 had ED. Median follow-up was 5.8 months (IQR 3.37.1). Objective responses are currently being reviewed by an independent radiology panel. Most common toxicities (of all grades) were anemia (39%), leukopenia (27%), neutropenia (28%), nausea (19%), diarrhoea (21%), fatigue (52%), peripheral neuropathy (19%). The only severe toxicity (grade $\geq$3) was neutropenia (9%). In 13 patients treatment is still ongoing while 3/55 (5%) patients discontinued treatment for toxicity.

Conclusions: This is the first prospective study of Nab-paclitaxel for relapsed SCLC. Nab-paclitaxel demonstrated a manageable toxicity profile. Final activity data will be available for the meeting.

Clinical trial identification: EudraCT: 2016-000408-27; NCT03219762.

Legal entity responsible for the study: GOIRC (Gruppo Oncologico Italiano di Ricerca Clinica).

Funding: Celgene.

Disclosure: All authors have declared no conflicts of interest.

1674P Safety of belotecan as second-line treatment for recurrent small cell lung cancer: A phase IIb randomized multicenter study

J.H. Kang[1], H.T. Kim[2], K.H. Lee[3], D-W. Kim[4], S-W. Kim[5], H.R. Kim[6], J-H. Kim[7], J.H. Choi[8], H.J. An[9], J-S. Kim[10], J.S. Jang[11], B-S. Kim[12]

[1]Department of Oncology, Seoul St. Mary's Hospital, Seoul, Republic of Korea, [2]Center for Lung Cancer, National Cancer Center, Goyang, Republic of Korea, [3]Department of Oncology, Chungbuk University Hospital, Cheongju, Republic of Korea, [4]Department of Oncology, Seoul National University Hospital, Seoul, Republic of Korea, [5]Department of Oncology, Asan Medical Center, Seoul, Republic of Korea, [6]Yonsei University College of Medicine, Yonsei Cancer Center, Seoul, Republic of Korea, [7]CHA University, CHA Bundang Medical Center, Seongnam, Republic of Korea, [8]Department of Oncology, Ajou University Hospital, Suwon, Republic of Korea, [9]Department of Oncology, St. Vincent's Hospital, Suwon, Republic of Korea, [10]Department of Oncology, Seoul National University Boramae Medical Center, Seoul, Republic of Korea, [11]Department of Oncology, Chung-Ang University Hospital, Seoul, Republic of Korea, [12]Department of Oncology, Veterans Health Service Medical Center, Seoul, Republic of Korea

Background: For extensive-stage small cell lung cancer (ES-SCLC) patients with progressive or recurrent disease after platinum-based combination chemotherapy, topotecan is recommended as second-line treatment. However, although some patients may achieve at least an objective response with topotecan, response duration is often short. Belotecan, a camptothecin derivative, inhibits topoisomerase I. Previous studies have demonstrated that belotecan has active antitumor activity against advanced SCLC and ovarian cancers. We report safety data from a phase IIb randomized multicenter study of belotecan as second-line treatment for progressive/recurrent limited-disease (LD)- or ES-SCLC.

Methods: This study, conducted from March 2010 to March 2018, was designed to prove the non-inferiority of belotecan to topotecan. Patients with recurrent ES-SCLC were randomized (1:1 ratio) to belotecan 0.5 mg/m^2 or topotecan 1.5 mg/m^2 intravenously for 5 consecutive days every 3 weeks for 6 cycles or until disease progression. Adverse events (AEs) were reported according to NCI-CTCAE (ver. 4.0) and categorized by System Organ Class and Preferred Term.

Results: Overall, 161 patients (belotecan, n = 80; topotecan, n = 81) were evaluable in the safety analysis set. Clinical characteristics were well balanced between the treatment arms. Although belotecan recipients received significantly more treatment cycles than topotecan recipients (p = 0.0210), there were no between-group differences in the number of patients who required dose reductions or who omitted treatment in each cycle. There were no statistically significant between-group differences in safety results: any AEs (including grade 3 or 4 AEs), adverse drug reactions (ADRs), severe AEs (SAEs) or severe ADRs (SADRs). The most common AEs in the belotecan and topotecan groups, respectively, were decreased neutrophil count (61 patients [76.3%] vs. 67 patients [82.7%]), anemia (37 [46.3% vs. 44 [54.3%]), decreased platelet count (33 [41.3%] vs. 43 [53.1%]), nausea (35 [43.8%] vs. 30 [37.0%), and anorexia (32 [40.0% vs. 36 [44.4%]).

Conclusions: Our study indicates that belotecan is a safe second-line treatment option for patients with progressive/recurrent LD- or ES-SCLC.

Clinical trial identification: NCT01497873.

Legal entity responsible for the study: Chong Kun Dang Pharmaceutical Corp.

Funding: Chong Kun Dang Pharmaceutical Corp.

Disclosure: All authors have declared no conflicts of interest.

1675P Retrospective study of paclitaxel in advanced therapy lines in the treatment of SCLC

D. von Eiff[1], F. Bozorgmehr[1], P. Christopoulos[1], I. Chung[1], D. Bernhardt[2], S. Rieken[2], S. Liersch[3], T. Muley[4], S. Kobinger[4], M. Thomas[1], M. Steins[1]

[1]Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital, Translational Lung Research Center Heidelberg (TLRC-H), German Center for Lung Research (DZL), Heidelberg, Germany, [2]Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg, Germany, [3]Pharmacy Department, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [4]Translational Research Unit, Thoraxklinik at Heidelberg University Hospital, Translational Lung Research Center Heidelberg (TLRC-H), German Center for Lung Research (DZL), Heidelberg, Germany

Background: Extensive-disease small cell lung cancer (ED-SCLC) is usually first treated with etoposide-/platinum-based chemotherapy. Despite high initial response rates, progression occurs frequently. While topotecan is approved as 2nd-line therapy, further treatment is not standardized. One of the drugs administered in progressed SCLC is paclitaxel. Here, we retrospectively analyzed prognostic factors and outcome of paclitaxel-treated SCLC patients.

Methods: SCLC patients treated with paclitaxel between 2005 and 2015 at Thoraxklinik at Heidelberg University Hospital were retrospectively reviewed. Significant prognostic factors were identified by univariate (Kaplan-Meier) and multivariate (Cox-Regression) analysis.

Results: 185 patients (119 men/66 women, median age 64 years, median ECOG performance status 1) were included. Paclitaxel was mainly given as 3rd- or 4th-line therapy (92%). The overall response rate was 17% and disease control rate (DCR) was 28%. Median progression-free survival (PFS) was 48 days (95%-CI: 42-54) and median overall survival (OS) 100 days (95%-CI: 84-116). Main toxicities were fatigue (25%) and peripheral neuropathy (17%), but no discontinuation of treatment was required. In 28%, the paclitaxel dose was reduced by 15-30%, mainly due to hematoxicities (in 57%). In univariate analysis, this was linked to a decrease in PFS ($p = 0,05$), while gender, age, performance status, number of metastatic sites, and presence of cerebral/hepatic metastases were not associated with changes in PFS. For OS, performance status, number of metastatic sites, cerebral/hepatic metastases, and dose reduction were significant ($p < 0,05$). In multivariate analysis, gender, age, and dose reduction retained as independent prognostic factors for PFS. In addition, performance status, cerebral/hepatic metastases, and pack years were identified as independent prognostic factors for OS.

Conclusions: With a DCR of 28% paclitaxel was still effective in heavily pretreated SCLC patients. However, patients should be selected carefully regarding age, performance status, and metastatic status. Especially, patients in good condition and without cerebral/hepatic metastases benefit from a paclitaxel therapy.

Legal entity responsible for the study: Martin Steins.

Funding: Thoraxklinik at Heidelberg University Hospital.

Disclosure: F. Bozorgmehr: Honoraria: MSD, Novartis; Research funding: BMS. S. Rieken: Honoraria and travel expenses: Elekta Inc., Accuray Inc., AstraZeneca GmbH, Bristol-Myers Squibb, Lilly, Roche, DGP, DKG, Degro; IITs and other research funding: Bristol-Myers Squibb, Accuray Inc., Merck KGaA; Consulting or advisory role: Accuray Inc., AstraZeneca GmbH. S. Liersch: Honoraria: MSD, Sanofi; Advisory board: BMS, Amgen, MSD. T. Muley: Research grants: Roche, Chugai Pharma; Travel expenses, patent applications: Roche. M. Thomas: Honoraria: Lilly, BMS, MSD, Roche, Pfizer, AstraZeneca; Advisory boards: Lilly, BMS, MSD, Roche, Pfizer, AstraZeneca, Cellgene, Mediolanum. All other authors have declared no conflicts of interest.

1676P Over-expression of shh is prognostic marker in patients with extensive stage small cell lung cancer

S. Lim[1], J. Kim[1], S.Y. Park[2]

[1]Hemato-Oncology, Wonju Severance Christianity Hospital, Gangwon-do, Republic of Korea, [2]Pathology, Konyang University Hospital, Daejeon, Republic of Korea

Background: Recent studies have reported that the sonic hedgehog (Shh) signaling pathway plays a crucial role during tumorigenesis, angiogenesis and cellular differentiation in various malignancies including lung cancer. The aim of this study is to investigate the value of Shh pathway as prognostic markers in extensive stage small cell lung cancer (ES-SCLC) patients.

Methods: We retrospectively analyzed the data of 36 patients with ES-SCLC between 2008 and 2012 in Yonsei Cancer Center. Using formalin fixed paraffin embedded tissues of primary tumors, immunohistochemistry was done for Gli1, Patched, Shh1, and Smo. We performed survival analysis to find out the prognostic impact of these markers.

Results: All the 36 patients were treated with platinum based doublet chemotherapy. Median progression free survival and median overall survival was 6.9 months (95% CI, 6.5-7.3) and 11.7 months (95% CI, 9.1-14.3), respectively. Overall response rate was 84%. Of the 36 specimens examined, the overexpression of Gli1, Patched, Shh, and Smo was found in 12 (33.3%), 5 (13.9%), 5 (13.9%), and 6 (16.7%), respectively. We found that high expression of Shh was associated with worse progression free survival (6.3 vs. 7.6 months, $p < 0.01$) and overall survival (9.2 vs. 12.0 months), whereas other markers were not related to the prognosis of patients.

Conclusions: To our knowledge, this is the first report of the relationship between components of the Shh signaling pathway and prognosis in SCLC. We found that a high proportion of tumors expressed proteins related to this pathway, and over-expression of Shh was correlated with worse survival in this analysis. Shh signaling in SCLC requires further investigation using a larger sample size.

Legal entity responsible for the study: IRB.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1677P UCHL1 has prognostic relevance and is a therapeutic target in high-grade neuroendocrine lung cancers

Y. Shimada, T. Okano, T. Ohira, N. Ikeda

Department of Surgery, Tokyo Medical University Hospital, Tokyo, Japan

Background: We discovered that ubiquitin carboxy-terminal hydrolase L1 (UCHL1), which was usually found in nerve cells throughout the brain, was widely shown in mesenchymal non-small cell lung cancers (NSCLC) and their exosomes and was partly responsible for promoting NSCLC invasion and metastasis. However, little is known about the biologic function of UCHL1 and its therapeutic potential in high-grade neuroendocrine lung cancers (HGNEC) including small cell lung cancer (SCLC) and large cell neuroendocrine cancer (LCNEC). Despite a high overall mutation rate in HGNEC, there are currently no molecularly targeted agents with proven clinical benefit for this disease. Here we show preclinical efficacy evoked by targeting UCHL1 that was relevant to prognosis in HGNEC.

Methods: We assessed the protein expressions of UCHL1 in SCLC cell lines (H69, H82, H526) and NSCLC cell lines, additive chemotherapeutic effects by using the combination of cisplatin/etoposide (PE) or cisplatin/irinotecan (PI) with selective UCHL1 inhibitors (WP1130 and LDN57444), whether the immunohistochemical (IHC) expression level of UCHL1 was associated with prognosis and recurrence in HGNEC patients, and the detectability of UCHL1 mRNA by circulating extracellular vesicles (EVs) in lung cancer patients.

Results: UCHL1 was overexpressed in all the SCLC cell lines and mesenchymal NSCLCs but not an epithelial NSCLC cell line. In SCLC model in vitro, combined the target of UCHL1 by selective UCHL1 inhibitors significantly improved the response of PE and PI therapies. IHC analysis of 72 HGNEC patient's tumor samples (SCLC/LCNEC = 34/38) demonstrated that UCHL1 expression significantly correlated with unfavorable overall and recurrence-free survival and contributed to distinguishing SCLC from LCNEC. EVs isolated from lung cancer cell lines and the serum from SCLC and adenocarcinoma patient were verified by electron microscopy and nanoparticle tracking analysis. Increased EVs-derived UCHL1 level was shown in the serum from 2 out of 5 SCLC patients with immunohistochemically high UCHL1 expression while no expression was observed in that from 5 adenocarcinoma patients.

Conclusions: UCHL1 can be a potential prognostic marker and a promising druggable target in HGNEC.

Legal entity responsible for the study: Norihiko Ikeda.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1678P Robustness of DLL3 (SP347) immunohistochemistry assay for detection of DLL3 protein in small cell lung cancer

C. Powell[1], E. Elgabry[2], B. Holmes[2], D. Tyree[2], R. Marati[2], B. Admire[2], T. Birdi[2], A.E. Hanlon Newell[2], B. Damadzadeh[2], D. Dalvi[2], R.S.P. Huang[2]

[1]Development, Ventana Medical Systems, Inc., Tucson, AZ, USA, [2]Medical Affairs, Ventana Medical Systems, Inc., Tucson, AZ, USA

Background: Delta-like protein 3 (DLL3) is a transmembrane protein that is implicated in the tumorigenesis of small cell lung cancer (SCLC). The ability to quantify DLL3 protein may be useful to select patients that may be responsive to DLL3-targeted therapies; thus, the VENTANA DLL3 (SP347) Assay was developed for this purpose. Here, we present data on the robustness of the VENTANA DLL3 (SP347) Assay in SCLC.

Methods: Formalin-fixed, paraffin-embedded (FFPE) SCLC resection and biopsy specimens were used in a series of studies addressing robustness. These samples were stained with the VENTANA DLL3 (SP347) Assay and assessed by pathologists for percent tumor cell staining (%TC) at $\leq$ 4X magnification at any stain intensity. The %TC scores were stratified into bins (0-24, 25-49, 50-74 and 75-100 %TC) and assessed for precision across different antibody and detection kit lots, replicates, days, instruments, and platforms. For each case, the modal staining result based on %TC bin was determined and the result from each test sample was compared to its respective case-level modal staining result and deemed concordant or discordant. Results were aggregated across cases and the overall percent agreement (OPA) was calculated for each study.

Results: All studies (Table) showed >90% OPA for concordance to the %TC bins.

Table: 1678P Precision across lots, replicates, days, instruments, and platforms

Study	# of Cases	# DLL3 Observations	OPA
Intra-day	10	50	100.0%
Inter-day	10	100	94.0%
Inter-antibody lot, inter-detection kit lot, and intra-platform	24	648	95.8%
Intra-platform (GX)	14	84	98.8%
Intra-platform (XT)	14	84	97.6%
Intra-platform (ULTRA)	14	84	98.8%
Inter-platform (GX, XT, and ULTRA)	14	252	98.4%

Conclusions: The data shows that the VENTANA DLL3 (SP347) Assay can precisely evaluate DLL3 expression in SCLC.

Legal entity responsible for the study: Ventana Medical Systems, Inc.

Funding: Ventana Medical Systems, Inc.

Disclosure: C. Powell, E. Elgabry, B. Holmes, D. Tyree, R. Marati, B. Admire, T. Birdi, A.E. Hanlon Newell, D. Dalvi, R.S.P. Huang: Employee: Ventana Medical Systems, Inc./Roche.

1679P Residential radon and small cell lung cancer: A systematic review

Á. Rodríguez Martínez[1], A. Ruano Ravina[2], M. Torres Duran[3]

[1]Medical Oncology, Complejo Hospitalario de Pontevedra, Pontevedra, Spain, [2]Preventive Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain, [3]Neumologia, Complejo Hospitalario de Vigo, Vigo, Spain

Background: Residential radon exposure is considered the second cause of lung cancer (LC) and the first in never smokers. Nevertheless, the association between the different histological types of LC and radon is not completely clear, and radon effect on small cell lung cancer (SCLC) is not completely understood. We aim to asses the effect of residential radon exposure on the risk of SCLC in general population and miners through a systematic review applying predefined inclusion and exclusion criteria.

Methods: We performed a literature research in PubMed and EMBASE following PRISMA methodology. We included: studies performed in humans; studies showing the specific effect of radon on SCLC histological type separately; studies with at least 10 SCLC cases and the overall sample size higher than 50 individuals; systematic reviews, pooling studies, cohort studies, case-control studies and mortality studies with comparison group; studies performed both in general population and on miners; studies with anatomopathological confirmation; studies in English, Spanish and French. To asses the quality of each of the included studies we designed a quality scale with 5 items which scored characteristics of the included papers: sample size, number of SCLC cases, results adjusted by covariates, study design, and method of assesment of radon concentration. We have given different weights to these characteristics creating a continuous scale from 0 to 10.

Results:

Conclusions: Exposure to radon increases the risk of SCLC. Nevertheless, more research should be addressed in order to know exactly the magnitude of this risk. It seems that SCLC is the LC histological type most associated to radon exposure, with this fact happening both in miners' and general population studies. To this end, more well-designed case-control studies are necessary. It is also necessary to increase radon awareness among citizens and administrations in order they can establish the necessary protective and mitigation measures against residential radon.

Legal entity responsible for the study: Angeles Rodriguez Martinez.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1680P Nomogram for predicting the benefit of surgery for stage IA-IIB small cell lung cancer

Y. Wang[1], Z. Wang[1], Q. Zheng[2]

[1]Department 1 of Thoracic Oncology Medicine, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China, [2]Department of Epidemiology and Biostatistics, Peking University, Beijing, China

Background: The role of surgical resection remains controversial in small cell lung cancer (SCLC) although there are some retrospective and population-based studies indicate that patients with very early stage SCLC has longer survival compared with those not given surgery. The specific aim of this study was to identify the survival benefit of surgery for patients with Stage IA-IIB SCLC and nomogram predictive model was created to select patients who are eligible to surgery.

Methods: Patients diagnosed with stage IA-IIB SCLC between 2004 and 2014 were selected from the SEER database. The primary endpoint was overall survival. Multivariate Cox proportional regression and coefficients of the predictors were calculated. A nomogram was constructed for predicting 1- and 3-year overall survival probability. All statistical analysis was performed with R software.

Results: 2246 patients with stage I-II were enrolled. 618 (27.5%) received surgery and 1628 (72.5) not. Unadjusted median overall survival (OS) was 23 months (95% CI: 21-24), which was 35 months (95% CI: 31-44) vs. 19 months (95% CI: 18-21) in surgery and non-surgery groups respectively ($p < 0.0001$). We used a propensity score to balance observed covariates. OS benefit was observed in all subgroups between the surgery and non-surgery group except in the non-White race, well or moderately grading, stage IIA or IIB and N1 lymph involvement. Multivariate Cox proportional hazards regression analysis showed a survival benefit in the surgery group compared with non-surgery group no matter balanced by propensity score weighting or not. The competing-risks nomogram was built for predicting 1-year and 3-year survival. The age, tumor size, extent of tumor, N0/1 and surgery with radiation and chemotherapy were introduced as variables. The calibration of internal validation for predicting survival at 1 and 3-year by this nomogram-predicted probability was identical to the actual probability.

Conclusions: Surgery was proved to benefit patients with stage IA-IIB SCLC by this relatively large number population-based study and a nomogram built from a parametric survival model from the SEER database can be used to predict which patients with stage IA-IIB SCLC may benefit from surgery.

Legal entity responsible for the study: Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department 1 of Thoracic Oncology Medicine, Peking University Cancer Hospital & Institute.

Funding: National Natural Science Foundation of China, Award (81401914) and Beijing Municipal Administration of Hospitals' Youth Programme (20161112).

Disclosure: All authors have declared no conflicts of interest.

Table: 1679P

Author (year)	Study design and location	Sample size	Lung cancer risk	Significance	Conclusion	Score
Biberman 1993	Case-control Israel	n = 70 20	Median radon level in SCLC group of 1.09 vs 0.9 pci/L. OR 1.5 (0.4-5.4).	Non significant	Exposure to radon was identified as an etiological agent of SCLC.	3
Darby 2004	Pooling study of 13 case-control studies Europe	n = 21,356 1,379	ERR per 100 Bq/m3 31,2%(12,8-60,6%) for SCLC vs 2,6% (0-10%) for other subtypes. p = 0.03	Statistically significant	Strong evidence of an association between residential radon concentration and SCLC. The dose-response relation was to be linear. The absolute risk to smokers was greater.	9
Wilcox 2007	Case-control New Jersey	n = 1,301 105	ERR 100-149 Bq/m3 3,05 (for men) and 2,46 (for women) For >150 Bq/m3 0,00 (for men) y 2,67 (for women)	Statistically significant	No significant increase of the risk of lung cancer with increasing radon levels; however, radon exposure showed stronger effect with SCLC on both males and females.	8

Continued

Table: 1679P *Continued*

Author (year)	Study design and location	Sample size	Lung cancer risk	Significance	Conclusion	Score
Wichmann 2005	Pooling study of 2 case-control studies Germany	n = 7,195 712	ERR per 100 Bq/m3 of 0,29 (0,04-0,78)	Non significant	The effect of radon is stronger for SCLC, whereas no association between radon and lung cancer was found.	8
Krewsky 2004	Pooling study of 7 case-control studies North América	n = 8,628 577	ERR per 100 Bq/m3 in 5-30 years of 0,23 (-0,08-0,88) for SCLC.	Non significant	Association between residential radon exposure and lung cancer, with strongest association for SCLC.	10
Field 1991	Case-control Iowa	n = 1,027 74	WLM 12,71-16,94 OR 1,36 (0,4-4,44) WLM > 16,95 OR 1,44 (0,47-4,35) p = 0.33	Non significant	Cumulative radon exposure in the residential environment is significantly associated with lung cancer risk, with strongest effect for SCLC.	5
Barros-Dios 2012	Case-control Galicia	n = 862 54	AOR p 101-147 Bq/m3 3,01 (1,01-8,97) AOR 147 Bq/m3 2,43 (0,79-7,45)	Statistically significant	Even with low exposures, radon is a risk factor of lung cancer, with greatest influence on SCLC. Additive interaction between radon exposure and tobacco consumption.	6
Sandler 2006	Case-control Connecticut and Utah	n = 3,285 51	ERR per 100 Bq/m3 increase in radon concentration for SCLC 0.165 (-0.35-0.69)	Non significant	No evidence of an increased risk for lung cancer (and SCLC) at the exposure level of radon observed.	7
Jonsson 2009	Cohort Sweden	n = 5,486 55	ERR p kBq year/m3 0,072 (-0,03-0,147)	Non significant	A significantly increased risk for SCLC was observed at low radon exposure levels. The proportion of SCLC among miners was high compared to the general population in Sweden.	5
Saccomanno 1988	Cohort Colorado	n = 383 121	For levels > 300WLM EOR of 57%.	Statistically significant	In levels > 300 WLM an increased risk of lung cancer was detected. The incidence in SCLC was significantly elevated (57%) over other types. An additive effect in smokers was observed.	5
Svensson 1989	Case-control Stockholm	n = 210 41	4500-6000 Bq/m3 RR 1,9 (1,2-5,8) +6000 Bq/m3 RR 4,7 (0,5-5,7) p = 0.01	Statistically significant	Association between cumulated radon exposure and lung cancer in women, particularly strong for SCLC.	2
Bochicchio 2005	Case-control Lazio	n = 788 43	EOR p 100 Bq/m3 0.22 (-0.21-0.89) for SCLC.	Non significant	A higher risk for SCLC at elevated radon levels was detected. Dietary antioxidants may act as an effect modifier.	4
Alavanja 1999	Case-control Mossouri	n = 1,058 117	OR of 3.33 for > 148Bq/m3 for SCLC. P = 0.3.	Non significant	A significant SCLC increased risk was found for radon concentrations at and above the action level for mitigation of houses in USA (148 Bq/m3).	5
Letourneau 1993	Case-control Canada	n = 1,476 117	OR 0.79 (0.44-1.41) cumulated exposure of radon 5-30 years. 3,750 Bq/m3-year	Non significant	No increase in the relative risk for any of the histologic types of lung cancer was observed in relation to cumulative exposure to radon.	7
Pershagen 1994	Case-control Sweden	n = 4207 166	ERR per unity of radon 0.15 (0.43) for SCLC, RR of 2.8 (1.3-5.9) for Ra > 400 Bq/m3.	Statistically significant	The risk of lung cancer increased in relation to both estimated cumulative and time-weighted exposure to radon. The strongest association was suggested for SCLC.	6
Blot 1990	Case-control North of China	n = 664 39	OR for SCLC increased with residential radon being SCLC de histological type with the highest risk.	There is no information on statistically significance	A moderate association of increased radon levels and SCLC is observed. A moderate association os increased radon levels and SCLC is observed.	6

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii603–viii640, 2018
doi:10.1093/annonc/mdy300

SUPPORTIVE CARE

1681O **Evaluation of practice patterns for prevention of chemotherapy (CT)-induced nausea and vomiting (CINV) and antiemetic guidelines (GLs) adherence based on real-world prescribing data**

M.S. Aapro[1], F. Scotté[2], Y. Escobar[3], L. Celio[4], R.D. Berman[5], A. Franceschetti[6], D. Bell[7], K. Jordan[8]

[1]*Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland,* [2]*Medical Oncology and Supportive Care Department, Foch Hospital, Suresnes, France,* [3]*Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain,* [4]*Department of Medical Oncology and Hematology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy,* [5]*The Christie NHS Foundation Trust, Manchester, UK,* [6]*Ipsos MORI, London, UK,* [7]*Ipsos Healthcare, Mahwah, NJ, USA,* [8]*Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany*

1683PD **Factors that influence oncology nutrition efficacy in breast cancer patients under antiestrogenic treatment**

D.V. Artene[1], A. Blidaru[2]

[1]*Oncology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania,* [2]*Surgical Oncology, Alexandru Trestioreanu Oncology Institute, Bucharest, Romania*

1685PD **Effects of 6-month exercise training on quality of life in pancreatic cancer patients: Results from a randomized controlled trial**

K. Steindorf[1], D. Clauss[1], C. Tjaden[2], F. Herbolsheimer[1], L. Schneider[2], C. Ulrich[3], T. Hackert[2], J. Wiskemann[4]

[1]Division of Physical Activity, Prevention and Cancer, German Cancer Research Center, Heidelberg, Germany, [2]Department of General Surgery, University Hospital Heidelberg, Heidelberg, Germany, [3]Department of Population Health Sciences, Huntsman Cancer Institute, Salt Lake City, UT, USA, [4]Medical Oncology, Nationales Zentrum für Tumorerkrankungen (NCT), Heidelberg, Germany

1686PD **Plinabulin (Plin), a novel non-G-CSF molecule for the revention of chemotherapy-induced neutropenia (CIN), has the potential to positively impact tumor micro environment**

D. Blayney[1], S. Ogenstad[2], Y-K. Shi[3], Q. Zhang[4], L. Du[5], L. Huang[6], R. Mohanlal[6]

[1]Medical Oncology, Stanford Comprehensive Cancer Institute, Stanford, CA, USA, [2]Biostatistics, Statogen Consulting, Durham, NC, USA, [3]Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS), Beijing, China, [4]Oncology, Third Affiliated Hospital of Harbin Medical University, Harbin, China, [5]Clinical, Wanchun Bulin Pharmaceutical, Co. Ltd., Dalian, China, [6]Clinical, BeyondSpring Pharmaceuticals, New York, NY, USA

1687PD **Neuropathy and health behaviors in cancer survivors treated with chemotherapy (CT)**

M. Matias[1], A. Di Meglio[2], A. Zingarello[2], S. Michiels[3], A.H. Partridge[4], M.K. Bendiane[5], M.P. Ducreux[1], F. André[2], I. Vaz Luis[2]

[1]Medical Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France, [2]INSERM UMR 981, Gustave Roussy, Université Paris-Saclay, Villejuif, France, [3]Biostatistics and Epidemiology, Gustave Roussy, Université Paris-Saclay, Villejuif, France, [4]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [5]INSERM UMR912, Provence-Alpes-Côte d'Azur Regional Health Observatory, Marseille, France

1688PD **Awareness of the cancer and non-cancer related harms of continued smoking in cancer survivors**

L. Eng[1], S. Liu[2], D. Farzanfar[1], E.C. Smith[2], A. McCartney[1], A. Basgaran[1], K. Balaratnam[1], S. Yeung[1], M.C. Brown[2], D. Howell[2], J.M. Jones[1], W. Xu[2], D. Goldstein[3], W.K. Evans[4], P. Selby[5], M.E. Giuliani[6], G. Liu[2]

[1]Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [2]Department of Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, ON, Canada, [4]Division of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, ON, Canada, [5]Prevention, McMaster University, Hamilton, ON, Canada, [6]Addictions, Centre for Addiction and Mental Health, Toronto, ON, Canada, [7]Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada

1689PD **Breast cancer (BC) related fatigue: A longitudinal investigation of its prevalence, domains and correlates**

I. Vaz Luis[1], A. Di Meglio[1], M. El-Mouhebb[1], A. Dumas[2], C. Charles[1], G. Menvielle[3], C. Mesleard[4], A.L. Martin[4], P.H. Cottu[5], F. Lerebours[5], C. Coutant[6], A. Lesur[7], S. Dauchy[8], P. Arveux[6], S. Delaloge[9], N. Lin[10], P. Ganz[11], A.H. Partridge[12], S. Michiels[13], F. André[14]

[1]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [2]Clinical Research, Institut Gustave Roussy, Villejuif, France, [3]IPLESP, Faculte de Medecine de Saint-Antoine, Paris, France, [4]Research & Develpment, UNICANCER, Paris, France, [5]Department of Medical Oncology, Institut Curie, Paris, France, [6]Medical Oncology, Centre Georges-François Leclerc, Dijon, France, [7]Medical Oncology, Institut de Cancérologie de Lorraine, Nancy, France, [8]Supportive Care, Gustave Roussy Institut de Cancérologie, Villejuif, France, [9]Medical Oncology, Gustave Roussy, Villejuif, France, [10]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, [11]Medical Oncology, UCLA, Los Angeles, CA, USA, [12]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [13]Team Oncostat, CESP, Gustave Roussy, Villejuif, France, [14]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France

1690PD **Acceptability in cancer outpatients of completing routine assessments of patient reported outcomes of common terminology criteria for adverse events (PRO-CTCAE) versus other patient reported symptom outcome tools**

H. Albaba[1], M.C. Brown[1], S. Shakik[1,2], S. Su[3], H. Naik[4], T. Wang[5], M. Liang[1], A. Perez-Cosio[1,2], L. Eng[1], N. Mittmann[6], W. Xu[3], G. Liu[1,2,8], D. Howell[1,7], T.A. Barnes[1]

[1]Medical Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [2]Epidemiology, Dalla Lana School of Public Health, Toronto, ON, Canada, [3]Biostatistics, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, [4]Department of Medicine, University of British Columbia, Vancouver, BC, Canada, [5]Faculty of Pharmacy, University of Toronto, ON, Canada, [6]CancerCare Ontario and Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [7]Lawrence S. Bloomberg School of Nursing, University of Toronto, Toronto, ON, Canada, [8]Medical Biophysics, University of Toronto, Toronto, ON, Canada

1691P Updated meta-analysis of randomized controlled trials (RCTs) to determine the CDK 4/6 inhibitors associated venous thromboembolism (VTE) risk in hormone receptor-positive breast cancer (BC) patients

K.Z. Thein[1], S. Ball[2], M.H. Zaw[3], A.M. Tun[4], M. Quirch[2], F. Hardwicke[1], N. D'Cunha[1], L. Tijani[1], C. Jones[1], T.H. Oo[5]

[1]Hematology Oncology, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [2]Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [3]Internal Medicine, The Brooklyn Hospital Center, Brooklyn, NY, USA, [4]Hematology Oncology, The Brooklyn Hospital Center, Brooklyn, NY, USA, [5]Benign Hematology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: Majority of BC express hormone receptors and cyclin dependent kinases especially CDK4/6 have been proven to mediate hormone therapy resistance. Many CDK 4/6 inhibitors have shown survival benefits. Yet, the VTE risk remains considerable. We undertook an updated meta-analysis of RCTs to determine the VTE risk among patients with hormone receptor-positive metastatic BC treated with CDK 4/6 inhibitors.

Methods: MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018 were queried. RCTs that mention VTE as adverse effect were incorporated in the meta-analysis. The primary meta- analytic approach was a fixed effects model using the Mantel-Haenszel (MH) method. It was used to calculate the estimated pooled risk ratio (RR) and risk difference (RD) with 95% confidence interval (CI).

Results: Five phase III studies and one phase II study with a total of 3,159 patients were eligible. The study arms used palbociclib-letrozole, palbociclib-fulvestrant, ribociclib-letrozole, abemaciclib-fulvestrant, abemaciclib-letrozole/anastrozole while the control arms utilized placebo in combination with letrozole or anastrozole or fulvestrant. The I^2 statistic for heterogeneity was 16.452, and the heterogeneity X^2 (Cochran's Q) was 5 ($P = 0.308$), suggesting homogeneity among RCTs. The VTE incidence was 40 (2.03%) in CDK 4/6 inhibitors group vs 5 (0.42%) in control group. The pooled RR for VTE in CDK 4/6 inhibitors group was 3.561 (95% CI: 1. 574 to 8.057, $P = 0.002$) and the absolute RD was 0.014 (95% CI: 0.002 to 0.027, $P = 0.022$) according to the fixed effects model. By the random effects model, the pooled RR was 3.072 (95% CI: 1.138 to 8.294, $P = 0.027$) and RD was 0.015 (95% CI: 0.007 to 0.023, $P < 0.0001$).

Conclusions: Our meta-analysis showed that the addition of CDK 4/6 inhibitors to letrozole or fulvestrant, contribute to higher incidence of VTE. Patients on CDK 4/6 inhibitors group experienced a significant increase in the VTE risk with a RR of 3.56. VTE remains the second leading cause of death in cancer patients receiving antineoplastic therapy and close monitoring is required.

Legal entity responsible for the study: Kyaw Zin Thein, Texas Tech University Health Sciences Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1692P Physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in BRCA-mutated breast cancer (BC) patients (pts): Results from the BCY3/BCC 2017 survey

M. Lambertini[1], M. Di Maio[2], F. Poggio[3], O. Pagani[4], G. Curigliano[5], L. Del Mastro[6], S. Paluch-Shimon[7], S. Loibl[8], A.H. Partridge[9], H.A. Azim Jr[10], F.A. Peccatori[11], I. Demeestere[12]

[1]Medical Oncology, Institute Jules Bordet, Brussels, Belgium, [2]Department of Oncology, University of Turin, Turin, Italy, [3]Medical Oncology, IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [4]Breast Unit, Institute of Oncology of Southern Switzerland, Lugano, Switzerland, [5]Early Drug Development for Innovative Therapies Division, Istituto Europeo di Oncologia, Milan, Italy, [6]Internal Medicine, IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [7]Medical Oncology, Shaare Zedek M.C, Jerusalem, Israel, [8]Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany, [9]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [10]Internal Medicine, American University of Beirut, Beirut, Lebanon, [11]Fertility and Procreation Unit, Istituto Europeo di Oncologia, Milan, Italy, [12]Fertility Clinic, Hopital Erasme, Brussels, Belgium

Background: No data are available on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in BRCA-mutated BC pts.

Methods: A 26-item survey exploring fertility preservation and pregnancy after BC was emailed to physicians attending the 2016 3rd ESO-ESMO BCY3 and the 2017 15th St. Gallen BCC 2017 conferences. The present analysis investigated potential differences in physicians' knowledge, attitudes and practice towards these issues in BC pts with or without BRCA mutations. The McNemar test for paired proportions was used for statistical comparison.

Results: The survey was completed by 273 physicians (105 at BCY3 and 168 at BCC 2017) with a median age of 46 years (range 38-55); the majority were medical oncologists (56%) practicing in an academic setting (86%). A comparable proportion of respondents suggested the use of either embryo (43% vs. 39%; $p = 0.11$) or oocyte (62% vs. 63%; $p = 0.77$) cryopreservation as available options for BC pts with or without BRCA mutations, respectively. Conversely, ovarian tissue cryopreservation (33% vs. 40%; $p = 0.009$) and GnRHa during chemotherapy (74% vs. 81%; $p = 0.001$) were less commonly suggested in BRCA-mutated BC pts than in BC pts without BRCA mutations. 42% agreed or were neutral on the statement that controlled ovarian stimulation should not be considered safe in BRCA-mutated BC pts. 45% and 30% agreed or were neutral on the statement that pregnancy in BC survivors may increase the risk of recurrence in BRCA-mutated BC pts and in BC pts overall, respectively ($p < 0.001$). 15% and 3% disagreed that transplanting the cryopreserved ovarian tissue harvested at the time of BC diagnosis can be considered safe in pts with or without BRCA mutations, respectively ($p < 0.001$).

Conclusions: These results highlight the presence of several misconceptions on fertility preservation and pregnancy after BC that persist even among physicians directly involved in BC care. Focused research efforts to address fertility and pregnancy-related issues in BRCA-mutated BC pts and education to improve physicians knowledge and adherence to available guidelines are urgently needed.

Legal entity responsible for the study: Matteo Lambertini.

Funding: Has not received any funding,

Disclosure: M. Lambertini: Support from the European Society for Medical Oncology (ESMO) for a Translational Research Fellowship at the Institut Jules Bordet (Brussels, Belgium). All other authors have declared no conflicts of interest.

1693P Analysis of parameters to predict the effectiveness of scalp cooling to prevent chemotherapy-induced alopecia in breast cancer patients

C.M. Kurbacher[1], S. Herz[1], A.T. Kurbacher[1], G. Kolberg[1], N. Kettelhoit[1], A. Schott[1], J.A. Kurbacher[2]

[1]Gynaecological Oncology, Gynaecological Center Bonn-Friedensplatz, Bonn, Germany, [2]General Gynaecology and Obstetrics, Gynaecological Center Bonn-Friedensplatz, Bonn, Germany

Background: Sensor-controlled scalp cooling (SCSC) has been found to be effective to prevent chemotherapy (Ctx)-induced alopecia (CIA). This retrospective study sought to obtain detailed information which clinical parameter is able to predict the success of SCSC in patients (pts) with primary (PBC) or recurrent/metastatic breast cancer (R/MBC) exposed to neoadjuvant (NACT), adjuvant (ACT), or palliative Ctx (PCT) using anthracyclines (A), taxanes (T), both given at different schedules (A+T/A→T, T→A) or none of them (non-A/non-T).

Methods: 109 pts who underwent SCSC were included: NACT, 47 (54.6%); ACT, 40 (45.4%); PCT 22; dose-dense (dd) Ctx, 38 (44.2%); non-dd Ctx 48 (55.8%); premenopausal, 48 (55.8%); postmenopausal, 38 (44.2%). Ctx regimens were: A+T/A→T, 41 (37.6%), T→A, 23 (26.7%), T, 34 (31.2%), non-A/non-T, 11 (10.1%). 3 wks after the last Ctx cycle, CIA was quantified according to the Dean score (DS). Data were analyzed in regard to the SCSC completion rate, and the quality of hair preservation (success: DS 0-2, failure: DS 3-4). The following parameters were investigated in regard to the success of SCSC: menopausal status, pretreatment, setting of Ctx, Ctx schedule, Ctx regimen.

Results: Success rate was 67.9% with 47 pts (43.1%) experiencing complete (DS 0), and 27 (24.8%) showing partial response (DS 1-2). 30 pts (27.5%) stopped SCSC prematurely with CIA being the reason in 21 pts (19.3%). Effectiveness of SCSC did not differ for most analyzed subgroups. The relative risk (RR) to experience CIA was 1.18 (CI: 0.91-1.53, p=NS) for post- vs premenopausal pts, 1.27 (CI: 0.99-1.64, p=NS) for Ctx-naïve vs pretreated pts, 1.18 (CI: 0.89-1.56, p=NS) for dd Ctx vs non-dd Ctx, 1.42 (CI: 1.03-1.80, $p = 0.05$) for NACT/ACT vs PCT, and 1.42 (1.11-1.85, 0.012) for A-based Ctx vs non A-based Ctx. Success rates for A+T/A→T, T→A, T, and non-A/non-T were 48.8%, 73.9%, 79.4%, and 90.9% ($p = 0.015$).

Conclusions: SCSC could effectively prevent CIA in a real-world population of pts with PBC or R/MBC with all subgroups of pts benefiting. NACT/ACT and A-based Ctx are associated with lower success rates of SCSC. However, the effectiveness of SCSC associated with A-based Ctx can be as high providing that Ctx does not start with an anthracycline.

Legal entity responsible for the study: Christian M. Kurbacher, Gynaecological Centre Bonn-Friedensplatz.

Funding: Has not received any funding,

Disclosure: All authors have declared no conflicts of interest.

1694P A phase I safety study of topical calcitriol (BPM31543) for the prevention of chemotherapy-induced alopecia (CIA): Final study results

M. Lacouture[1], H. Dion[2], S. Ravipaty[3], V.R. Akmaev[4], R. Sarangarajan[3], J.J. Jimenez[5], N.R. Narain[6], B. Berman[7], S. Goldfarb[8]

[1]Dermatology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Clinical Operations, BERG, LLC, Framingham, MA, USA, [3]Biosystems, BERG, LLC, Framingham, MA, USA, [4]Analytics, BERG, LLC, Framingham, MA, USA, [5]Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA, [6]Biosystems, Analytics, & Precision Medicine, BERG, LLC, Framingham, MA, USA, [7]Dermatology, University of Miami Miller School of Medicine, Miami, FL, USA, [8]Oncology, Hematology and Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: Chemotherapy-induced alopecia (CIA) negatively effects psychosocial health and quality of life. Currently there are no FDA approved pharmacologic agents available to prevent CIA. Topical calcitriol, a vitamin D3 analog, has been shown in

murine studies to reduce CIA, likely due to arrest of cell cycle in healthy hair follicles, and reduction in the sensitivity of follicular epithelium to chemotherapy.

Methods: A 3 + 3 dose-escalation Phase 1 study with 3-6 patients at 5, 10, 20, 40, 60, 80 μg/mL was examined in 23 patients (pts) with breast cancer, gynecologic cancer or sarcomas receiving a taxane-based chemotherapy regimen. Pts applied 1mL of topical calcitriol (BPM31543) to the scalp BID, ≥ 5 days prior to chemotherapy for 3 months or treatment completed. The maximum tolerated dose (MTD) was determined by dose escalation in stepwise increments of the prior dose, in the absence of dose-limiting toxicity (DLT) during the first 28 days of application. Adverse event (AE) monitoring, pharmacokinetics, blinded photographic assessments and patient self-assessment were assessed.

Results: 22 treated pts experienced 1 treatment emergent adverse event (TEAE). The most frequently experienced TEAEs were fatigue (47.8%), nausea (39.1%), peripheral sensory neuropathy (30.4%), maculopapular rash and elevated vitamin D (26.1%). Elevated vitamin D and rash were possibly or probably related to treatment, while fatigue, nausea, neuropathy were likely due to chemotherapy. The majority of AEs were mild to moderate in severity. 13 TEAEs were considered Grade 3, but were not considered treatment related by the investigators. Hair loss <50% from baseline was observed in 8 pts at Week 7. At Week 15, 2 pts had <50% hair loss maintained. There were no detectable effects of topical BPM31543 on serum levels of calcitriol.

Conclusions: BPM31543 applied topically twice daily to the scalp in patients receiving taxane-based chemotherapy is safe and well-tolerated with no apparent differences in safety between doses. Here, no DLT was observed at up to 80 μg/mL and MTD was not reached. Some efficacy was detected at each dose. These data are encouraging and support further investigation in Phase 2/3 trials.

Clinical trial identification: NCT01588522.

Editorial acknowledgement: Khampaseuth Thapa, BERG, LLC.

Legal entity responsible for the study: BERG, LLC.

Funding: BERG, LLC.

Disclosure: M. Lacouture: Research sponsorship: BERG, LLC, Veloce Pharma. H. Dion, S. Ravipaty, V.R. Akmaev: Employee and stock options: BERG, LLC. R. Sarangarajan: Co-founder, employee and stock options: BERG, LLC. J.J. Jimenez, S. Goldfarb: Research sponsorship: BERG, LLC. N.R. Narain: Co-founder, President, CEO, stock options: BERG, LLC. B. Berman: Research sponsorship; BERG, LLC., Leo, Biofrontera, Tigercat; Stock or other ownership: Dermira, Sonoma, Celumigen.

1695P Acupuncture for peripheral neuropathy in cancer patients: TCM diagnosis as a predictor of treatment response

W. Liu[1], A. Qdaisat[2], G. Lopez[1], S. Underwood[1], M. Spano[1], A.R. Akhila Reddy[1], Y. Guo[1], S-C. Yeung[2], E. Bruera[1], M.K. Garcia[1], L. Cohen[1]

[1]*Palliative, Rehabilitation & Integrative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA,* [2]*Emergency Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Background: Acupuncture has been recognized as an effective integrative modality for managing peripheral neuropathy. However, data regarding predictors for response to acupuncture in cancer patients experiencing neuropathy are limited. We explored associations between patient characteristics, including traditional Chinese medicine (TCM) diagnosis, and treatment response among cancer patients who received acupuncture for peripheral neuropathy.

Methods: We reviewed acupuncture records in cancer outpatients with a primary reason for referral listed as peripheral neuropathy from March 2016 to April 2018. Treatment response was assessed using numbness/tingling score with a modified Edmonton Symptom Assessment Scale (ESAS; 0-10 scale) administered before and after each acupuncture treatment. Associations between TCM diagnosis, individual patient characteristics, and treatment response rate were analyzed by Wilcoxon's test.

Results: A total of 1745 acupuncture records (333 patients) were identified. The majority were female (71%), and 96 (29%) had breast cancer. The median (IQR) reduction in numbness/tingling score was 20% (0-50; $P < 0.001$). The most frequent TCM diagnosis was qi stagnation (86%) followed by blood stagnation (79%). Presence of blood stagnation and damp accumulation were predictors of poorer response as indicated by less reduction in numbness/tingling score (20% vs. 25%, $P < 0.001$ and 17% vs. 20%, $P = 0.036$; respectively). Factors associated with greater reduction in numbness/tingling score included age ≥ 60 (20% vs.17%, $P = 0.006$), female sex (22% vs. 17% in males, $P = 0.039$), and BMI ≥ 30 (25% vs. 20% in BMI < 30, $P = 0.016$).

Conclusions: Certain features of TCM diagnoses were associated with a poorer response, while being older, female, and obese were associated with a better response to treatment with acupuncture for peripheral neuropathy in cancer patients. This data may help design future clinical trials to better understand these factors and evaluate overall response to acupuncture in patients with peripheral neuropathy.

Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1696P A randomized, open-label, non-inferiority study comparing the efficacy and safety of lipegfilgrastim versus pegfilgrastim in elderly patients with aggressive B-cell non-Hodgkin lymphomas (B-NHL): AVOID neutropenia

H. Link[1], G. Illerhaus[2], U.M. Martens[3], A. Salar[4], R. Depenbusch[5], A. Kohler[6], M.M. Engelhardt[7], S. Mahlmann[8], M. Zaiss[9], A. Lammerich[10], P. Bias[10], A. Buchner[10]

[1]*Praxis Professor Link, Kaiserslautern, Germany,* [2]*Klinik für Hämatologie, Onkologie und Palliativmedizin, Klinikum Stuttgart - Olgahospital, Stuttgart, Germany,* [3]*Klinik für Innere Medizin III, SLK-Kliniken Heilbronn GmbH, Heilbronn, Germany,* [4]*Hematology Department, Hospital del Mar, Barcelona, Spain,* [5]*Onkodok GmbH, Gütersloh, Germany,* [6]*Gemeinschaftspraxis für Hämatologie und Onkologie Dres. Köhler/Fuchs, Langen, Germany,* [7]*Hämatologie, Onkologie und Stammzelltransplantation, University of Freiburg Medical Centre, Freiburg, Germany,* [8]*Klinik für Innere Medizin I, Hämatologie, Onkologie und Stammzelltransplantation, Westpfalz-Klinikum GmbH, Kaiserslautern, Germany,* [9]*Praxis für Interdisziplinäre Onkologie & Hämatologie, Freiburg, Germany,* [10]*Clinical Development, Merckle GmbH, Ulm, Germany*

Background: Lipegfilgrastim (LONQUEX®) has proven to be non-inferior to pegfilgrastim (NEULASTA®) in the reduction of the duration of severe neutropenia (DSN) in breast cancer patients. The efficacy and safety of lipegfilgrastim versus pegfilgrastim in elderly patients with B-NHL at high risk for R-CHOP-21-induced neutropenia was investigated. The primary efficacy endpoint was the DSN in cycle 1.

Methods: One hundred and one patients with NHL, median age of 74 years, were randomized to receive either 6 mg of lipegfilgrastim or pegfilgrastim per cycle during 6 cycles of R-CHOP-21.

Results: Lipegfilgrastim was non-inferior to pegfilgrastim in the DSN in cycle 1: the mean DSN (days) in cycle 1 was 0.8±.96 and 0.9±1.08 in the per-protocol population, respectively with an adjusted mean difference (95% confidence interval) between groups of -0.3 (-0.70, 0.19). The upper boundary was below the predefined non-inferiority margin of 1. Non-inferiority was also demonstrated in the intent-to-treat population. The incidence of febrile neutropenia (FN) in cycle 1 was 2% (1/41) in the lipegfilgrastim and 0% (0/44) in the pegfilgrastim group. The incidence of severe neutropenia in cycle 1 was similar in the lipegfilgrastim (21/41; 51%) and pegfilgrastim (23/44; 52%) groups. The mean time to absolute neutrophil count recovery to a threshold of $\geq 2.0 \times 10^9$/L was similar in lipegfilgrastim (8.3 days) and pegfilgrastim (8.7 days) groups. Adverse events (AEs) occurred in 98% of patients; in 45/46 of lipegfilgrastim and 49/50 of the pegfilgrastim group. Serious AEs occurred in 46% of patients; 21/46 in the lipegfilgrastim and 23/50 in pegfilgrastim group; none were assessed as treatment-related by the investigator. Fatal AEs occurred in 4% (2/46) of lipegfilgrastim and 10% (5/50) of the pegfilgrastim group. Study withdrawal due to AEs occurred in 2% (1/46) of the lipegfilgrastim and 18% (9/50) of the pegfilgrastim group.

Conclusions: Lipegfilgrastim was non-inferior to pegfilgrastim in the reduction of the DSN in elderly patients with B-NHL. The safety of lipegfilgrastim was comparable to pegfilgrastim.

Clinical trial identification: EudraCT: 2013-001284-23.

Legal entity responsible for the study: Merckle GmbH (part of Teva Pharmaceuticals group).

Funding: Merckle GmbH (part of Teva Pharmaceuticals group).

Disclosure: H. Link: Advisory boards, investigator in sponsored trial: Teva. G. Illerhaus, U.M. Martens, A. Salar, R. Depenbusch, A. Kohler, M.M. Engelhardt, S. Mahlmann, M. Zaiss: Investigator in Teva sponsored trial. A. Lammerich, P. Bias, A. Buchner: Employee and stock options: Teva.

1697P Use of lipegfilgrastim for the prophylaxis of chemotherapy-induced neutropenia: Pan-European non-interventional study

G. Steger[1], P. Pichler[2], M. Airoldi[3], P. Mazza[4], C. Fontaine[5], J. Timmer Bonte[6], J.A. Walewski[7], J. Katolicka[8], M. Mikulova[9], M. Gasparic[10]

[1]*Department of Medicine I, Oncology Division, Medical University Vienna, Gaston H. Glock Research Center, Vienna, Austria,* [2]*Innere Medizin 1, Landesklinikum St. Poelten, St. Poelten, Austria,* [3]*Oncologia Medica, AOU S. Giovanni Battista - Molinette, Turin, Italy,* [4]*Hematology, SS Annunziata Hospital, Taranto, Italy,* [5]*Medical Oncology, Vrije Universiteit Brussel-Campus Jette, Brussels, Belgium,* [6]*Medical Oncology, Alexander Monro Breast Cancer Clinic, Bilthoven, Netherlands,* [7]*Lymphoid Malignancies, The Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology (MCMCC), Warsaw, Poland,* [8]*Medical Oncology, St. Anne's University Hospital Brno, Brno, Czech Republic,* [9]*Medical Oncology, St. Elisabeth Cancer Institute, Bratislava, Slovak Republic,* [10]*Medical Affairs Europe, Teva Pharmaceuticals Europe B.V., Amsterdam, Netherlands*

Background: Lipegfilgrastim (Lonquex®) is a long-acting glycopegylated G-CSF, which was proven to be non-inferior to pegfilgrastim in breast cancer patients. The objectives of this study were to evaluate effectiveness and safety of lipegfilgrastim in everyday clinical practice in adult patients with different tumor types, who are treated with cytotoxic chemotherapy.

Methods: Patients with different tumor types treated with cytotoxic chemotherapy, who received lipegfilgrastim in primary (PP) or secondary prophylaxis (SP) were included in this prospective non-interventional study. Evaluation of chemotherapy (CT) and biological therapy (BT) dose modifications as well as neutropenic events following the first lipegfilgrastim supported treatment cycle is presented here.

Results: A total of 1,313 patients were included in the safety set. Mean age of included patients was 58.4±13.3 and 70.2% were female. The majority of patients had breast cancer (46.7%) and lymphoma (26.4%). A total of 895 (68.2%) patients received lipegfilgrastim in PP starting from CT cycle 1 and 192 (14.6%) patients received it in SP for

the first time. They were included in the effectiveness analysis. In the first cycle febrile neutropenia (FN) was reported in 1.8% of patients receiving lipegfilgrastim in PP and in 1.0% of patients receiving lipegfilgrastim in SP. Grade 3/4 neutropenia was reported in 7.5% (PP) and 6.7% (SP) of patients. CT and/or BT was delayed, reduced or omitted in 20.1% of patients receiving lipegfilgrastim in PP and in 28.1% of patients receiving it in SP. This was associated with FN and grade 3/4 neutropenia in only 1.0% and 2.2% of these patients in case of PP and 2.1% and 5.5% in case of SP. A total of 284 (21.6%) patients reported at least one adverse drug reaction (ADR) throughout the study. The most common ADRs were bone pain (5.86%), myalgia (3.43%) and back pain (1.83%). Serious ADRs were reported by 42 (3.2 %) of patients.

Conclusions: Lipegfilgrastim is effective and well tolerated in the real world setting administered either in PP or SP. Both effectiveness and safety data obtained in this study are in line with published data for lipegfilgrastim.

Legal entity responsible for the study: Teva.

Funding: Teva.

Disclosure: G. Steger, P. Pichler, M. Airoldi, P. Mazza, C. Fontaine, J. Timmer Bonte, J.A. Walewski, J. Katolicka, M. Mikulova: Investigator in Teva sponsored study. M. Gasparic: Employee: Teva Pharmaceuticals Europe B.V.

1698P Safety analysis of proposed biosimilar pegfilgrastim in phase I and phase III studies

N. Harbeck[1], J. Wang[2], G. Otto[3], A. Krendyukov[4]

[1]Breast Cancer Dept. Ob & Gynae and CCCLMU, University of Munich, Munich, Germany, [2]Biostatistics, Sandoz Inc., Princeton, NJ, USA, [3]Clinical Research, Hexal AG, Holzkirchen, Germany, [4]Medical Oncology/Hematology, Hexal AG, Holzkirchen, Germany

Background: Granulocyte colony-stimulating factors (G-CSFs), including filgrastim and its long-acting form pegfilgrastim, are widely used to prevent chemotherapy-induced neutropenia in patients undergoing cytotoxic chemotherapy. Bone pain is the most frequently reported adverse event (AE) associated with G-CSF. In cancer patients receiving pegfilgrastim, bone pain incidence ranges from 25–38%, compared with 52–84% in healthy volunteers (HVs).[1] This study compares safety data for Sandoz proposed biosimilar pegfilgrastim in Phase I and III studies.

Methods: Three studies were included: 103, a single-dose, randomized, double-blind, crossover phase I study in HVs receiving proposed biosimilar (n = 92) or reference pegfilgrastim (n = 92)[2] and 2 randomized, double-blind Phase III confirmatory studies (PROTECT1[3] and 2[4]) in breast cancer (BC) patients undergoing cytotoxic chemotherapy (≤6 cycles) receiving proposed biosimilar (PROTECT1: n = 159; PROTECT2: n = 155) or reference pegfilgrastim (PROTECT1: n = 157; PROTECT2: n = 153). Results were compared for a single dose of pegfilgrastim in 103, and for 1st treatment cycle in PROTECT1 and 2.

Results: Differences in baseline characteristics between 103 and PROTECT included younger age, lower BMI and inclusion of men in 103 (Table). Treatment related bone pain was reported by 58% (biosimilar) and 53% (reference) in 103; in 4.4% (biosimilar) and 5.1% (reference) in PROTECT1, and 4.5% (biosimilar) and 8.5% (reference) in PROTECT2. AEs were generally mild in 103 and mild/moderate in PROTECT.

Table: 1698P

	Study 103[2]	PROTECT1[2]	PROTECT2[3]
Baseline characteristics			
Age, mean (SD)			
Proposed biosimilar	26.7 (7.35)	49.9 (9.53)	48.8 (10.50)
Reference		50.5 (10.87)	49.1 (10.07)
Female gender, n (%)			
Proposed biosimilar	67 (36)	159 (100)	155 (100)
Reference		157 (100)	153 (100)
BMI, mean (SD)			
Proposed biosimilar	23.9 (2.17)	27.5 (5.67)	26.6 (5.77)
Reference		27.4 (5.60)	26.5 (5.13)
Safety			
Bone pain, n (%)			
Proposed biosimilar	102 (58)	7 (4.4)	7 (4.5)
Reference	94 (53)	6 (3.8)	13 (8.5)
RR (CI)	1.10 (0.93 - 1.30)	1.15 (0.40 - 3.35)	0.53 (0.22 -1.30)
Headache, n (%)			
Proposed biosimilar	100 (57)	2 (1.3)	3 (1.9)
Reference	99 (56)	3 (1.9)	3 (2.0)
RR (CI)	1.02 (0.87 - 1.20)	0.66 (0.11 - 3.89)	0.99 (0.20 - 4.81)

BMI, body mass index; CI, confidence interval; RR, relative risk; SD, standard deviation.

Conclusions: Bone pain was similar with proposed biosimilar and reference pegfilgrastim, in studies of BC patients and HVs. Pivotal Phase I and Phase III studies support the matching safety and efficacy of Sandoz proposed biosimilar and reference pegfilgrastim. References: 1. Lambertini et al Crit Rev Oncol Hematol 2014;89:112–28. 2. Nakov et al Cancer Res 2018;78:P3-14-10. 3. Harbeck et al Future Oncol 2016;12:1359–7. 4. Blackwell et al Oncologist 2016;21:789–4.

Editorial acknowledgement: Caroline McGown, Spirit Medical Communications.

Legal entity responsible for the study: Hexal AG, Holzkirchen, Germany.

Funding: Hexal AG, Holzkirchen, Germany.

Disclosure: N. Harbeck: Advisory and consulting services: Amgen, Hexal. AG. J. Wang: Employee: Sandoz Inc. G. Otto, A. Krendyukov: Employee: Hexal AG.

1699P New approach to evaluate survival benefit of granulocyte colony-stimulating factor in cancer patients receiving myelosuppressive chemotherapy

A. Krendyukov[1], L. Yau[2]

[1]Medical Oncology/Hematology, Hexal AG, Holzkirchen, Germany, [2]Biostatistics, Hexal AG, Holzkirchen, Germany

Background: In cancer patients undergoing myelosuppressive chemotherapy, granulocyte colony-stimulating factor (G-CSF) reduces the risk of neutropenic complications and decreases need for dose reductions,[1] allowing potential improvement of survival. A recent meta-analysis found that those receiving G-CSF have significantly improved overall survival (OS) versus those who do not.[2] Deemed a "gold standard" approach for estimating probabilities of survival for time-to-event data,[3] Kaplan-Meier (KM) estimates are a non-parametric method with no underlying distributional assumptions, allowing comparison between studies. Meta-analysis methods based on KM curves have been proposed.[4,5] We present a new approach of pooling KM curves, improving their accuracy in assessing survival probabilities.

Methods: Our new approach pinpoints specific coordinates on KM curves using web-based digital graphics data extraction tools. When the amount of at risk patients during a specific time period is known, the number of patients experiencing events can be calculated, or if unknown, imputed by "borrowing" event percentages from a study with a similar KM survival profile. Using minimum squared distances between pairs, the similarity between two KM curves can be determined. Reconstructed event times can be used for meta-analyses, using fixed or random effect modeling with weights for each study.

Results: This approach was applied to 70 reports of OS in cancer patients receiving chemotherapy with or without G-CSF prophylaxis, including recent meta-analysis data.[2] Preliminary results are in line with published data. Supporting reports of better survival in patients receiving G-CSF, the new approach provides synthesized KM curves, allowing comparisons of survival probabilities between treatments at any given time points.

Conclusions: Our preliminary results support findings of significantly improved OS in cancer patients receiving G-CSF. References: 1. Aapro et al. Support Care Cancer 2010;18:529–41. 2. Lyman et al. Blood 2017:130;3424. 3. Land et al. Procedia Comput Sci. 2011;6:267–72. 4. Parmar et al. Statist Med. 1998; 17:2815–34. 5. Tierney et al. Trials 2007;8:16.

Editorial acknowledgement: Terri Penfold, Spirit Medical Communications.

Legal entity responsible for the study: Hexal AG, Holzkirchen, Germany.

Funding: Hexal AG, Holzkirchen, Germany.

Disclosure: A. Krendyukov, L. Yau: Employee: Hexal AG.

1700P Safe switch of treatment from the reference product to RGB-02, a proposed biosimilar pegfilgrastim: Analysis of the results of three clinical trials

A. Illes[1], L. Perjesi[1], K. Horvat-Karajz[1], N. Jeszenoi[1], I. Aradi[1], N.K. Singh[2], S.J. Mair[2], Z. Kahan[3]

[1]Clinical Development of Biologics, Gedeon Richter Plc., Budapest, Hungary, [2]Medical Department, Quotient Sciences, Ruddington, UK, [3]Department of Oncotherapy, University of Szeged, Szeged, Hungary

Background: Treatment with recombinant human granulocyte-colony stimulating factor (G-CSF) is an accepted standard for prevention of chemotherapy-induced neutropenia. RGB-02, a pegylated G-CSF (pegfilgrastim) developed by Gedeon Richter is a proposed biosimilar to the reference product Neulasta®. Therapy switch from a reference product to its biosimilar is expected to occur in the daily practice. Here we are presenting the outcome of treatment switch in two randomized cross-over design comparative PK/PD studies (EudraCT nr: 2011-001737-17 and 2016-005051-25) and a randomized, comparative, multicenter efficacy and safety study of RGB-02 (EudraCT nr: 2013-003166-14).

Methods: Efficacy, safety and PD data of two PK/PD studies (enrolling 110 and 150 healthy volunteers, respectively) and a comparative efficacy and safety study (enrolling 239 breast cancer patients) were analyzed in order to assess whether treatment switch from Neulasta® to RGB-02 has any impact on the PD response, efficacy or safety. The PK/PD studies had a cross-over design. Patients in the reference arm of the comparative

efficacy and safety study were switched to RGB-02 treatment following the first two chemotherapy cycles. Endpoints assessed were related to the change in ANC count in healthy volunteers, duration of severe neutropenia (DSN; ANC $< 0.5 \times 10^9$/L) in the comparative efficacy and safety study, as well as safety data including immunogenicity collected in each clinical study.

Results: None of the PD endpoints showed any difference following the cross-over in the comparative PK/PD studies. The mean DSN values after the therapy switch were similar to the values prior to the switch and the switched arm (mean DSN: 0.6) did not show decreased efficacy compared to the arm received RGB-02 from the first cycle (mean DSN: 0.9). Safety results, including immunogenicity of the 3 studies did not reveal any negative impact of the treatment switch.

Conclusions: Treatment switch from Neulasta® to RGB-02 can be considered safe while maintaining the therapeutic effect of pegfilgrastim therapy.

Clinical trial identification: EudraCT: 2011-001737-17; EudraCT: 2016-005051-25; EudraCT: 2013-003166-14.

Legal entity responsible for the study: Gedeon Richter Plc.

Funding: Gedeon Richter Plc.

Disclosure: A. Illes L. Perjesi, K. Horvat-Karajz, N. Jeszenoi, I. Aradi: Employee: Gedeon Richter Plc. N.K. Singh, S.J. Mair, Z. Kahan: Principal investigator of one of the studies (EudraCT Nr. 2016-005051-25) sponsored by Gedeon Richter Plc; Investigator grant from the sponsor.

1701P Use of primary and secondary pegfilgrastim prophylaxis for reducing incidence of neutropenia: Findings from a large study in German clinical practice (PROTECT)

C.M. Kurbacher[1], M. Schmidt[2], M. Geberth[3], B. Otremba[4], H. Eschenburg[5], P. Ramdohr[6]

[1]*Gynecologic Center, Medizinisches Zentrum Bonn Friedensplatz, Bonn, Germany,* [2]*Johannes Gutenberg-Universität Mainz, Mainz, Germany,* [3]*Praxisklinik am Rosengarten, Mannheim, Germany,* [4]*Onkologische Praxis, Oldenburg, Germany,* [5]*Internistische Gemeinschaftspraxis Duda/Eschenburg/Wilhelm, Güstrow, Germany,* [6]*Medical Development, Amgen GmbH, Munich, Germany*

Background: The EORTC guidelines recommend primary prophylaxis with G-CSF when the overall risk of febrile neutropenia (FN) is $\geq$ 20% (high risk [HR]) or if the chemotherapy FN risk is 10–20% (medium risk [MR]) with additional patient (pt)-related risk factors. This study assessed the acceptance of these guidelines in German routine practice.

Methods: Non-interventional study of pegfilgrastim use in pts receiving Ctx for solid tumors or lymphomas (2007–2014 in 123 German centers). Pts were >18 yrs, had breast, ovarian, gastric, prostate or lung cancer, or aggressive lymphoma, EORTC-defined FN risk $\geq$10%, and prophylactic pegfilgrastim use. Primary endpoint: proportion of pts receiving pegfilgrastim as primary (prior to neutropenia) or secondary (following neutropenia occurrence) prophylaxis.

Results: Data were available from 1914/2069 pts (average age 58 yrs, 79% female, 60% had breast cancer, 69% had prior tumor-related therapy and 20% prior Ctx). Of those receiving prior Ctx, 39% needed neutropenia treatment. Of the 1914 pts, pegfilgrastim was used as primary and secondary prophylaxis in 78% and 22%, respectively (primary endpoint). Primary prophylaxis was more frequent than secondary in the HR (87 vs 13% of 936 pts) and MR (73 vs 27% of 835 pts) groups. At a pt level, overall FN rate was 8% and varied across tumors: gastric 12%, breast 9%, lung 7%, lymphoma 8% and ovarian 3%. Across these tumors, the number of cycles with FN were 1.9%, 3.2%, 1.9%, 1.9%, 2.1% and 0.6%, respectively. Overall, 2% had a dose reduction or therapy switch due to FN. In breast cancer, dose reductions or therapy switches occurred in 1% of pts receiving primary prophylaxis and 3% receiving secondary prophylaxis.

Conclusions: In this study of pts receiving pegfilgrastim prophylaxis in routine German practice, the majority of HR pts with overall FN risk of > 20% were treated with primary pegfilgrastim prophylaxis in concordance with the EORTC guidelines. Primary prophylaxis with pegfilgrastim was associated with a low FN incidence and a low rate of dose reductions and treatment delays.

Clinical trial identification: NCT02178475.

Legal entity responsible for the study: Amgen.

Funding: Amgen GmbH.

Disclosure: C.M. Kurbacher: Honoraria and travel expenses, advisory role: Amgen. M. Schmidt: Honoraria: Pierre-Fabre, Roche, Pfizer, Novartis, AstraZeneca, Eisai, Amgen, Celgene; Research grants: Pierre-Fabre; Non-financial support: Roche, Pfizer, Amgen, Celgene. H. Eschenburg: Honoraria: Roche AG; Other financial support: Bristol-Myers Squibb. P. Ramdohr: Employee and holds stock: Amgen. All other authors have declared no conflicts of interest.

1702P Associations between hematologic toxicity and health-related quality of life during first-line chemotherapy in advanced non-small-cell lung cancer: A pooled analysis of two randomized trials

A. Kristensen[1], T.S. Solheim[1], Ø Fløtten[2], B.H. Grønberg[1]

[1]*The Cancer Clinic & European Palliative Care Research Centre (PRC), Department of Clinical and Molecular Medicine, St. Olav's Hospital & NTNU, Norwegian University of Science and Technology, Trondheim, Norway,* [2]*Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway*

Background: Many patients experience toxicity from chemotherapy that can negatively impact their health-related quality of life (HRQoL), but side effects often go undetected by health care personnel. Hematologic toxicity (HT) is the main dose-limiting toxicity of chemotherapy. Our aim was to investigate whether patients who experienced severe HT had more negative changes in HRQoL than those who did not. If so, blood counts could represent a simple and objective method for identifying patients at risk of severely impaired HRQoL who may benefit from more supportive care during the treatment period.

Methods: Data from two phase III trials of first-line chemotherapy in advanced non-small-cell lung cancer (NSCLC) were analyzed (n = 873). Blood counts were measured weekly. We categorized patients as having severe (CTCAE grade 3-4) or non-severe (grade 0-2) HT during the first chemotherapy cycle. HRQoL was reported on the EORTC QLQ-C30 and LC13 before and at the end of the cycle. The primary endpoints were changes in global quality of life, fatigue, nausea/vomiting and dyspnea (LC13). Mean differences of 5-10 points was considered to represent a small clinical difference.

Results: Of the 766 patients with complete data set, 177 (23%) developed severe HT during the first chemotherapy cycle. Severe neutropenia and thrombocytopenia was observed in 149 (19%) and 67 (9%) patients, respectively, while only three (0.4%) patients had severe anemia. Changes in fatigue and nausea/ vomiting were significantly worse for patients experiencing severe compared to patients with non-severe HT (difference in mean change of 4.9 points; $p = 0.01$, and 6.4 points; $p = 0.01$, respectively), but this association was limited to neutropenia, not thrombocytopenia or anemia. There were no significant associations between HT and global quality of life or dyspnea (difference in mean change of 2.1 points; $p = 0.28$, and 3.3 points; $p = 0.053$, respectively).

Conclusions: Patients developing severe HT had worse changes in two out of four HRQoL endpoints, but the association was not strong enough to use blood counts to identify patients who experience deterioration of HRQoL during chemotherapy.

Legal entity responsible for the study: European Palliative Care Research Centre (PRC), Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1703P Incidence of hypocalcemia in a non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) with denosumab (DN) administered every 4 weeks (q4w) versus every 12 weeks (q12w): SAKK 96/12 (REDUSE)

R. von Moos[1], H. Hawle[2], S. Hayoz[3], R. Cathomas[4], A. Müller[5], S. Schmid[6], O. Pagani[7], T. Wehrhahn[8], D. Rauch[9], S. Anchisi[10], T. Hermanns[11], M. Fehr[12], S. Stoll[13], P. Bützberger[14], M. Zweifel[15], U. Huber[16], A.C. Fuhrer[17], C. Schär[17], S. Gillessen[18], A.J. Templeton[19]

[1]*Department of Oncology/Hematology, Kantonsspital Graubünden, Chur, Switzerland,* [2]*Medical Advisor, Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland,* [3]*Statistics, Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland,* [4]*Oncology/Hematology, Kantonsspital Graubünden, Chur, Switzerland,* [5]*Department of Medical Oncology, Kantonsspital Winterthur, Winterthur, Switzerland,* [6]*Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, Switzerland,* [7]*Breast Unit, IOSI - Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland,* [8]*Oncology/Hematology, Kantonsspital Aarau, Aarau, Switzerland,* [9]*Oncology and Hematology, Spital STS AG Thun, Thun, Switzerland,* [10]*Cancerology/Oncology, Hôpital Régional Sion-Hérens-Conthey, Site de Champsec Centre du Cancer Lausanne, Sion, Switzerland,* [11]*Department of Urology, University Hospital Zürich, Zurich, Switzerland,* [12]*Gynäkologie & Geburtshilfe, Kantonsspital Frauenfeld, Frauenfeld, Switzerland,* [13]*Medical Oncology and Hematology, Stadtspital Triemli, Zurich, Switzerland,* [14]*Oncology/Hematology, Kantonsspital Baden, Baden, Switzerland,* [15]*Oncology, Spitalzentrum Biel, Biel, Switzerland,* [16]*Swiss Tumor Institute, Klinik im Park Oncology Center, Zurich, Switzerland,* [17]*Clinical Trial Management, Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland,* [18]*Division of Cancer Sciences, University of Manchester and the Christie, Manchester, UK and Division of Medical Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, University of Bern, Switzerland,* [19]*Medical Oncology, St. Claraspital AG, Basel, Switzerland*

Background: DN has shown superiority in delaying skeletal related events when given q4w over zoledronic (ZA) acid given q4w. Newer data have shown that ZA given q12w is non-inferior to ZA q4w. The primary endpoint of REDUSE is to show non-inferiority

for DN q12w versus q4w (SSE). Here we present the data for the secondary endpoint hypocalcemia (HC).

Methods: Patients with metastatic breast cancer (BC) or metastatic castration resistant prostate cancer (PC) (planned N = 1380) were randomized 1:1 to receive DN q4w (Arm A) versus q12w (Arm B) after a 3-month induction phase with application q4w. All patients received vitamin D 400 U (ViD) and calcium (Ca) 500 mg daily. Measurement of serum-calcium was mandatory before each DN injection. This safety interim analysis was performed after 3.5 years of accrual. (N = 634; BC N = 351, PC N = 283).

Results: Patients who received at least 1 dose of DN were considered evaluable. HC was the most common side effect with 23.7% overall (BC 18.6%, PC 30.2%). While HC occurred in 31.6% in Arm A, the rate was 15.8% in Arm B. Grade 3/4 HC was rare (overall: 1.3%, all with PC). After 1 year of treatment, the incidence of HC was lower in both arms (A: 27.2%, B: 14.3%). Since HC improved in more patients in Arm B than Arm A whereas it got worse in Arm A compared to Arm B, a remarkable difference for HC was noticed between the two arms (Table).

Table: 1703P

Change in HC grade after week 16 in patients with HC during induction treatment (196/634) (week 1 – 12: DN q4w Arm A+B, thereafter q4w Arm A, q12w Arm B)	Arm A (N = 106) n (%)	Arm B (N = 90) n (%)
Worsening	48 (45.3%)	23 (25.6%)
Stable	29 (27.4%)	15 (16.7%)
Improving	29 (27.4%)	52 (57.8%)

Arm A: Denosumab q4w, Arm B: Denosumab q12w.

Conclusions: In our trial up to 30% of all patients treated with DN experienced HC in the q4w induction phase despite mandatory supplementation and measurement of ViD and Ca. This rate was considerably higher than reported in the registration trials of DN (PC 13.0%, BC 5.5%). After randomization the appearance of HC is remarkably lower in the q12w arm compared to q4w. This suggests that DN given q12w has a more favorable long time toxicity profile (HC) compared to DN q4w.

Clinical trial identification: NCT02051218.

Legal entity responsible for the study: Swiss Group for Clinical Cancer Research (SAKK).

Funding: Swiss State Secretariat for Education, Research and Innovation (SERI) and Santésuisse.

Disclosure: R. von Moos: Advisory board: Amgen, Novartis, Roche. S. Gillessen: Compensated consultancy and advisory roles (including IDMC): AAA International, Active Biotech, Astellas Pharma, Bayer, Bristol-Myers Squibb, CellSearch (Menarini Silicon Biosystems), Clovis, Curevac, Dendreon, Ferring, Innocrin, Janssen, MaxiVAX SA, Millennium, Novartis, Orion, Pfizer, Roche, Sanofi Aventis; Speakers Bureaus (compensated): Janssen, Novartis; Patent application for a biomarker method (WO 2009138392 A1). All other authors have declared no conflicts of interest.

1704P A prospective randomized controlled trial of metoclopramide combined with triple antiemetic therapy to prevent anthracycline-based chemotherapy-induced nausea and vomiting in patients with breast cancer

U. Oflazoglu[1], U. Varol[1], A. Alacacioglu[1], T. Salman[1], Y. Kucukzeybek[1], H. Taskaynatan[1], Y. Yildiz[1], G. Dissiz[1], S. Iriz[1], M.O. Tarhan[2]

[1]Medical Oncology, Izmir Katip Celebi University, Izmir, Turkey, [2]Medical Oncology, Dokuz Eylul University Institute of Oncology, Izmir, Turkey

Background: Triple antiemetic therapy, such as a 5-HT3 receptor antagonist (5H3-RA), aprepitant and dexamethasone, is recommended for the prophylaxis of highly emetogenic chemotherapy induced nausea and vomiting in patients with breast cancer. In the present study, we aimed to verify whether adding metoclopramide to the triplet antiemetic therapy is superior to the triplet antiemetic therapy in preventing CINV in patients with breast cancer.

Methods: A single-blind, randomized trial was performed on ninety-seven patients who received HEC among chemotherapy-naive patients with breast cancer. The visual analogue scale (VAS) utilized to detect nausea, and FLIE was used in order to determine its impact on the patients' quality of life. The patients were randomized to arm A(n:48, dexamethasone and 5HT3RA on day 1, aprepitant on day 1-3, and metoclopramide on days 1-5) and arm B (n:49, dexamethasone and 5HT3RA on day 1and aprepitant on day 1-3). The primary endpoint was complete response (CR) (no nausea, no vomiting, and no rescue medication) during the overall phase (days 1–5).

Results: The demographic and clinical features such as age, educational background, height and weight measurements were similar in both groups. The CR was found in twenty patients (45.8%) of the forty-eight patients in the arm A, while it was found in thirteen patients (26.5%) of the forty-nine patients in the arm B (p:0.038).The mean total FLIE score was 31.31 (SD: 20.5) in arm A, which was42.29 (SD: 26.4) in arm B (p:0.045).

Conclusions: A triple or quadruple antiemetic combination is proposed to alleviate CINV for female patients with breast cancer treated with HEC. In patients receiving anthracycline-based chemotherapy, quadruple antiemetic therapy with dexamethasone, aprepitant, palonosetron and metoclorpropamide is associated with a significant CR and clinically relevant improvement in FLIE score, compared to dexamethasone, aprepitant and palonosetron. Therefore, a quadruple antiemetic combination including metpamid might be a treatment option for patients receiving highly emetogenic chemotherapy.

Legal entity responsible for the study: Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1705P Ramosetron versus palonosetron in combination with aprepitant and dexamethasone for the control of highly emetogenic chemotherapy-induced nausea and vomiting

J.H. Kwon[1], J-H. Kang[2], Y-G. Lee[3], K.U. Park[4], H.J. An[5], J. Sohn[6], Y.M. Seol[7], H. Lee[8], H-J. Yun[9], J.S. Ahn[10], H.J. Kim[11]

[1]Division of Hemato-Oncology, Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea, [2]Oncology, The Catholic University of Korea, Seoul ST. Mary's Hospital, Seoul, Republic of Korea, [3]Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [4]Internal Medicine, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Republic of Korea, [5]Department of Medical Oncology, St. Vincent's Hospital, College of Medicine, Catholic University of Korea, Suwon, Republic of Korea, [6]Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [7]Internal Medicine, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Republic of Korea, [8]Hematology-Oncology, Ajou University Hospital, Ajou University School of Medicine, Suwon, Republic of Korea, [9]School of Medicine Chungnam National University and Chungnam National University Hospital, Department of Internal Medicine, Daejeon, Republic of Korea, [10]Hematology & Oncology, Samsung Medical Center, Seoul, Republic of Korea, [11]Clinical Epidemiology and Biostatistics, ASAN Medical Center, Seoul, Republic of Korea

Background: The combination of palonosetron (PAL), aprepitant (APR) and dexamethasone (DEX) is the standard regimen in controlling highly emetogenic chemotherapy-induced nausea and vomiting (HEC CINV) in cancer patients. We previously demonstrated that ramosetron (RAM), 5-HT3 receptor antagonist, is superior to ondansetron. This prospective, multicenter, single blind, randomized and phase IV study compares RAM, APR and DEX (RAD) with PAL, APR and DEX (PAD) to prove the non-inferiority of RAD in controlling HEC CINV.

Methods: Patients were randomly assigned at 1:1 ratio to receive either RAD or PAD regimen: RAM(0.3mg IV) or PAL(0.25mg IV), D1 in combination with APR(125mg PO, D1 and 80mg PO, D2-3) and DEX(12 mg PO or IV, D1 and 8 mg PO, D2-4). They were stratified by gender, chemotherapy (cisplatin vs non-cisplatin) and administration schedule (single vs multi-day). The primary endpoint, overall complete response (CR) was defined as no emesis and no rescue regimen within 5 days of HEC. The secondary endpoints were overall complete protection (CP: CR + nausea score<25mm) and total control (TC: CR + nausea score<5mm). Quality of life (QOL) was assessed by Functional Living Index–Emesis (FLIE) questionnaire on D0 and D6.

Results: A total of 279 patients receiving RAD (n = 137) or PAD (n = 142) were evaluated for the efficacy and safety. The overall CR rates of RAD vs PAD were 72.3% vs 74.6% (relative difference [RD] -2.4%, 95% CI: -12.8 to 8.0), respectively. The overall CP and TC rates in RAD vs PAD were 52.6% vs 57.0%(RD -4.5%, 95% CI: -16.2 to 7.2) and 45.3% vs 43.0%(RD 2.3%, 95% CI: -9.4 to 14.0%), respectively. FLIE score≥108 (no impact of daily life) was comparable between RAD (n = 134) and PAD (n = 139) (73.9% vs 73.4%, p = 1.00 respectively). Each nausea and vomiting domain (FLIE score≥ 54) was 67.2% vs 64.0 %(p = 0.61) and 91.8% vs 90.6 %(p = 0.83), respectively. The adverse events were similar between the two groups.

Conclusions: In all aspects of the efficacy, safety and QOL, our data suggested RAD was comparable to PAD for the control of CINV in cancer patients receiving HEC.

Clinical trial identification: NCT02532634.

Legal entity responsible for the study: Jin-Hyoung Kang, Ph.D, The Catholic University of Korea.

Funding: Astellas Pharma Korea. Inc.

Disclosure: J.S. Ahn: Honoraria: Eiasi, Jassen, Menarini, Roche; Advisory role: Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1706P Prognostic factors associated with prevalence of nausea, and time to development of nausea in patients receiving guideline-based anti-emetic prophylaxis: A prospective, observational, real world study

T. Smit, B.L. Rapoport

Pharmacy, The Medical Oncology Centre of Rosebank, Sandton, South Africa

Background: The development of effective anti-emetic treatments has contributed to the resolution of emesis in chemotherapy patients (pts). There is a growing concern that the emesis focus is primarily on vomiting. Nausea seems to be underestimated and its incidence and impact remains a major unmet medical need. The study focused primarily on nausea in patients undergoing highly-, moderately- or low emetogenic chemotherapy (HEC, MEC, LEC). The primary endpoint was no nausea during the 120-hours overall phase after cycle 1. The analysis focused on the prevalence of nausea and time to nausea development following the first cycle of chemotherapy.

Methods: This prospective, observational single centre study enrolled 95 patients undergoing LEC (25 pts), MEC (24 pts) or HEC (46 pts) for malignancy. Prophylactic antiemetics were administered according to MASCC/ESMO 2016 guidelines. Patient diaries were used to collect data from day-1 to day-5, day-7 and day-10 beginning with cycle-1 for up to 3 cycles.

Results: The incidence of nausea of the entire population was 59% compared to only 24% pts experiencing vomiting. ($Chi^2 = 23.5956$; $p > .000001$). Significant variables predicted for nausea included gender, age and history of motion sickness. The level of emetogenicity did not correlate with the incidence of nausea (LEC = 25%, MEC = 60%, HEC = 67%), ($Chi^2 = 5.1893$; $p > .07$). On univariate analysis, factors associated with shorter time to the first nausea episode included; age < 60 years (log-rank test $p < 0.0213$, Chi sq = 2), then motion sickness ($p < 0.0229$), gender ($p < 0.0321$) and emetogenicity ($p < 0.29$). In a Cox-proportional multivariate proportional hazard model age < 60 years, ($p < 0.0213$), gender ($p < 0.0321$) and motion sickness ($p < 0.0229$) retained its significance – while emetogenicity lost its significance.

Conclusions: Chemotherapy induced nausea is underreported and remains a major unmet medical need. Gender, age and motion sickness are significant risk factors associated with nausea independent of the level of emetogenicity of the chemotherapy utilized in patients receiving guideline-based antiemetic prophylaxic treatment.

Legal entity responsible for the study: The Medical Oncology Centre of Rosebank.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1707P Usefulness of bone modifying agents for non-weight bearing bone metastasis in breast cancer

K. Kawaguchi[1], M.A.H.M. Latif[2], K. Hayashi[2], S. Ogita[3]

[1]Orthopedic Surgery, Lizuka Hospital, Lizuka, Japan, [2]Statistics, St. Luke's International University, Tokyo, Japan, [3]Medical Oncology, St. Luke's International Hospital, Tokyo, Japan

Background: Bone metastasis is common in breast cancer. No previous study evaluated the usefulness of bone modifying agents (BMA) in breast cancer patients whose metastases are limited to non-weight bearing bones.

Methods: We retrospectively collected data at St. Luke's International Hospital between 2006 and 2016. Weight bearing bones were defined as vertebral body, lower limbs, and pelvis, and all the other bones were defined as non-weight bearing bones. Breast cancer patients, age ≥20 years old, who were newly diagnosed to have bone metastasis only in non-weight bearing bones were included in this study. Bone metastases were detected by either bone scintigraphy or PET-CT. The selected patients were divided into 2 groups: patients of Group A started BMA within 3 months from the diagnosis, and those of Group B did not start BMA within the 3 months. We are interested in comparing the Groups A and B in terms of time to skeletal related events (SRE) and overall survival (OS), where SRE were defined as orthopedic surgery, percutaneous vertebroplasty, and/or palliative radiation to bone metastasis.

Results: Out of 418 breast cancer patients with bone metastasis, only 101 patients were found to have bone metastasis only in non-weight bearing bones. The median follow-up time was 32 months. The number of patients in Group A and B were 54 and 47, respectively. Eight patients in Group A and 5 patients in Group B developed SRE ($p = 0.568$). Median SRE free survival (i.e. timeto SRE) was 118.5 months, and 117.3 months in Group A and Group B, respectively ($p = 0.490$, Hazard ratio: 1.48). Median overall survival (OS) was 39.7 months in group A and 78.3 months in group B ($p = 0.203$, Hazard ratio: 1.45).

Conclusions: Early initiation of BMA did not improve SRE free survival or OS in breast cancer patients who have only non-weight bearing bone metastasis. Further prospective studies are needed to confirm this finding.

Legal entity responsible for the study: St. Luke's International Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1708P Analysis of bone events in patients with aromatase inhibitors (AI)

S.F. Arrojo[1], E. Garcia-Carús[2], C. Gómez[2], P. Rodriguez[3], D. Rivas[3], L. Faez[1], C. Iglesias Gomez[1], M.E. Izquierdo Manuel[1], Y. Fernandez Perez[1]

[1]Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain, [2]Internal Medicine, Hospital Universitario Central de Asturias, Oviedo, Spain, [3]University of Oviedo, Hospital Universitario Central de Asturias, Oviedo, Spain

Background: Nowadays breast cancer (BC) may have high cure rate, so is important how to prevent or resolve adjuvant treatments adverse effects. AI are an essential treatment in patients with early diagnosed estrogen-dependent BC. Our aim is to analyse bone mass loss in BC, focussing on fractures incidence and their risk as well as preventive methods. The latest consensus establishes as intervention criteria a BMD value> -2T Score and 2 or more risk factors.

Methods: 114 BC patients and 272 without BC sent to our centre in 2010 to perform densitometry (DXA) were included in our review. Beyond DXA and anthropometry we carried out an extensive clinical questionnaire on co-morbidity, risk factors for osteoporosis, medication, personal and relatives history of fractures. Hospital and primary care records were reviewed in BC patients until May 2017 to determine fractures incidence.

Results: There were significant differences in age (BC 59 ± 11 vs 62 ± 11 years, $p = 0.01$). No differences in weight, height, menarche/menopause or toxic habits. 25% had personal history of fracture (31% control $p = 0.05$) and 17% relatives history (27% control $p = 0.03$). 4.3% of corticosteroid intake (16% control $p = 0.01$). There were no differences in T Lumbar Score (0.97 ± 1.3 vs -0.94 ± -1.2) or in femur neck (-.0.93 ± 1.2 vs-1.1 ± 1) but yes in the fracture risk assessment tool (FRAX) for major fractures with BMDM (BC 7 ± 5% vs 11 ± 6% p0.02) and hip fractures (1.2 ± 2 vs 2.4 ± 4 p 0.02). Patients with AI lost bone mass at two years (BMD 0.96 ± 1.87 to 0.921 ± 0.18 g / cm2 p0.03), without changes in control group. At 7 years follow-up, 8 fractures appeared in patients with AI (3 Colles, 3 vertebral and 2 humerus), 4 patients with Exemestane (E), 2 with Letrozole (L) and 2 with Anastrozole (A) (40% took E, 26% A and 20% L). Only 3 of the 8 had baseline T Lumbar Score <-2. 7% BC patients received antiresorptives and 9% vitamin D.

Conclusions: There were more fractures and bone mass loss in BC pacients treated with AI in our sample. Despite the small sample size, it is striking that, patients with BC would not meet the indication of preventive treatment according to the latest recommendations, since only 30% of the patients would be covered. It could be considered to associate other diagnostic measures to treat patients with greater risk of fracture (FRAX).

Legal entity responsible for the study: Central Univesity Hospital of Asturias.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1709P Assessment and treatment of breakthrough cancer pain in Spain: A self-audit study

R. Lopez Lopez[1], J.J. Reina Zoilo[2], D. Monge[3], F. Caballero[3], V. Guillem Porta[4], E. Aranda Aguilar[5], A. Carrato Mena[6], E. Diaz Rubio[7], J. Garcia Foncillas[8], M. Feyjoo[9], C. Camps[10]

[1]Medical Oncology, Complejo Hospitalario Universitario de Santiago de Compostela SERGAS, Santiago De Compostela, Spain, [2]Medical Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, [3]Department of Health Sciences, Francisco de Vitoria University, Madrid, Spain, [4]Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [5]Medical Oncology, University Hospital Reina Sofia, Cordoba, Spain, [6]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [7]Vicepresidente, Real Academia de Medicina, IdISCC, CIBERONC, Madrid, Spain, [8]Medical Oncology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [9]Medical Oncology, Hospital Universitario La Moraleja, Sanitas, Madrid, Spain, [10]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain

Background: In Spain 77% of the episodes of Breakthrough cancer pain (BTcP), a common condition for cancer patients, are not properly diagnosed or treated. The ECO Foundation (Excellence and Quality in Oncology) has promoted this study with the collaboration of Francisco de Vitoria University, to compare the real-life clinical practice with the previous perception of the oncologists of the management of BTcP and to determine if clinical inertia exists in the approach of the BTcP episodes.

Methods: Observational and descriptive study consisting in two phases: a) opinion poll (self-completed online) answered by Spanish oncologists, and b) BTcP episodes screening and assesment (performed by the oncologist surveyed) in patients with a prior or current history of cancer pain (5 patients per oncologist). A recent expert consensus (1) and Davies algorithm were used to evaluate the correct diagnosis and optimal management of BTcP. A total of 108 oncologists participated in the study and 540 patients were evaluated.

Results: Although most oncologists (>80%) refer questioning their patients about the possibility of BTcP, only 34% of them do it systematically in their clinical practice. Most specialists believed that BTcP episodes were unlikely to go unnoticed in their consultations (62%). After evaluating real-life clinical practice, the overall prevalence of BTcP obtained was 91% (493/540). The doctors had previously detected the BTcP condition in 59% of patients (291/493), demonstrating that the under-diagnosis of BTcP exceeds 40%. In addition, 42% of patients with known BTcP were not able to control their episodes of pain and, despite the persistence, in 13% of them, no changes or adjustments had been made in the dose intensity or schedule.

Conclusions: The study confirms that there is a significant prevalence of BTcP and a notable inertia in the management of BTcP episodes, which seems to be poorly detected and treated in patients with cancer. Expanding the use of tools to diagnose BTcP, such as Davies algorithm, might be useful to improve the QoL of patients suffering pain.

Legal entity responsible for the study: ECO Foundation.

Funding: Kyowa Kirin Pharmaceutical.

Disclosure: All authors have declared no conflicts of interest.

1710P Clinical practice evaluation of opioids induced constipation management in oncologic patients: The EIO-50 project

J. Salvador Bofill[1], V. Guillem Porta[2], M. Feyjoo[3], A. Anton Torres[4], E. Aranda Aguilar[5], C. Camps[6], A. Carrato Mena[7], M. Constenla Figueiras[8], J.J. Cruz Hernandez[9], E. Diaz Rubio[10], J. Garcia Foncillas[11], P.N. Gascon[12], R. Lopez Lopez[13], B. Soler[14], Y. Escobar[15]

[1]Medical Oncology, Hospital Virgen del Rocio, Seville, Spain, [2]Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, [3]Medical Oncology, Hospital Universitario La Moraleja, Sanitas, Madrid, Spain, [4]Medical Oncology, Hospital Miguel Servet, Zaragoza, Spain, [5]Medical Oncology, University Hospital Reina Sofia, Cordoba, Spain, [6]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain, [7]Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain, [8]Medical Oncology, Complejo Hospitalario de Pontevedra, Pontevedra, Spain, [9]Medical Oncology, Hospital Universitario de Salamanca, Salamanca, Spain, [10]Real Academia de Medicina, IdISCC, CIBERONC, Madrid, Spain, [11]Medical Oncology, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [12]Division of Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, [13]Medical Oncology, Complejo Hospitalario Universitario de Santiago de Compostela SERGAS, Santiago de Compostela, Spain, [14]Medical Department, E-C-BIO, S.L, Madrid, Spain, [15]Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background: Opioid-induced constipation (OIC) is a common distressing symptom associated with cancer pain opioid treatment. Beyond the recommendations for the treatment of OIC, there are no specific guidelines for the management of the patient with OIC and little is known about the decision tree health care professional (HCP) use to manage OIC. The ECO Foundation (Excellence and Quality in Oncology) has promoted this study to learn about the diagnostic and treatment criteria of OIC in clinical practice.

Methods: An on-line survey was completed by 135 investigators: 122 medical oncologists (90.4%) and 13 palliative care specialists (9.6%). The questionnaire included 50 items about the management of OIC.

Results: According to HCP, most of the cancer patients with pain (71.2%), received opioid treatment for more than 6 months and 54.4% developed OIC. Although 97% of HCP considered OIC as a major health problem only 14.8% of HCP used algorithms for the diagnosis of OIC and 14.1% for OIC treatment. Laxatives were considered second-line treatment for 60% of HCP, after healthy life-style recommendations. Laxatives were prescribed by 99.3% of HCP, but only 38.3% recommended them throughout the opioid treatment period. HCP considered laxatives did not achieve a therapeutic response on 33% of the cases. Peripherally Active μ-Opioid Receptor Antagonist (PAMORA) were considered by 80% of HCP a good alternative for the specific treatment of OIC in cancer patients. Indeed, PAMORA were considered the most effective measure with a score of 8 out of a 10 points scale.

Conclusions: OIC is considered a frequent and relevant opioid side effect among cancer patients in Spain. Although most HCP are aware of the potential for OIC with opioid treatment, there is limited consensus on the OIC diagnostic and treatment criteria. The insufficient efficacy of traditional therapies and the emerging of more specific and effective pharmacological approaches, suggest new clinical guidelines are needed for the management of OIC in cancer patients.

Legal entity responsible for the study: ECO Foundation.

Funding: Kyowa Kirin Pharmaceutical.

Disclosure: All authors have declared no conflicts of interest.

1711P Opioid-induced constipation in patients with cancer pain in Japan: Prospective observational study using Rome IV OIC diagnostic criteria (OIC-J Study)

H. Imai[1], S. Fumita[2], T. Harada[3], T. Noriyuki[4], M. Gamoh[5], Y. Akashi[2], H. Sato[6], Y. Kizawa[7], A. Tokoro[8]

[1]Division of Respiratory Medicine, Gunma Prefectural Cancer Center, Ota, Japan, [2]Department of Medical Oncology, Kindai University Nara Hospital, Ikoma, Japan, [3]Center for Respiratory Diseases, JCHO Hokkaido Hospital, Sapporo, Japan, [4]Department of Surgery, Onomichi General Hospital, Onomichi, Japan, [5]Department of Medical Oncology, Osaki Citizen Hospital, Osaki, Japan, [6]Medical Affairs, Shionogi & CO., Ltd., Osaka, Japan, [7]Department of Palliative Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, [8]Department of Psychosomatic Internal Medicine and Supportive and Palliative Care Team, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan

Background: Opioid-Induced Constipation (OIC) is a common side effect of opioid analgesic therapy. However, there were no prospective studies to assess the incidence of OIC of cancer patients. The aim of this study was to evaluate the incidence of OIC from the start of opioid therapy.

Methods: This study was a multicenter, prospective, observational study of cancer patients who started opioid therapy in Japan (UMIN000025864). The incidence of OIC was determined by ROME IV OIC diagnostic criteria based on the record of patient diary for 14 days. The proportion of patients with OIC was calculated for each 1-week period (Week 1 and Week 2) and overall 2-week period. Medication for constipation was allowed during the study period. Patients with <3 bowel movements in the previous week before starting opioid therapy were not allowed to be enrolled. Bowel Function Index (BFI; score >28.8), spontaneous bowel movement (SBM; <3 SBM/week), and physicians' assessment were also utilized to assess OIC and compare the results.

Results: In total, 212 cancer patients (145 males; mean age 69.1 years)—inpatients and outpatients—with ECOG Performance Status score of 0-2 were included in the study. Mean morphine equivalent dose was 21.9 mg/day. Overall incidence rate of OIC during 2 weeks by weekly diagnosis of Rome IV criteria (total proportion diagnosed as OIC in either Week 1 or Week 2) was 56.1%. The proportion of patients with OIC in Week 1 was 47.6% and in Week 2 was 36.8%. Use of prophylactic laxative reduced the overall incidence rate of OIC from 65.0% to 47.7%. Other diagnostic criteria instead of Rome IV criteria varied the rate; BFI (59.1%), physicians' assessment (61.4%), SBM frequency (44.8%). When overall 2-week period data were applied to Rome IV OIC criteria, the incidence rate was reduced to 44.2%. Sex and age were not considered as risk factors as opposed to the previous report in some cross-sectional studies. The frequency of SBM/week before starting opioids was identified as the most influencing factor for OIC.

Conclusions: OIC can occur quickly after the initiation of opioid therapy in cancer patients, even if laxatives were utilized prophylactically. The current tools for diagnosing OIC result in varied rates of diagnosis.

Clinical trial identification: UMIN000025864.

Legal entity responsible for the study: Shionogi & Co., Ltd.

Funding: Shionogi & Co., Ltd.

Disclosure: T. Harada: Honoraria: Taiho Pharmaceutical, AstraZeneca K.K., Boehringer Ingelheim, Hisamitsu Pharmaceutical Co, Inc. H. Sato: Employee: Shionogi & Co., Ltd. All other authors have declared no conflicts of interest.

1712P Efficacy and tolerability of naldemedine in patient with cancer and opioid-induced constipation: A pooled subgroup analysis of 2 randomized placebo-controlled studies

E. Satomi[1], H. Ishiki[1], T. Yokota[2], Y. Tada[3], H. Sato[4], M. Okamoto[5], I. Osaka[6]

[1]Palliative Medicine, National Cancer Center Hospital, Tokyo, Japan, [2]Project Management, Shionogi & Co., Ltd., Osaka, Japan, [3]Biostatistics Center, Shionogi & Co., Ltd., Osaka, Japan, [4]Medical Affairs, Shionogi & Co. Ltd., Osaka, Japan, [5]Medical Affairs, Shionogi & Co., Ltd., LTD, Osaka, Japan, [6]Palliative Medicine, Shizuoka Cancer Center Hospital, Tokyo, Japan

Background: Opioid-Induced Constipation (OIC) is a common side effect of opioid analgesic therapy. Naldemedine (NAL), an orally available peripherally-acting μ-opioid receptor antagonist (PAMORA), has been shown to improve OIC without affecting analgesic effect of opioids across several clinical studies. However, the predictive factors determining the response to OIC treatment have not been elucidated. We conducted a subgroup analysis with the pooled data to explore the predictive factors in patient population for the efficacy and safety of NAL.

Methods: Data were pooled from 2 randomized, double-blinded, placebo (PBO)-controlled studies of NAL 0.2mg QD (Ph2b and Ph3) for cancer patients (JapicCTI-132340, JapicCTI-111510). Subgroup analysis (age, BMI, gender, opioid type or dosage, concomitant laxatives, with or without anti-cancer therapy, with or without possible disruption of blood brain barrier (BBB)) of spontaneous bowel movement (SBM) responder rate (percentage of patients with $\geq$ 3 SBMs/week and an increase from baseline of $\geq$ 1 SBM/week) was conducted. Overall safety and the incidence of diarrhea were evaluated. The pain intensity numerical rating scale (NRS) and clinical opiate withdrawal scale (COWS) were also analyzed in the population with or without possible BBB disruption.

Results: SBM responder rate was 73.5% (114 of 155 patients) for the NAL group and 35.5% (54 of 152 patients) for the PBO group for all subjects. The difference between the groups was 38.0% and was statistically significant ($P < 0.0001$). In the subgroup analysis, the difference of proportion between NAL vs PBO for each efficacy and safety endpoint was consistent across all subgroups (The all point estimates were greater than zero). Although the difference of the incidence of diarrhea between the groups was relatively larger in the possible disruption of BBB group, there was no difference between with or without possible BBB disruption for NRS and COWS.

Conclusions: Overall, this analysis of subgroups supported that the benefits of NAL were observed regardless of background factor, and its safety profile in various subgroups was consistent with that observed in the overall population.

Clinical trial identification: JapicCTI-132340, JapicCTI-111510.

Legal entity responsible for the study: Shionogi & Co., Ltd.

Funding: Shionogi & Co., Ltd.

Disclosure: T. Yokota: Employee and stock owner: Shionogi & Co., Ltd. Y. Tada, H. Sato, M. Okamoto: Employee: Shionogi & Co., Ltd. I. Osaka: Honoraria: Shionogi & Co., Ltd. All other authors have declared no conflicts of interest.

1713P Left ventricular ejection fraction (LVEF) change for the first 6 months predicts development of trastuzumab-related cardiotoxicity in patients with breast cancer: An implication for the more efficient cardiac surveillance

J.H. Yeo[1], H. Ahn[2], I. Park[2], Y.S. Kim[2], S.J. Sym[2], E.K. Cho[1], D.B. Shin[2]

[1]Internal Medicine, Gachon Univeristy Gil Medical Center, Incheon, Republic of Korea, [2]Medical Oncology, Gachon University Gil Medical Center, Incheon, Republic of Korea

Background: Current guidelines recommend cardiac function monitoring every 3 months in patients receiving trastuzumab, however evidences for optimal cardiac surveillance strategy are lacking. The aim of this study is to identify risk factors and to characterize clinical patterns of trastuzumab related cardiac dysfunction(TRCD) within 1 year of treatment in patients with breast cancer.

Methods: We identified and reviewed consecutive patients with breast cancer received trastuzumab and adequate cardiac monitoring (baseline and subsequent cardiac echocardiogram at least every 4 months) between Jan 2010 - Apr 2017 at a single center. TRCD were defined as an absolte decrease of ejection fraction(EF) $\geq$15% or $\geq$ 10% to below the lower limit of normal.

Results: Among 364 patients(median age 51 years), TRCD was developed in 33 patients (9.3%). Median time from trastuzumab to TRCD was 6.3 months(range 2.6-12.3). Incidence of TRCD was significantly higher in patients with prior anthracycline (12.1% vs. 5.1%, $p = 0.026$). In 20 out of 33 patients (60.6%), TRCD was diagnosed within the first 6 months of trastuzumab. Earlier TRCD was significantly associated with prior anthracycline (72% vs. 25%, $p = 0.035$). Among the patients with later TRCD development after 9 months of trastuzumab ($n = 13$), absolute EF decrease >5% in the first 6 months preceded in 10 patients (76.9%). Incidence of later TRCD was significantly lower in patients whose absolute EF decrease < =5% in the first 6 months (2.1%) than in whom with more than 5% of absolute EF decrease (11.8%).

Conclusions: TRCD development occurs earlier within the first 6 months of trastuzumab in patients with prior anthracycline use. The degree of absolute EF decrease in the first 6 months can predict later development of TRCD. Therefore, cardiac monitoring for the first 6 months of trastuzumab treatment should not be missed, especially in whom with prior exposure to anthracyclie. Adaptive less frequent cardiac surveillance strategy after 6 months may be considered in patients without significant EF change.

Legal entity responsible for the study: Hee Kyung Ahn.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1714P Predicting the occurrence and prevention of early anthracycline cardiotoxicity of chemotherapy in patients with breast cancer

A. Askolskyi[1], L. Syvak[1], O. Zharinov[2], N. Khranovska[3]

[1]Chemotherapy of Solid Tumors, National Cancer Institute, Kiev, Ukraine, [2]Department of Functional Diagnostics, Shupyk National Medical Academy of Postgraduate Education, Ministry of Healthcare of Ukraine, Kiev, Ukraine, [3]Laboratory of Experimental Oncology and Laboratory of Molecular-Genetics Diagnostics, National Cancer Institute, Kiev, Ukraine

Background: Methylenetetrahydrofolate Reductase (MTHFR) is the key enzyme of xenobiotic detoxification, involved in the metabolism of anticancer drugs. Genotyping of the polymorphism MTHFR allows to make prognosis of chemotherapy side effects in different patients, personalize pharmacotherapy.

Methods: QTc interval and myocardial systolic and diastolic function of 100 patients with breast cancer stages T1-3N0-3M0 treated with neo/adjuvant anthracycline chemotherapy were investigated. In the main study group 50 patients received cardioprotective medications (enalapril 2.5 mg orally twice daily and carvedilol 6.25 mg orally twice daily). The polymorphisms of MTHFR gene in control group were evaluated using Real-Time PCR. Statistica10.0 software was used to perform analysis of variance.

Results: It was established that the specific manifestations of early cardiotoxicity of doxorubicin at a cumulative dose 300 mg/m^2 were QTc prolongation over 460 msec in the main group in 5 (10%) patients, in the control group – 13 (26%) patients, as well as diastolic dysfunction (DD) of the left ventricle type 1 in the main group in 5 (10%) patients, in the control group – 15 (30%) patients.The absence of cardioprotective therapy in our study was a risk factor for these complications: QTc interval prolongation (OR = 3.15, 2.05 – 4.21, $p = 0.03$) and DD (OR = 3.85, 2.75 – 4.96, $p = 0.01$).A molecular genetic analysis had shown that QT prolongation and DD were detected in 36.4% of patients with T/T genotype, in 36.6% – with C/T genotype and only 9.1% patients with genotype C/C. The risk of cardiotoxicity of chemotherapy in patients with breast cancer, which is the carrier of one or two mutant alleles of the gene MTHFR (genotype C/T and T/T) is 2.68 times higher (OR = 2.68; 95% CI = 1.24 – 5.78; $p < 0.01$) in comparison with carriers of genotype C/C.

Conclusions: It is reasonable to determine the MTHFR gene polymorphism in patients with early breast cancer prior to treatment which allow to identifying a high-risk cardiotoxicity group for timely and adequate cardioprotective therapy administration.

Legal entity responsible for the study: National Cancer Institute, Kiev, Ukraine.

Funding: National Cancer Institute, Kiev, Ukraine.

Disclosure: All authors have declared no conflicts of interest.

1715P Baseline prevalence of cardiovascular disease (CVD) risk factors in women with breast cancer

N. Bhoo-Pathy[1], S. Subramaniam[2], H. Zaharah[3], Y.C. Kong[4], N.A. Taib[5], A. Deniel[6], K-H. Chee[7], R.S. Bustamam[6], M-H. See[5], A. Fong[8], C.H. Yip[9]

[1]Centre for Clinical Epidemiology and Evidence Based Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [2]Clinical Epidemiology Unit, National Clinical Research Centre, Ministry of Health Malaysia, Kuala Lumpur, Malaysia, [3]Radiotherapy and Oncology, National Cancer Institute, Putrajaya, Malaysia, [4]Clinical Epidemiology Unit, National Clinical Research Centre, Kuala Lumpur, Malaysia, [5]Department of Surgery, University Malaya Medical Center, Kuala Lumpur, Malaysia, [6]Radiotherapy and Oncology, Kuala Lumpur Hospital, Kuala Lumpur, Malaysia, [7]Cardiology Unit, University Malaya Medical Center, Kuala Lumpur, Malaysia, [8]Heart Centre, Sarawak General Hospital, Kuching, Malaysia, [9]Breast Clinic, Subang Jaya Medical Centre, Subang Jaya, Malaysia

Background: Pre-existing CVD risk factors in women with breast cancer increases their risk of developing adjuvant therapy induced cardiotoxicity. We measured the prevalence of major CVD risk factors in women newly diagnosed with breast cancer in a multiethnic setting.

Methods: From 2015 to 2017, 2159 women with newly diagnosed invasive breast cancer were consecutively recruited from four tertiary hospitals in Malaysia. Demographic, medical and drug history were collected through interviews and verified with medical records. Pre-treatment height, weight, blood pressure, serum glucose, and cholesterol levels were measured. Risk of cardiotoxicity was estimated using the Cardiotoxicity Risk Score proposed by Herrmann, et al.

Results: Median age at diagnosis was 54 years. Median tumor size at presentation was 2.7 cm and 54% had node-negative disease. A majority (70%) of patients had estrogen receptor positive tumors. Prevalence of hypertension was 43%, while hypercholesterolemia was found in 48%. Seventeen percent of patients had diabetes mellitus and 19% were obese. Only 2% were current smokers. Four percent of patients had pre-existing coronary heart disease, arrhythmias or valvular disease. Overall, 40% of patients presented with two or more major CVD risk factors (clustering). The clustering of CVD risk factors was substantial across all age groups; age < 40 years: 16%, 40-49 years: 24%, 50-64 years: 46%, > =65 years: 62%. The Malay and Indian patients were twice more likely to have CVD risk clustering than the Chinese. Of 1880 patients with non-metastatic breast cancer, 45% were planned for anthracycline-based chemotherapy, and 54% for adjuvant radiotherapy. Taking the adjuvant treatment plan into account, it appeared that approximately one in two women with breast cancer in our settings were at high risk of developing cardiotoxicity.

Conclusions: Our findings highlight the need to accelerate the establishment of coordinated partnerships between the oncology and cardiology specialties to improve cardiac outcomes following breast cancer. In the era of precision medicine, these findings also lend support to the notion that the next generation adjuvant therapy decision-making tools in breast cancer should incorporate data on major CVD risk factors.

Legal entity responsible for the study: Nirmala Bhoo-Pathy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1716P Cardiovascular and other competing causes of death among cancer patients, 2006-2015: An Australian population-based study

Y. Ye[1], P. Otahal[1], T. Marwick[2], K. Wills[1], A. Neil[1], A. Venn[1]

[1]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia, [2]Baker Heart and Diabetes Institute, Baker Heart and Diabetes Institute, Melbourne, Australia

Background: Cardiovascular disease (CVD) is the leading cause of death worldwide. With improved cancer treatment and survivorship, CVD and other non-cancer events compete with cancer as the underlying cause of death. However, their mortality risk in competing risk settings is not well characterised.

Methods: We identified 21,637 individuals with a first cancer registered between January 2006 and December 2013 in the population-based Tasmanian Cancer Registry, Australia. Cumulative incidence functions were applied to assess the cumulative incidence of deaths due to specific competing events with follow-up to December 2015. Standardised mortality ratios (SMRs) and absolute excess risks (AERs) for non-cancer deaths were calculated to allow comparison with the general population.

Results: Overall, 8,844 deaths were observed with 1,946 (22.0%) from competing events (332 from subsequent cancer, 741 from CVD and 873 from other non-cancer events). The cumulative incidence of deaths due to CVD increased significantly with age at first cancer diagnosis (5-year cumulative mortality by age group: 15-64y – 0.7%; 65-74y – 2.1%; 75-84y – 6.0%; 85+y – 13.1%) and exceeded other competing events for those with a first cancer diagnosis at age 65 years or older. For the whole follow-up period, CVD deaths were as expected for the general population (SMR, 0.97; 95%CI 0.90-1.04), however within the first follow-up year, CVD deaths were more common than expected (SMR, 1.44; 95%CI 1.26-1.64; AER, 36.8/10,000 person-years). The SMR and AER for CVD deaths varied by first cancer sites showing an increased risk after a first diagnosis of lung cancer, haematological malignancies and urinary tract cancers. For other non-cancer events, the SMRs significantly increased for infectious disease and respiratory disease for the whole follow-up and within the first year of diagnosis.

Conclusions: CVD was the leading cause of competing mortality among Tasmanian cancer patients diagnosed from 2006-2013. The higher than expected risk of death due to CVD and other non-cancer events was greatest during the first year after cancer diagnosis highlighting the importance of early preventive interventions.

Legal entity responsible for the study: Menzies Institute for Medical Research, University of Tasmania.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1717P Cancer associated thrombosis with primary prophylaxis in a tertiary hospital in the Philippines from 2010-2015

A.T.B. Gerona

Medical Oncology, St. Luke's Medical Center, Quezon City, Philippines

Background: Venous thromboembolism, consisting of pulmonary embolism or peripheral venous thrombosis is the second most common leading cause of death in cancer. Prophylactic measures are now being done to prevent its occurrence. In an financially-challenged patient does primary prophylaxis really protect our patients?

Methods: Data from the hospital's database for year 2010-2015 with either Venous Dupplex Scan or Computed Tomographic Pulmonary Angiography (CTPA). Each result were reviewed for presence of acute pulmonary embolism or acute venous thrombosis. Only the first event after the diagnosis of cancer was considered therefore, all subsequent events were ignored. Among those with positive venous thromboembolism results, review of chart and computerized data system on histologic diagnosis of carcinoma.

Results: A total of 10,380 CTPA/Venous duplex scan were performed for year 2010-2015, where 916 (8.8%) had positive venous thromboembolism (VTE). Of patients with VTE, 712(6.8%) were not associated with malignancy, 204(2%) had malignancy. Average age of patient 61.3(range 19-90), mostly female (61.7%) and had normal body mass index (62.2%). Most common symptom was swelling of the extremity(54%) followed by pain(32%) and dyspnea (12.6%). Lower extremity (77.4%) thrombosis was more common than upper extremity thrombosis (9.8%). Breast cancer (n = 37, 18.9%) had the most number of VTE, followed by lung (n = 31, 15%). Gynecologic malignancies had up to 21.5%, followed by gastrointestinal malignancies 21.5% (n = 44). Most patients had prior hospitalization (n = 146, 71.5%) within the past three months prior to the diagnosis of VTE. Up to 81.8% (n = 167) had no VTE prophylaxis while 9.8% (n = 20) had primary prophylaxis prior to the occurrence of VTE. However, among those who had prophylaxis with heparin, two had no prior hospitalization for three months prior to the VTE diagnosis, and mostly had gynecologic malignancy, breast cancer, and hepatocellular cancer. Seventy percent of them had normal BMI and were mostly <65 years of age.

Conclusions: Cancer patients still develop VTE even with primary prophylaxis and no hospitalization for the past three months which were the leading risk factors for developing VTE in prior studies. There is no difference in patient profile for those who received primary prophylaxis in our center compared to the general profile.

Legal entity responsible for the study: Agnes Gorospe.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1718P The incidence of recurrent venous thromboembolism (VTE) and bleeding depending on practical treatment pattern of anticoagulation in the cancer patients with VTE

S-M. Bang[1], J-H. Kang[2], M.H. Hong[3], J.S. Ahn[4], S.Y. Oh[5], J.H. Baek[6], Y.J. Choi[7], S.H. Shin[8], Y-J. Kim[9], J-H. Cha[9], J. Lee[10]

[1]Hematology and Medical Oncology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [2]Internal Medicine and Medical Oncology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [3]Internal Medicine, Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, [4]Hematology and Medical Oncology, Samsung Medical Center, Seoul, Republic of Korea, [5]Hematology and Medical Oncology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea, [6]Hematology and Medical Oncology, Ulsan University Hospital, Ulsan, Republic of Korea, [7]Hematology and Medical Oncology, Korea University Anam Hospital, Seoul, Republic of Korea, [8]Hematology and Medical Oncology, Kosin University Gospel Hospital, Busan, Republic of Korea, [9]Outcomes Research/Real World Data Team, Corporate Affairs and Health & Value Division, Pfizer Pharmaceuticals Korea Ltd., Seoul, Republic of Korea, [10]Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea

Background: Even low molecular weight heparin (LMWH) for 3 to 6 months (Ms) is recommended for cancer-associated VTE, little has been known about practical treatment (Tx) pattern of anticoagulants and clinical outcome in Asia.

Methods: This retrospective cohort study was conducted from Oct 2016 to Jul 2017 at 8 university hospitals in Korea. Data was extracted from the medical chart of each individual hospital. Active cancer patients (pts), ≥19 years, with cancer-associated deep vein thrombosis or pulmonary embolism diagnosed from 2013 to 2015, and on anticoagulants, were enrolled and followed for 1 year. Demographic data will be published in abstract book of ISPOR 2018. Pts were classified by the form of anticoagulants; the group with LMWH Tx over 3 consecutive Ms allowing at most 14 days of temporary discontinuation and the non-LMWH group with other anticoagulants. The cumulative incidence of 1st recurrent VTE and bleeding for 1st 6 Ms of Tx was compared between LMWH and non-LMWH groups. LMWH group was further divided into ≤ 6 and > 6 Ms of Tx period. 3-group comparison was completed for the cumulative incidence of 1st recurrent VTE and bleeding from 6 to 12 Ms of Tx.

Results: Of total 748 pts (age: 63.8±11.5, male: 50.3%), the major cancer type was lung cancer (24.6%). 15.2% received LMWH over 3 Ms whereas 84.8% had various non-LMWH anticoagulants. The incidence of recurrent VTE was 17.5% in LMWH and 19.4% in non-LMWH. Bleeding events of LMWH and non-LMWH were 12.3% and 21.6%. Of the pts with bleeding, 28.6% in LMWH had major bleeding while 33.6% in non-LMWH. Up to 6 Ms after the 1st Tx, the cumulative incidence of first recurrent VTE in LMWH (8.4, CI: 3.09, 13.67) was lower than that of non-LMWH (9.7, CI: 7.33, 12.11) (p = 0.0048). Likewise, the cumulative incidence of 1st bleeding until 6 Ms was significantly lower in LMWH (8.9, CI: 3.28, 14.48) than non-LMWH (9.7, CI: 7.32, 12.02) (p = 0.0006). For following 6 Ms after 1st 6 Ms of Tx, the group with LMWH > 6 Ms (6.7, CI: 0.00, 19.29) had the lowest cumulative incidence of VTE recurrence among 3 groups (p = 0.0024).

Conclusions: Our data suggest that LMWH be used for 3 to 6 Ms and be maintained even afterwards to minimize the incidence of recurrence and bleeding in the cancer patients with VTE.

Legal entity responsible for the study: Pfizer Pharmaceuticals Korea Ltd.

Funding: Pfizer Pharmaceuticals Korea Ltd.

Disclosure: Y-J. Kim, J-H. Cha: Pfizer Pharmaceuticals Korea Ltd. All other authors have declared no conflicts of interest.

1719P Prevention and prophylaxis of thrombosis in cancer patients

N.G. Tsoukalas, P. Papakotoulas, A.N. Christopoulou, A. Ardavanis, G. Koumakis, C. Papandreou, G. Papatsimpas, P. Papakostas, C. Andreadis, G. Aravantinos, N. Ziras, H. Kalofonos, E. Samantas, M. Sougleri, P. Makrantonakis, G. Pentheroudakis, A. Athanasiadis, E. Bournakis, I.I. Varthalitis, I. Boukovinas

HeSMO - Hellenic Society of Medical Oncology, Athens, Greece

Background: Cancer Associated Thrombosis (CAT) is a significant problem in oncology that is underestimated sometimes. Venus ThomboEmbolism (VTE) is the 2nd cause of death in cancer patients. Currently, the standard of care not only for the treatment but also for the prophylaxis of CAT is the Low Molecular Weight Heparines (LMWHs). Thromboprophylaxis is an important medical decision for cancer patients in daily clinical practice.

Methods: This is an observational study conducted by HeSMO in Greek Oncology units, for 1 year, aiming to record CAT management. Patients with active cancer received antithrombotic agents for thromboprophylaxis were enrolled, after signing informed consent.

Results: All participating centers reported that approximately 4.300 cancer patients are managed on monthly basis, where the majority (80%) as outpatients. 426 cancer patients enrolled from 18 oncology units with mean age 65.2 years old and mean Body Mass Index (BMI) 26.10. Primary cancers were: lung 25%, pancreas 14%, stomach 8.6%, breast 8.6%, ovarian 7.7%, colorectal 7.5%, bladder 5.6% and other 22.8%. 50% of patients received LMWH at prophylactic doses while the rest received therapeutic doses [mean duration 4.42 months (SD +/- 2.68)]. 126 (30%) patients had Khorana score ≥3. 300 (70%) had Khorana score ≤2 and of these patients 68% were metastatic and 58% were receiving High Thrombotic Chemotherapy Agents (HTCA, e.g. platinum). 16 (3.8%) patients experienced VTE while 9 (56%) of them were incidental. Lower VTE risk [OR: 0.32 (95% CI 0.10, 1.0) p = 0.04] was observed in patients on therapeutic doses LMWH while higher VTE risk [OR: 3.14 (1.01, 9.9)] was observed in patients on prophylactic doses LMWH. High BMI>35 was related to significant higher risk for VTE [OR 5.37 (1.6, 18). Only six (1.4%) grade 1 bleedings were recorded in all patients who receive thromboprophylaxis.

Conclusions: CAT is an important problem in oncology. Therapeutic doses of LMWH for thromboprophylaxis are effective and safe. Apart from Khorana score, some other factors such as disease stage and administration of HTCA might be taken into consideration for better CAT risk assessment in oncology patients.

Legal entity responsible for the study: Hellenic Society of Medical Oncology (HeSMO), Athens, Greece.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1720P Is it appropriate to use a fixed prophylactic dose of enoxaparin for hospitalized cancer patients? Results from a prospective tertiary referral single center study

C. Maurice-Dror[1], M. Litvak[1], A. Keren[2], S. Akerman[2], B. Brenner[2], N. Haim[1], Y. Nadir[2]

[1]Oncology, Rambam Health Care Center, Haifa, Israel, [2]Hematology, Rambam Health Care Center, Haifa, Israel

Background: Thromboprophylaxis with low molecular weight heparin (LMWH) is recommended in hospitalized cancer patients with reduced mobility and/or other risk factors for venous thromboembolism. An unresolved issue is whether the commonly used LMWH, enoxaparin should be given in a fixed dose for thromboprophylaxis or adjusted to weight. The aim of this study was to examine whether hospitalized cancer patients, treated with a fixed dose of enoxaparin (40 mg/day) reach appropriate target level of anti-Xa, and whether anti-Xa level in these patients is correlated to body size, gender, and blood creatinine level.

Methods: Between Oct 2015 to June 2017 hospitalized cancer patients with indication for thromboprophylaxis and without contraindication for SC enoxaparin (40 mg/day) were entered into the study. Prior to the initiation of enoxaparin, patients were weighed and measured and blood samples were collected for PT/PTT, CBC and Creatinine. Blood samples for peak anti Xa level were collected at 48-120 hrs post initiation of enoxaparin (3 hrs after injection). Target anti-Xa was defined as 0.2-0.5 U/ml.

Results: Eighty patients were enrolled (male/female: 46/34; age: 25-84, median 66yrs). 72 patients met inclusion criteria and had full data for analysis. The most common indication for prophylactic enoxaparin treatment was ECOG performance status 3-4 (82%). Median anti Xa level was 0.255 U/ml (range 0.01-0.77). Anti Xa levels were within target range in 40 patients (55.6%), below target in 26 patients (36.1%) and above target in 6 patients (8.3%). Anti Xa was higher in females (median 0.3 vs. 0.19 U/ml; $p < 0.001$) and correlated positively with serum creatinine ($p = 0.003$), and negatively with body weight ($p < 0.001$). Optimal threshold weight for predicting sub-therapeutic levels of anti Xa was identified at 78kg (sensitivity 43%, specificity 85%).

Conclusions: Using a policy of fixed dose enoxaparin resulted in under-treatment in more than one-third of a non-selective population of cancer patients, mainly in those whose weight was above 78kg. We suggest that prophylactic dosage of enoxaparin higher than 40 mg should be considered for patients with body weight above 80 kg.

Legal entity responsible for the study: Helsinki committee Rambam Health Care Campus.

Funding: Has not received any funding.

Disclosure: B. Brenner: Honoraria for lectures and advisory board contributions: Pfizer, Leo Pharma, Sanofi, Rovi Laboratories, Bayer Pharmaceuticals. All other authors have declared no conflicts of interest.

1721P Long-term prognosis of acute pulmonary embolism: A focus on idiopathic and neoplastic etiologies

I.M.C. Guerreiro[1], H. Magalhães[1], S. Coelho[1], A.M. Ribeiro[2], S. Ferreira[2], E. Araújo[2], M. Fontes-Sousa[1], P. Bettencourt[3], P. Lourenço[2]

[1]Department of Medical Oncology, Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal, [2]Department of Internal Medicine, Hospital Centre of São João, Porto, Portugal, [3]Department of Internal Medicine, CUF Hospital Centre Porto, Porto, Portugal

Background: Acute pulmonary embolism (PE) is a fatal condition when untreated. Long term prognosis of acute PE in the 21st century has not been fully reported. We aimed to determine the long-term prognosis of acute PE and assess if there were survival differences between patients with idiopathic and secondary PE.

Methods: We retrospectively analysed a cohort of patients hospitalized with acute PE between 2006 and 2013. Excluded: 1) <18 years old, 2) embolism of non-pulmonary veins and 3) chronic pulmonary embolism. The vital status was ascertained by consulting the National Registry of Portuguese Patients platform. Patients were grouped according to acute PE aetiology: idiopathic, secondary to a neoplastic condition and secondary to conditions other than a neoplasia. A Cox-regression analysis was used to study the prognostic implications of PE aetiology. Multivariate models were built.

Results: A total of 872 patients with acute PE were admitted, median age: 70 years old, 496 (56.9%) were female. In 36.8% the PE was of central arteries and in 56.9% bilateral. PE was considered idiopathic in 376 (43.1%), secondary to a neoplastic condition in 284 (32.6%) and secondary to a condition other than neoplasia in 212 (24.3%). Patients were followed for a median period of 25 months and 508 (58.3%) patients died. Patients with acute PE attributed to a neoplastic condition had the worst survival and those with PE secondary to a non-neoplastic condition the best survival. Patients with idiopathic PE had a multivariate adjusted HR of mortality of 1.46 (1.08-1.99) during the over 2-year follow-up period when compared to those with acute PE secondary to a non-neoplastic condition.

Conclusions: Acute PE attributed to a neoplasia portended the worst prognosis. Patients with idiopathic PE had 46% higher risk of death than those with PE secondary to a non-neoplastic condition. Idiopathic PE should probably be looked at more carefully by physicians treating acute PE patients.

Legal entity responsible for the study: Hospital Centre of São João.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1722P Systematic literature review and network meta-analysis of oral anticoagulants for the treatment of venous thromboembolism in patients with cancer

H. Park, J-C. Kim, J. Cho, J.H. Lim, M.H. Lee

Hemato-Oncology, Inha University Hospital, Incheon, Republic of Korea

Background: Based on the current guideline, treatment options for cancer-associated thrombosis include low molecular weight heparin (LMWH), unfractionated heparin (UFH), warfarin, and fondaparinux. However, in patients who do not have cancer, direct oral anticoagulants are preferred for the treatment of VTE. In some cases, the use of LMWH is limited due to administration by the subcutaneous route. In this study, we compared the efficacy and safety of oral anticoagulants including vitamin K antagonists (VKA) and direct-acting oral anticoagulants (DOAC) for the treatment of cancer-associated VTE.

Methods: We conducted a systematic literature review to identify all eligible randomized controlled trials (RCT) by searching PubMed, Web of Science, ASH, ASCO, EHA, and ESMO databases. The relative risks (RR) of recurrent VTE (efficacy) and major bleeding (safety) were analyzed using Bayesian network meta-analysis with a fixed-effect model.

Results: Four DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) were identified in five RCTs. When comparing the efficacy between VKA and DOACs, the recurrence rate of VTE was lower in the treatment with DOACs than with VKA, but not statistically significant. (apixaban: odds ratio [OR] 0.55, 95% credible intervals [CrI] 0.10-2.4; dabigatran: OR 0.76, 95% CrI 0.32-1.8; edoxaban: OR 0.49, 95% CrI 0.12-1.7; rivaroxaban OR 0.57, 95% CrI 0.19-1.7). In safety, the risk of major bleeding was relatively low in the use of DOACs compared to VKA, except for edoxaban (apixaban: OR 0.42, 95% CrI 0.058-2.2; dabigatran: OR 0.82, 95% CrI 0.25-2.7; edoxaban: OR 1.6, 95% CrI 0.38-8.4; rivaroxaban OR 0.47, 95% CrI 0.14-1.5).

Conclusions: For the treatment of VTE in cancer patients, DOAC has a favorable tendency for the efficacy and safety compared to VKA. DOACs could be one of the standard treatment options for management of VTE in cancer patients. Among DOACs, epixaban has a relatively good outcome.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1723P Comparison of venous thromboembolism risk assessment models in patients receiving chemotherapy

K. Talasiewicz, P. Ozdowska, B. Milanowska, K. Gepner, B. Jagielska

Department of Oncology Diagnostics, Cardioncology and Palliative Medicine, Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology (MCMCC), Warsaw, Poland

Background: Venous thromboembolic events (VTEs) remain one of the most common causes of morbidity and mortality in cancer patients. Various risk scores were developed to help oncologists in the decision-makingprocess relating to VTE in this challenging group of patients.

Methods: We retrospectively analyzed a group of 124 cancer patients diagnosed with VTE between September 2012 and June 2017 in M.Sklodowska-Curie Memorial Cancer Center and Institute, Warsaw, Poland and selected patients receiving chemotherapy ($n = 72$). We compared the patients KHORANA, PROTECHT and CONKO scores in order to determine which of them would be more precise in terms of VTE prediction during chemotherapy. Statistical analysis was made using descriptive statistics, differences between scales were tested using chi-squared test applying Bonferroni correction.

Results: VTE's were observed mainly during chemotherapy treatment (n = 72, 58.1%). VTE's occurred significantly more frequently in patients who received Cisplatin- or Gemcitabine- basedchemotherapy ($p < 0,05$). In 27 (21.8%) cases VTE was the first manifestation of the disease and/or appeared during the diagnostic process. Most of the patients (69,64% - 88,89% depending of the scale) were classified as having low/intermediate risk, without the potential need for thromboprohylaxis use. The PROTECHT score was the best indicator to discriminate between patients with high or low/intermediate risk, followed by the CONKO score and finally by the KHORANA score. The PROTECHT score more often assigned patients to the "high-risk group" and this difference was statistically significant comparing with the KHORANA score, p = 0,016 (Table).

Table: 1723P

Risk	KHORANA		PROTECHT		CONKO	
	N	%	N	%	N	%
Low	21	29,17%	17	23,61%	26	36,11%
Intermediate	43	59,72%	33	45,83%	34	47,22%
High	8	11,11%	22	30,56%	12	16,67%
chi^2	10,99					
df	4					
p	0,0267					
	KHORANA vs. PROTECHT		KHORANA vs. CONKO		PROTECHT vs. CONKO	
chi^2	8,27		2,38		4,84	
df	2		2		2	
p	0,0160		0,3036		0,0889	
Bonferroni	0,0480		0,9108		0,2667	

Conclusions: The PROTECHT score discriminated better between low- and high-risk patients and appeared to have the highest sensitivity. The implementation of VTE prophylaxis in patients assessed as high-risk patients, according to the PROTECHT score, could potentially prevent the largest amount of VTEs.

Legal entity responsible for the study: Maria Sklodowska-Curie Memorial Cancer Center and Institute, Warsaw, Poland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1724P Personalised nutritional care during chemotherapy using survey on taste changes during chemotherapy: First experience from tertiary chemotherapy day care center in Northern India

A. Vora[1], S. Chatterjee[1], A. Upadhyay[1], N. Hazarika[1], G.S. Bhattacharya[2]

[1]Medical Oncology, H.O.P.E. Oncology Clinic, New Delhi, India, [2]Medical Oncology, Fortis Hospital, Kolkata, India

Background: Personalised care is the current practice of treating cancer patients. Taste changes during chemotherapy also should be personalised depending on changes observed during chemotherapy. We attempted the same using a survey in each patient of chemotherapy at our center. This is first of its kind from india to the best of our knowledge.

Methods: Every patient coming for chemotherapy at our center was given one page survey along with consent form. Survey included: specifying taste changes for sweet, salt, bitter, sour and humami. Taste of water was included. Based on survey findings, nutrition advice was given to patient. Feedback from patient also was taken about food items they like, religious belief and any other preferences. Weight loss and albumin level was checked during each chemotherapy.

Results: Total 71 patients participated in the study. 24 makes and 47 females. Age range: 13 to 77. Diagnosis: breast: 17; ovary:14; GI:19;hematological:6; head neck:5; lung:4; CNS:3; sarcoma:3. All patients completed at least 2 cycles of chemotherapy (range: 2 -16). Survey of taste changes: except 1, all other 70 patients preserved sweet taste during chemotherapy. Highest change was in salt: 59% (42/71) followed by bitter 22%. Surprisingly, 24% reported water to be tasteless. Intervention: with the help of endocrinologist; all patients were advices to take fresh fruits and sweets. Salt and bittertaste was overcome by use of sour (lemon pickle etc). In fact, majority of patients loved addition of sour food items. Coconut water, lemon flavoured water were easily consumed in patients with water taste problems. Except 5 patients, all patients preserved weight n albumin.

Conclusions: This is first experience of personalised nutrition care in cancer patients with chemotherapy. Patients really enjoyed eating to their taste and thus were happy and were able to retain their weight n albumin. We are continuing this study with help of taste bud strips and professional nutritionists.

Editorial acknowledgement: Purvish M Parikh.

Legal entity responsible for the study: Phoenix Innovation LLP.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1725P Role of megestrol acetate versus dexamethasone for improvement in appetite in patients with cancer associated anorexia cachexia: A randomized controlled pilot trial

S.P. Ostwal[1], N.S. Salins[2], J.K. Deodhar[2], M. Maryann[2]

[1]Palliative Medicine, Gujarat Cancer and Research Institute, Ahmadabad, India, [2]Palliative Medicine, Tata Memorial Hospital, Mumbai, India

Background: Loss of appetite, also known as anorexia, is a frequent and distressing symptom in patients with advanced cancer and other life-limiting illnesses. Prolonged periods of anorexia, can lead to both serious physical and psychological distress to patients and their families, which ultimately can contribute to a poorer quality of life. This study compare the clinical benefits between Dexamethasone and Megestrol acetate in an Indian setting, its positive impact on appetite, QOL, and lean body mass.

Methods: A prospective, randomized controlled pilot study conducted in outpatient clinic of Palliative Medicine from September to December 2015. Registered adult advanced cancer patients meeting the inclusion criteria and exclusion criteria were assessed for anorexia, measured by ESAS scale, lean body weight (by Hume's Formula) and QOL (EORTC-QOL PAL15). Patients received either Dexamethasone (4mg) or MA (160mg in divided doses) for 21 days. No associated appetite stimulants or multivitamins were prescribed to study patients. All patients were encouraged to eat normal diet and provided standard medical care. Follow up done at days 7, 21 and 35.

Results: Total 40 patients were enrolled in the study. Patients in both groups showed statistically significant improvement in appetite, lean body weight and quality of life at weeks 3 and 5, compared to baseline. However, study failed to show any significant difference for primary (appetite improvement) and secondary (lean body weight and quality of life) objectives between two groups, at weeks 3 and 5. Dexamethasone was found to be associated with more side effects.

Conclusions: Comparison between Megestrol acetate and dexamethasone failed to show any statistical significant difference in improvement of anorexia, lean body weight and quality of life. Both drugs individually improved the same, as compared to baseline. Improvement in fatigue and other symptom scores were seen to be statistically significant in megestrol acetate arm. There is no significant difference in side effect profiles of both dexamethasone and megestrol acetate arms except for difficulty in standing from sitting position and nausea and vomiting.

Clinical trial identification: CTRI: REF/2015/10/009871.

Legal entity responsible for the study: Tata Memorial Hospital Mumbai.

Funding: Tata Memorial Hospital Mumbai.

Disclosure: All authors have declared no conflicts of interest.

1726P Population pharmacokinetics (PPK) of anamorelin (ANAM), an oral selective ghrelin receptor agonist

A. Bernareggi[1], S. Kaasa[2], M. Fallon[3], R.J.E. Skipworth[4], D. Currow[5]

[1]Helsinn Healthcare SA, Lugano, Switzerland, [2]Department of Oncology, Oslo University Hospital and University of Oslo, Oslo, Norway, [3]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK, [4]Clinical Surgery, University of Edinburgh, Edinburgh, UK, [5]ImPACCT – Improving Palliative, Aged and Chronic Care through Clinical Research and Translation, Faculty of Health, University of Technology Sydney, Sydney, Australia

Background: ANAM, in advanced clinical development, showed benefits in cachectic patients with advanced non-small cell lung cancer (NSCLC). Typical values (TV) of ANAM PPK parameters, effects of demographic and physiopathologic covariates on PK parameters and their variability, and individual ANAM steady-state PK profiles in patients were assessed by PPK modeling.

Methods: Cachectic (body mass index $<20\ kg/m^2$ or $\geq 5\%$ weight loss in prior 6 months) NSCLC patients (ROMANA 1 [NCT01387269; N = 477]) were randomized 2:1 to 100 mg once daily oral ANAM/placebo up to 12 weeks. Sparse blood samples were collected (day 43, 0.5–6 h post-treatment) in 70 patients consenting to the PK analysis. For modeling purposes, patients' PK dataset was enriched with PK profiles from phase 1 (healthy subjects) and phase 2 studies. The PPK analysis included 243 PK profiles, 70 of which were from ROMANA 1. Non-linear mixed effect modeling with first-order conditional estimation with interaction was used for the PPK analysis. Correlations between ANAM PK parameters and continuous or categorical covariates were assessed by Spearman's correlation coefficient or analysis of variance models, respectively. Individual steady-state ANAM PK profiles in the 70 patients were simulated by post-hoc empirical Bayes estimates of ANAM PK parameters, and used to assess ANAM exposure and elimination.

Results: The final model selected was a two-compartment model with first-order absorption and lag time, and no covariates as fixed effects. Patient vs healthy subject status was considered to cause no significant difference. TV of PPK parameters for absorption rate constant ($5.39\ h^{-1}$), lag time (0.24 h), volume of central (135 L) and peripheral (67.8 L) compartments, systemic clearance (CL/F, 49.5 L/h), and

inter-compartmental clearance (8.8 L/h) were characterized by low relative standard errors (1.6%–15.9%). In patients, predicted ANAM peak plasma concentration, exposure ($AUC_{0–24}$), and CL/F averaged 675 ng/mL, 2775 ng·h/mL, and 46.1 L/h, respectively.

Conclusions: The final PPK model described ANAM's PK profile in healthy subjects and patients, and is suitable for predicting ANAM exposure in various clinical settings.

Clinical trial identification: NCT01387269.

Editorial acknowledgement: Editorial and medical writing assistance was provided by Oana Draghiciu, PhD, CMPP, TRM Oncology, The Hague, The Netherlands, funded by Helsinn Healthcare (SA), Lugano, Switzerland.

Legal entity responsible for the study: Helsinn Therapeutics (U.S.), Inc.

Funding: Helsinn Therapeutics (U.S.), Inc.

Disclosure: A. Bernareggi: Employee: Helsinn Healthcare SA. S. Kaasa: Holds stocks: EIR Solution A/S. R.J.E. Skipworth: Research funding: Novartis; Previously unpaid member of advisory board: Helsinn. D. Currow: Unpaid member of advisory board: Helsinn Pharmaceuticals; Consultant to specialised therapeutics, Intellectual property payments: Mayne Pharma. All other authors have declared no conflicts of interest.

1727P Health care providers' experiences of positive and negative effects of parenteral nutrition therapy in cancer patients

K. Sand[1], L. Thoresen[2], T.S. Solheim[1], R.G. Helgås[1], E.T. Løhre[1], T.R. Balstad[1]

[1]Department of Clinical and Molecular Medicine and Cancer Clinic, Norwegian University of Science and Technology and St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [2]Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Background: As of today, health care providerś (HCP) have little evidence in research to guide decisions for parenteral nutrition (PN) therapy in cancer patients. Uncertainties prevail concerning both the initiation and the duration of the treatment, as well as the benefits of the intervention. The aim of this study was to explore community HCP's experiences of benefits and challenges with PN in cancer patients.

Methods: An 18-item online survey was emailed to 309 community care HCP. In two of the questions, respondents were asked to describe in free text their positive and negative experiences with PN therapy in cancer patients, and these answers were analysed by use of content analysis.

Results: Out of total 135 responses, 102 (75.6%) reported experience with cancer patients receiving PN and completed the entire survey. The majority of the respondents were female (93%); nurses/cancer nurses (86.4%); and worked in home care (48.5%) or nursing homes (37.9%). The most common positive effect of PN reported was an impression that it increased patients' quality of life through increased vitality, increased hope and the ability to spend time at home (reported by 40.2%). Other reported positive effects were the experience that PN improved tolerance to, and enhanced recovery after, cancer treatment; reduced the family's eating-related distress; and was regarded a good treatment alternative for patients with symptoms such as swallowing problems, nausea or obstruction. The most common negative effect reported was the difficulties of knowing when to terminate PN, primarily because this removes patients' and family's hope (reported by 26.4%). Poor information to patients and their family at initiation of PN, made termination even more difficult. PN therapy was also reported to cause side effects such as fluid retention and oedema and prolong suffering at end of life.

Conclusions: Despite a limited evidence-base in support of benefits of PN treatment in cancer patients, HCP in this study reported several positive effects based on their clinical experience. Some of the positive effects were related to earlier phases of the disease, while the negative effects mainly regarded communication and decision challenges when ending PN therapy at the end of life.

Legal entity responsible for the study: Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

Funding: Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

Disclosure: All authors have declared no conflicts of interest.

1728P Assessment of anorexia and weight loss in newly diagnosed upper gastrointestinal cancer patients with localised and metastatic disease, using the functional assessment of anorexia cachexia therapy anorexia/cachexia subscale (FAACT A/CS)

M. Abraham[1], Z. Kordatou[2], W. Mansoor[3]

[1]Nutrition & Dietetics, The Christie NHS Foundation Trust, Manchester, UK, [2]Medical Oncology, Bank of Cyprus Oncology Center, Nicosia, Cyprus, [3]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK

Background: Anorexia often predisposes to weight loss, leading to poor outcomes in cancer patients. Therefore early recognition is clinically important. Although no gold standard exists to diagnose anorexia, the FAACT A/CS has been suggested to identify cancer patients with anorexia. A previous study has validated the cut-off score of ≤ 37 to diagnose anorexia. In our study we assessed the incidence of anorexia and weight loss in patients with gastric and gastro-oesophageal junction (GOJ) cancer based on the FAACT A/CS.

Methods: Newly diagnosed gastric and GOJ adenocarcinoma patients of all stages, attending outpatient clinics at The Christie Hospital NHS Foundation Trust, from September 2016 to December 2017 completed the FAACT A/CS at initial consultation. BMI and weight change over the last 3-6 months were recorded as standard of care. SPSS was used for statistical analysis.

Results: Based on the FAACT A/CS questionnaire, 127 (69%) out of the 182 patients included in this analysis had anorexia. The mean anorexia score of all the patients was 29.5 (4-48). The incidence of anorexia was greater in metastatic compared to non-metastatic patients (82% vs 52%: $p < 0.01$). Overall, the metastatic group achieved lower mean anorexia scores than the non-metastatic group (25.9 vs. 34.7, $p < 0.01$). Patients in the metastatic group had lower mean body weight compared to those in the non-metastatic group (74 vs 79 kg, $p = 0.069$). Their mean BMI was also lower (25 vs 27, $p = 0.05$). 76% of the metastatic group and 33% of the non-metastatic group had $\geq$5% of weight loss that may classify them as high risk for cancer cachexia, despite their normal or high BMI ($p < 0.01$).

Conclusions: 69% of the patients with gastric/GOJ cancer who attended clinic were anorexic on initial consultation. The incidence of anorexia was higher in patients with metastatic disease (82%). Assessment of anorexia using the FAACT A/CS along with classification of weight loss prior to treatment should be integrated into nutritional assessment. BMI used independently may be unsuitable for identifying patients at nutritional risk.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1729P Body composition factor is independent prognosticator in advanced pancreatic cancer patients

S. Kang[1], H.S. Park[2], H-C. Jeung[1]

[1]Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Internal Medicine, St. Vincent Hospital, Suwon, Republic of Korea

Background: The purpose of this study is to evaluate the body composition including skeletal muscle and fat component as a prognostic factor in advanced pancreatic cancer patients.

Methods: Body composition factor comprised skeletal muscle index (SMI), muscle Hounsfield Unit (HU), subcutaneous fat index (SFI), and visceral fat index (VFI), which were measured at L3 level in abdomino-pelvic computed tomography (CT). region was quantified using the pre-established HU thresholds for skeletal muscle tissue (HU: -30∼150). Visceral fat and subcutaneous fat areas (HU:-150∼-30) were also measured. Continuous variables were dichotomized according to the normal range or the best cut-off values by Contal and O'Quigley method. Kaplan-Meier analysis was applied for relevance between each body composition factor and overall survival (OS).

Results: A total of 414 patients was enrolled. Median age was 66 years old with male predominance (49.8%). Median baseline values were 38.7 cm^2/m^2 for SMI, 33.4 HU, 32.2 cm^2/m^2 for SFI, and 30.1 cm^2/m^2 for VFI. Patients with lower value of the body composition factor has poorer survival (median OS; SMI, 6.9 vs. 10.0 months, $P < 0.001$; HU, 7.6 vs. 9.3 months, $P = 0.0004$; SFI, 6.6 vs. 9.8 months, $P = 0.0008$; VFI, 6.6 vs. 9.8 months, $P = 0.0008$). A body composition risk score was devised by summing the number of lower value of body composition factors, and patients were divided into two groups (low risk = score 0∼1, high risk = score$\geq$2). Patients with high risk score had shorter OS (6.4 vs. 11.5 months). In multivariate analysis, age, ECOG performance status, WBC, neutrophil-lymphocyte ratio (NLR), carcinoembryonic antigen (CEA) at initial presentation was significant. In addition, body composition risk score was independent prognostic factors (hazard ratio, HR 1.56, 95% confidence interval 1.24-1.95, $P < 0.001$).

Conclusions: The body composition risk score significantly predicted prognosis in patients of pancreatic cancer. CT data are readily obtainable during routine clinical practice, which makes this approach useful for identifying prognostic biomarkers.

Legal entity responsible for the study: Gangnam Severance Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1730P Current use of clinical nutrition in oncology patients: Real world evidence from big data in Italy

F. Di Costanzo[1], R. Caccialanza[2], A. Santoro[3], C. Gavazzi[4], P. Pedrazzoli[5]

[1]SOD Medical Oncology, AOU Careggi, Florence, Italy, [2]Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [3]Department of Medical Oncology and Hematology, Istituto Clinico Humanitas, Rozzano, Italy, [4]Clinical Nutrition Unit, IRCCS Istituto Nationale die Tumori, Milan, Italy, [5]Division of Medical Oncology, Department of Hemato-Oncology Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy

Background: In cancer patients, research indicates that approximately half of selected patients may suffer from malnutrition. Insufficient nutritional intake, muscle protein depletion and systemic inflammation are key clinical problems. Little is known about the current use of clinical nutrition (CN) in the real world. We set out to investigate the use of CN in patients with metastasized cancer in Italy.

Methods: This observational, retrospective study used an integrated administrative database from 10 Italian Local Health Units covering 5.9 million people. Between 2009 and 2015, CN use, based on Anatomical Therapeutic Chemical Classification codes and ICD-9-CM procedural codes for Enteral/Parenteral Infusion of Concentrated Nutritional Substances and at home nutritional product prescription was examined in patients with metastatic head and neck, gastrointestinal, respiratory, genitourinary or hematologic malignancies (ICD-9-CM diagnosis).

Results: Out of 58,468 metastatic cancer patients with the diagnoses of interest, only 8.2% received clinical nutrition (89% had parenteral nutrition (PN)). Only 4.9% of patients who received CN had concomitant chemotherapy. Among those who received CN, only 11% of patients were diagnosed with malnutrition. The mean time between the diagnosis of metastasis and first use of CN and between the first use of CN and death were 6.6 and 3.5 months, respectively. About half of the patients commenced CN therapy in their last 20 days. Receiving PN was associated with a statistically significant improvement in survival of over 3 months in patients with gastrointestinal and genito-urinary cancer who were diagnosed with malnutrition.

Conclusions: CN is under-utilized among cancer patients with metastasis and there is a discrepancy between malnutrition diagnosis rates and uptake of clinical nutrition, which appears to have been used mainly as an end of life measure. Overall, our big data highlights an important unmet need and potential for improved procedures for malnutrition diagnosis and earlier nutritional care, which may improve outcomes of cancer patients.

Editorial acknowledgement: Medical writing support for this abstract was provided by Anne-Kathrin Fett, IQVIA, Frankfurt, Germany.

Legal entity responsible for the study: Baxter S.p.A, Zürich, Switzerland.

Funding: Baxter SA, Zürich, Switzerland.

Disclosure: F. Di Costanzo, R. Caccialanza, P. Pedrazzoli: Consultant and/or on advisory panel: Baxter Healthcare Corporation. All other authors have declared no conflicts of interest.

1731P Nutritional cancer care: Slowly evolving clinical practice reveals regional and professional HCP variability

F. Strasser[1], J. Arends[2], A. Laviano[3], A. O'Callaghan[4], R.A. Audisio[5], M.B. Sawyer[6], S. Kaasa[7]

[1]Clinic for Oncology/Hematology, Kantonsspital St. Gallen, St. Gallen, Switzerland, [2]Department of Medicine, Universitätsklinikum Freiburg Klinik für Innere Medizin Hämatologie, Onkologie und Stammzelltransplantation, Freiburg, Germany, [3]Clinical Medicine, Sapienza University, Rome, Italy, [4]Global Medical Affairs, Nutricia Advanced Medical Nutrition, Schiphol Airport, Netherlands, [5]Department of Surgery, Institute of Clinical Sciences, Sahlgrenska University Hospital, Göteborg, Sweden, [6]Medical Oncology, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, [7]Department of Oncology, Oslo University Hospital, Oslo, Norway

Background: Cancer-related weight loss correlates with poor anticancer treatment (Tx) outcomes and reduced quality of life (QoL). A survey at ESMO 2016 suggested that integration of nutritional care in clinical practice is inadequate. Outcomes of a follow-up survey conducted at ESMO 2017 are reported.

Methods: ESMO 2017 delegates visiting the Nutricia booth took part in the survey. The 2017 survey questions were identical to 2016, except 1 new question: "What source helps to determine patient need for nutritional support?"

Results: The 1,894 participants (75% medical oncologists; 64% European) demonstrated consistent overall practice patterns (malnutrition screening and assessment methods, eligibility criteria for nutritional support, goals of nutritional treatment, multimodal management) between 2016–2017. Unfortunately, >40% of HCPs still underestimate the impact of malnutrition on anticancer Tx continuity or toxicity, and QoL or function. Timely and individual tailored dietary advice to minimize/avoid weight loss increased significantly (36% to 49%; P <.001), surpassing medications, but only in Western countries (53%). Further geographic differences were seen. For example, in Africa (n = 183) compared with Europe (n = 1,215), nutritional aspects were more often considered in tumor boards (70%, 54%), but physical exercise programs were less often combined with nutrition (29%, 42%); perceived impact of malnutrition was more about anticancer treatment discontinuation (67%, 28%) than toxicities (44%, 62%); and meetings (42%, 33%) surpass guidelines (44%, 73%) for nutritional decision-making. Concerning HCP specialty, nutritionists (n = 20) estimated the impact of malnutrition 50% less than medical oncologists, and consulted guidelines less (26%, 60%). Surgeons (n = 64) and radiation oncologists (n = 65) judged eligibility for nutritional support and its goals differently than medical oncologists, with less emphasis on weight loss and QoL.

Conclusions: HCP recognition of the impacts of malnutrition and its assessment remains insufficient, while dietary advice is increasing. Our survey data may suggest tailoring nutritional care recommendations at regional and HCP levels.

Editorial acknowledgement: Medical writing support was provided by Joanne Franklin, PhD, CMPP, from TRM Oncology, The Hague, The Netherlands, and funded by Nutricia Advanced Medical Nutrition.

Legal entity responsible for the study: Nutricia Advanced Medical Nutrition.

Funding: Nutricia Advanced Medical Health.

Disclosure: F. Strasser: Honoraria: Danone, Grünenthal, Helsinn, ISIS Global, Mundipharma, Novartis, Novelpharm, Obexia, Ono Pharmaceutical, Psioxus Therapeutics, Prime Oncology, Sunstone Captial, Vifor; Clinical research industry grants: Celgene, Fresenius, Helsinn. A. O'Callaghan: Corporate-sponsored research: Nutricia Medical; Employee: Nutricia Medical. M.B. Sawyer: Honoraria: Nutricia Advanced Medical Nutrition. S. Kaasa: Stock ownership: Eir Solution. All other authors have declared no conflicts of interest.

1732P Unidentified cachexia patients in the oncologic setting: Cachexia UFO's do exist

E. De Waele[1], J. Demol[1], R. Caccialanza[2], P. Cotogni[3], H. Spapen[1], M. Malbrain[1], J. De Grève[4], J.J. Pen[5]

[1]Intensive Care, UZ Brussel, Brussels, Belgium, [2]Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [3]Pain Management and Palliative Care, Department of Anesthesia and Intensive Care, S. Giovanni Battista Hospital, University of Turin, Turin, Italy, [4]Medical Oncology, UZ Brussel, Brussels, Belgium, [5]Diabetes Clinic, UZ Brussel, Brussels, Belgium

Background: Cachexia is an important outcome-modulating parameter in cancer patients. In the context of a randomized controlled trial on cachexia and nutritional therapy, the TiCaCONCO trial (NCT03058107 on Clinicaltrials.gov), the contacts between cancer patients and health care practitioners/oncologists were screened. The aim of this retrospective study is to identify in the charts the input of data on body weight (necessary to identify cachexia stage), relevant nutritional data and nutritional interventions triggered or implemented by oncologists and dieticians.

Methods: In a tertiary, university oncology setting, over a time span of 8 months (34 weeks), the charts of patients admitted to an oncology, gastroenterology or abdominal surgery unit were screened for the presence of information contributing to a cancer cachexia diagnosis. Data (patient characteristics, tumor type and location) was gathered.

Results: We analyzed 9694 files. In > 90% of patients, data on body weight was present. 118 new diagnoses of cancer were present in 9694 screenings (1.22% of patient contacts). Information on weight evolution or nutritional status was absent in 46% of cases. In contacts between oncologists and cancer patients, at the time of diagnosis, the prevalence of cachexia was 42%. In 14% of these patients, no nutritional information was present in the notes. In those 50 patients with cachexia, a nutritional intervention was initiated by the physician in 8 patients (16%). Nutritional interventions were documented in the medical note in 9% of the overall study population. Dieticians made notes regarding nutrition and weight in 42% of patients.

Conclusions: Newly diagnosed cancer patients are not systematically identified as being cachectic and if they are interventions in the field of nutrition therapy are largely lacking. Important barriers exist between Oncologists and Nutritionists, the former being mandatory to the success of a nutrition trial in cancer.

Clinical trial identification: NCT03058107.

Legal entity responsible for the study: Elisabeth De Waele.

Funding: Baxter, Nutricia.

Disclosure: All authors have declared no conflicts of interest.

1733P The effect of sarcopenia on acute chemotherapy toxicity in gastrointestinal cancer patients undergoing systemic therapy

N. Ozdemir[1], O. Yazici[2], K. Silay[3], G. Ucar[4], T. Eren[4], D. sener dede[1], M.A.N. Sendur[1], M.B. Akinci[1], A. Baykal[4], B. Yalcin[1], N. Zengin[1]

[1]Department of Medical Oncology, Ankara Yildirim Beyazıt University Faculty of Medicine, Ankara, Turkey, [2]Medical Oncology, Gazi University, Ankara, Turkey, [3]Department of Geriatrics, Ankara Yildirim Beyazıt University Faculty of Medicine, Ankara, Turkey, [4]Medical Oncology, Ankara Numune Education and Research Hospital, Ankara, Turkey

Background: We aimed to evaluate the effect of sarcopenia on tolerability of chemotherapy during systemic treatment of pts with gastrointestinal system cancer (GISC).

Methods: Patients with GISC who had not previously received chemotherapy or radiotherapy were included. All of the pts muscle mass was evaluated by bioimpedance prior to the first cycle of chemotherapy, and pts who had normal muscle mass according to first bioimpedance evaluation were re-evaluated after 2-3 cycles of chemotherapy. The acute toxicities were compared in sarcopenic and non-sarcopenic pts. To define the sarcopenia results of a Turkish validation study was used (sarcopenia for male $<9.2\ kg/m^2$, female: $7.4\ kg/m^2$).

Results: A total 116 pts who had nosarcopenia in the first evaluation were included in the study population. Median age was 57 (min:26-max:76) and 2/3 of them were male (67.6%). Primary tumor locations were colorectal (51.8%), gastric (44.1%), esophagus (4.1%). Chemotherapy was given as adjuvant (46.9%), neoadjuvant (22.1%) and palliative (31%). In the second bioimpedance evaluation sarcopenia was detected in 36 (31%) pts. Basal body-mass index (BMI) evaluation of pts showed that rate of obese and overweight pts was significantly lower in sarcopenic pts compared to non-sarcopenic pts (44.4% vs 68.8%, $p < 0.05$). At the time of thesecond bioimpedance measurement, there was no significant difference between BMI of sarcopenic and non-sarcopenic pts. The rate of chemotherapy toxicities of the sarcopenic and non-sarcopenic group is shown in the table:

Table: 1733P

Toxicity	Sarcopenic (n = 36) %	Non-sarcopenic (n = 80) %	p
Thrombocytopenia Yes, No	33.3, 66.7	58.8, 41.3	0.011
Neutropenia Yes, No	55.6, 44.4	72.5, 27.5	0.073
Anemia Yes, No	63.9, 36.1	67.2, 32.9	0.73
Delay of chemotherapy Yes, No	27.8, 72.2	43.0, 57.0	0.11
Dose reduction Yes, No	28.4, 71.4	37.5, 62.5	0.35

Conclusions: In GISC pts non-sarcopenic at time of diagnosis, BMI remains unchanged after 2-3 cycles of chemotherapy. However, muscle loss had developed in 1/3 of them. Pts who developed sarcopenia had lower rates of chemotherapy-associated toxicity. The reasons for this difference should be further investigated. However, the different lipophilic and hydrophilic properties of chemotherapy agents might be one of possible explanation.

Legal entity responsible for the study: Yildirim Beyazit University, Medical Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1734P Early detection of skeletal muscle atrophy using a multiple plasma-free amino acid index in the advanced aged patients with advanced pancreatic cancer

S. Mitsunaga[1], M. Takada[2], S. Nishikawa[2], A. Imaizumi[2], M. Ishii[2], M. Ikeda[3]

[1]Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [2]Institute for Innovation, Ajinomoto Co., Inc., Kawasaki, Japan, [3]Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: Loss of skeletal muscle mass (SMM) is related to aging, pancreatic cancer (PCa) and the deterioration of symptoms and quality of life (QOL). This study aimed to identify the factors associated with SMM atrophy in PCa patients during first-line chemotherapy. At the end of our study, the biomarker of early detection of SMM atrophy was established using a multivariate index composed of plasma free amino acid (PFAA) levels.

Methods: Patients with treatment-naïve advanced PCa were enrolled. The whole body skeletal muscle index (wSMI) and symptoms were measured at baseline and one month later using bioelectrical impedance analysis and the MD Anderson Symptom Inventory, respectively. Each patient was assigned to an atrophy or a non-atrophy group based on the change in wSMI after one month. The concentrations of 19 PFAAs were measured using liquid chromatography–mass spectrometry. An index consisting of the PFAAs at baseline was evaluated for its ability to discriminate atrophy one month later.

Results: The advanced aged group (≥ 70 years, $N = 52$) showed a decrease of wSMI ($-0.35\ kg/m^2$ in mean) to be compared to younger group (< 60 years, $N = 34$, $0.35\ kg/m^2$, $P = 0.09$). The change of wSMI in the middle aged group (≥ 60 and < 70 years, $N = 75$) was $0.03\ kg/m^2$ in mean. Atrophy was observed in 60% of the advanced aged group. The worsened activity, fatigue and appetite loss became more severe after one month in the advanced aged group with atrophy. The areas under the curves (AUCs) based on a receiver operating characteristic (ROC) curve analysis of the PFAA index for discriminating atrophy from non-atrophy were calculated using single or multiple PFAAs. The best AUC for the multiple PFAA indices was 0.83 in the advanced aged group.

Conclusions: SMM atrophy was related to aging, the deteriorated activity, fatigue and appetite loss in patients with advanced PCa during first-line chemotherapy. A multiple PFAA index is a promising biomarker for the early detection of atrophy.

Legal entity responsible for the study: National Cancer Center.

Funding: Ajinomoto Co., Inc.

Disclosure: M. Takada, S. Nishikawa, A. Imaizumi, M. Ishii: Employee: Ajinomoto Co., Inc. All other authors have declared no conflicts of interest.

1735P Trajectory of skeletal muscle index (SMI) loss during palliative systemic treatment (Tx) predicts time to progression (TTP) in metastatic colorectal cancer (mCRC) patients

S.A. Kurk[1], R.K. Stellato[2], P.H.M. Peeters[2], M. Oskam[2], B.D. Dorresteijn[3], M. Jourdan[3], C.J.A. Punt[4], M. Koopman[5], A.M. May[6]

[1]Medical Oncology, UMC - University Medical Center Utrecht, Utrecht, Netherlands, [2]Epidemiology, Julius Center for Health Sciences and Primary Care, Utrecht University, Utrecht, Netherlands, [3]Nutricia Advanced Medical Nutrition, Danone Nutricia Research, Utrecht, Netherlands, [4]Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [5]Medical Oncology, University Hospital Utrecht, Utrecht, Netherlands, [6]Julius Center, University Hospital Utrecht, Utrecht, Netherlands

Background: In mCRC patients, SMI loss is suggested to be related with poor survival. Little is known on the trajectory of SMI and its relation with TTP. The CAIRO3 study (Simkens, Lancet 2015) randomized 557 mCRC patients after 6 cycles CAPOX-B to maintenance CAP-B vs. observation (obs). Upon 1st disease progression (PD1), CAPOX-B or other Tx was reintroduced until 2nd progression (PD2). Here we study if SMI trajectory predicts TTP in CAIRO3.

Methods: 104 randomly selected CAIRO3 patients (mean age 65.4 ± 8.3 years) were analyzed for SMI (skeletal muscle area at the L3 level in cm^2/m^2) using 9-weekly repeated CT scans (854 in total). Joint longitudinal-survival modeling, using mixed effects models for longitudinal SMI measures and Cox regression models for TTP analysis, was used to estimate hazard ratios (HR) for absolute SMI and SMI trajectory (per unit SMI loss per month) during two time periods: p1) from randomization to PD1 and p2) from PD1 to PD2. SMI trajectories were modeled throughout each time period and change was investigated at 9 and 4 weeks pre-PD.

Results: During p1 (less intensive CAP-B / obs), patients gained SMI (mean $+1.1 \pm 3.2\ cm^2/m^2$). Absolute SMI was not related with PD1 (HR SMI 9 weeks pre-PD1 0.99 [0.96-1.02], 4 weeks pre-PD1 0.99 [0.96-1.02]). A decrease in SMI preceding PD1 showed a higher, but non-significant, risk of early PD1 (HR SMI change 9 weeks pre-PD1 1.04 [0.83-2.56], 4 weeks pre-PD1 1.53 [0.91-2.55]. During p2, (more intensive CAPOX-B / other Tx), patients lost SMI (mean $-2.7 \pm 3.4\ cm^2/m^2$). Both SMI and SMI trajectory were significantly related to PD2 (HR SMI 9 weeks pre-PD2 1.03 [1.01-1.08], 4 weeks pre-PD2 1.04 [1.01-1.08], SMI change 9 weeks pre-PD2 1.37 [1.07-1.75], 4 weeks pre-PD2 1.23 [0.83-1.82]).

Conclusions: In mCRC patients, a decrease in SMI tended to predict shorter TTP during less intensive CAP-B or obs. SMI and SMI trajectory predicted shorter TTP during more intensive CAPOX-B or other reintroduction Tx. This large longitudinal analysis is the first to show that the trajectory of SMI loss predicts early TTP. These data suggest that SMI preservation may be a therapeutic goal.

Clinical trial identification: NCT00442637.

Legal entity responsible for the study: Anne May.

Funding: Province of Utrecht, The Netherlands and the Dutch Colorectal Cancer Group (DCCG).

Disclosure: B.D. Dorresteijn, M. Jourdan: Employee: Nutricia Research. All other authors have declared no conflicts of interest.

1736P Clinical impact of whey protein and nutritional counseling in gastrointestinal cancer patients

M. Roberto[1], E. Sarfati[1], M. Di Girolamo[2], F.M. Schipilliti[1], E. Crimini[3], A. Botticelli[1], L. Marchetti[4], M. Muscaritoli[5], P. Marchetti[1], F. Mazzuca[1]

[1]Clinical and Molecular Medicine, Az. Ospedaliero-Universitaria St. Andrea, Rome, Italy, [2]Radiology Department, Az. Ospedaliero-Universitaria St. Andrea, Rome, Italy, [3]Oncology Unit, Sapienza University of Rome, Rome, Italy, [4]Oncology Unit, San Pietro FBF Hospital, Rome, Italy, [5]Clinical Medicine Department, Sapienza University of Rome, Rome, Italy

Background: Malnutrition frequently affects gastrointestinal (GI) cancer patients. It is known how protein supplementation could prevent loss of lean body mass and sarcopenia. Therefore, we present a placebo-controlled study, to explore the effect and safety of whey proteins in GI cancer patients.

Methods: Patients with GI cancer referred for 5-fluorouracil based chemotherapy, without metabolic alteration, were considered eligible. After informed consent was obtained, they were blind-randomized 1:1 to whey protein (PROLYOTIN®) (arm A) vs placebo (arm B). Patients were assessed, before chemotherapy, after 3 and 6 months, on a physical-nutritional examination, Body Impedance Assessment, MNA® and MUST questionnaire. At the same time frames, tumor characteristics, dietary practices and laboratory values were collected by a specialist team of medical oncologists and dieticians.

Results: Forty subjects with a median age of 65.53 years old were included in this preliminary analysis. Baseline patients characteristics were well balanced between the two arms (A and B) for age, sex, localization and stage of disease, clinical status, nutritional condition and laboratory values (Vitamin D proved to be insufficient in both groups:17,3 ng/ml in A and 15,4 ng/ml in B). After three months of chemotherapy, 32 patients were reevaluated. Overall, no patient was found underweight or malnourished, nor were any differences in blood analysis. Meanwhile, clinical and anthropometric parameters (PS ECOG= 0: 89% A vs 59% B; lean body mass 69,7 % to 71,8% A vs 67,6% to 63,6% B, p value=0,013), nutritional status (MNA>27=34% to 100% A vs 42% to 65% B, p value=0,001) and toxicity (hematological: no adverse effects 86% A vs 29% B, p value 0,005; gastrointestinal: 94% A vs 29% B, p value 0,001) resulted to be significantly different between the two groups.

Conclusions: The nutritional counselling and whey proteins intake during chemotherapy showed a significant benefit in nutrition, performance status and treatment tolerability in GI cancer patients. However, further studies are needed to improve the knowledge of whey protein protective role against chemotherapy toxicity and to select more accurately those patients who may benefit from a preventive whey protein supplements.

Clinical trial identification: EudraCT number: 2018-000122-64.

Legal entity responsible for the study: Sapienza University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1737P Impact of taste alterations during systemic anti-tumour therapy on the liking of oral nutritional supplements with adapted flavours

J.J. De Haan[1], Y. Moshage[1], D. Kluifhooft[1], R. Renken[2], C. Corbier[3], H. Blanchard[3], A.K.L. Reyners[1]

[1]Medical Oncology, University Hospital Groningen (UMCG), Groningen, Netherlands, [2]Neuro Imaging Center, University Hospital Groningen (UMCG), Groningen, Netherlands, [3]Danone Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, Netherlands

Background: Taste alterations are often reported by cancer patients, especially during systemic anti-tumour therapy, with a negative impact on food intake and quality of life. Little is known about the relation between taste alterations and taste preferences. This study aimed to explore the occurrence of taste alterations (i.e. changes in taste perception or intensity) in patients receiving systemic anti-tumour therapy, and to investigate overall likings of oral nutritional supplements (ONS) with flavours designed to better address the needs of patients with taste alterations.

Methods: Fifty adult patients with cancer undergoing systemic anti-tumour therapy were recruited. Exclusion criteria were allergies/intolerances to ONS ingredients or coexisting morbidities affecting taste or smell. Participants filled out a questionnaire on taste alterations, and evaluated overall liking of 5 Nutridrink® Compact Protein on a 10-point scale via a sip test (hot tropical ginger, hot mango, cool red fruits, cool lemon and neutral). Permutation analysis was performed to investigate differences between patients with and without taste alterations.

Results: Various types of cancer and treatments (n = 34 chemotherapy, n = 5 chemoradiation, n = 4 immunotherapy, n = 2 targeted therapy, n = 5 other form of systemic therapy) were observed. Thirty patients (60%) reported taste alterations. Overall liking scores were: cool red fruits 6.8 ± 1.7 (mean ± SD); neutral 6.5 ± 1.9; hot tropical ginger 6.0 ± 2.0; cool lemon 5.5 ± 2.3 and hot mango 5.5 ± 2.0. Larger variation in overall liking per product was observed in patients with taste alterations (range 4.9 - 7.0) versus without taste alterations (range 5.9 – 6.5). Posthoc analysis showed that taste alteration was associated with a difference in overall liking for neutral ($\Delta = 1.0$; $p < 0.05$) and hot mango flavours ($\Delta = -1.1$; $p < 0.05$).

Conclusions: More than half of patients undergoing anti-tumour therapy experienced taste alterations. Patients without taste alterations were less discriminant in liking score compared to patients with taste alterations. These findings indicate that the presence of taste alterations should be taken into account when selecting or developing ONS for cancer patients.

Legal entity responsible for the study: University Medical Center Groningen, Groningen, the Netherlands.

Funding: Danone Nutricia Research.

Disclosure: J.J. De Haan, A.K.L. Reyners: Studies support: Danone Nutricia Research. C. Corbier, H. Blanchard: Employee: Danone Nutricia Research. All other authors have declared no conflicts of interest.

1738P Overweight, obesity and weight gain after breast cancer (BC): A prospective clinical study

A. Di Meglio[1], M. El-Mouhebb[1], S. Michiels[2], L. Jones[3], M. Annonay[4], A. Zingarello[5], M. Matias[1], S. Everhard[6], A.L. Martin[7], P. Arveux[8], O. Tredan[9], P. Soulie[10], P.H. Cottu[11], A.H. Partridge[12], L. Del Mastro[13], J.A. Ligibel[12], F. André[1], I. Vaz-Luis[1]

[1]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [2]Team Oncostat, CESP, Gustave Roussy, Villejuif, France, [3]Exercise Oncology Research Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [4]Institute Bergonié, Bordeaux, France, [5]INSERM UMR 981, Gustave Roussy, Université Paris-Saclay, Villejuif, France, [6]UCBG, UNICANCER, Paris, France, [7]Research & Develpment, UNICANCER, Paris, France, [8]Medical Oncology, Centre Georges-François Leclerc, Dijon, France, [9]Medical Oncology, Centre Léon Bérard, Lyon, France, [10]Medical Oncology, Centre Paul Papin, Angers, France, [11]Medical Oncology, Institut Curie, Paris, France, [12]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [13]Medical Oncology, Ospedale Policlinico San Martino, Genoa, Italy

Background: Overweight and obesity are a growing health problem worldwide and are linked to poor quality of life and BC outcomes. Fewer data are available that describe patterns of weight change or evaluate robust associations with weight gain following BC in a European population.

Methods: We used data collected from 4875 women with Stage I-III BC included in an ongoing prospective French multicenter clinical study from 2012-14 (CANTO, NCT01993498). Body Mass Index (BMI) and physical activity (PA) were assessed at diagnosis (dx), 3-6 (T1) and 12 (T2) months after primary treatment. Weight changes ≥ 5% of weight at dx were considered significant. Group based trajectory models (GBTM) described risk of overweight or obesity over time. Multivariate logistic regression assessed factors associated with significant weight gain at T1 and T2.

Results: At dx, mean age was 56 y (range 22-88), median BMI was 24.6 (range 14.7-59.0), 29% pts were overweight and 19% obese. 54% pts received chemo (CT) and 82%

Table: 1738P Multivariate logistic regression of factors associated with weight gain after BC in the overall population (N = 4875)

	T1 (3-6 months after treatment)		T2 (12 months after treatment)	
	% pts who gained weight	aOR* (95% CI)	% pts who gained weight	aOR* (95% CI)
Total	17	-	24	-
Age (years) <50 50-65 >65	25 17 8	2.8 (1.8-4.2) 2.2 (1.6-3.0) ref	35 24 11	2.1 (1.3-3.2) 2.0 (1.5-2.7) ref
BMI at diagnosis (kg/m^2) Underweight (<18.5)	25 18 16 14	1.7 (0.9-3.0) 1.3 (1.1-1.7)	33 26 24 18	1.9 (1.1-3.4) 1.7 (1.2-2.3)
Normal (18.5-24.9) Overweight (25.0-29.9)		1.4 (1.1-1.9) ref		1.7 (1.3-2.4) ref
Obese (≥30)				
Level of Physical Activity^	16 17	1.0 (0.8-1.2) ref	26 22	1.3 (1.1-1.6) ref
Failing to reach 10 Reach/maintain ≥10				
Receipt of chemotherapy Yes No	21 12	1.3 (1.1-1.7) ref	29 18	1.6 (1.3-2.1) ref
Receipt of endocrine therapy Yes No	16 19	1.1 (0.7-1.5) ref	24 25	1.7 (1.1-2.7) ref
Weight gain at T1 Continuous, for 1 Kg gained	-	-	-	1.6 (1.5-1.6)

[a]OR= adjusted odds ratio; CI= confidence interval.

*Adjusted for all variables in the table + menopausal status, education, smoking status, alcohol, tumor stage, subtype, breast and axillary surgery.

^In Metabolic Equivalent of Task (MET)-hours/week, based on World Health Organization recommendations on physical activity and expressed as change in physical activity behavior from diagnosis to T1 and to T2, respectively.

endocrine therapy (ET). GBTM found that the majority of overweight and obese pts remained so over time. By T2, weight increased in 24% pts (median gain + 5 Kg [range 2-33]), was stable in 63% pts and decreased in 13% pts in the overall population. Factors associated with higher risk of significant weight gain by T2 included age <50 vs > 65 (adjusted odds ratio 2.1 [95% Confidence Interval 1.3-3.2]), receipt of CT vs no (1.6 [1.3-2.1]), receipt of ET vs no (1.7 [1.1-2.7]), PA < 10 MET-hours/week vs ≥ (1.3 [1.1-1.6]) and having already gained weight by T1 (for each Kg gained, 1.6 [1.5-1.6]) (Table).

Conclusions: In this large contemporary epidemiology study of French BC survivors, a significant proportion of pts were overweight or obese at dx, and one in four of all pts gained substantial weight after treatment. Weight gain is particularly common in pts who are younger, treated with CT or ET and less physically active. Our data will inform weight loss survivorship programs targeting pts at higher risk of overweight, obesity and weight gain after BC.

Clinical trial identification: NCT01993498.

Legal entity responsible for the study: UNICANCER.

Funding: Has not received any funding.

Disclosure: A. Di Meglio: Recipient of the 2017 ESMO Clinical Research Fellowship Award. I. Vaz-Luis: Recipient of research grants from Susan Komen for the Cure and the "Association pour la recherche sur le cancer (ARC)". All other authors have declared no conflicts of interest.

1739P Weight loss, physical and psychological patient reported outcomes (PROs) among obese patients (pts) with early breast cancer (BC)

A. Di Meglio[1], M. El-Mouhebb[2], S. Michiels[3], L. Jones[4], E. Martin[1], M. Matias[1], A.E. Lohmann Palhares[5], F. Joly[6], L. Vanlemmens[7], S. Everhard[8], A.L. Martin[9], J. Lemonnier[9], P. Arveux[10], P.H. Cottu[11], C. Coutant[12], L. Del Mastro[13], A.H. Partridge[14], F. André[15], J.A. Ligibel[14], I. Vaz-Luis[1]

[1]Medical Oncology, Institut Gustave Roussy, Villejuif, France, [2]Team Oncostat, CESP, Gustave Roussy, Villejuif, France, [3]Exercise Oncology Research Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [4]Medical Oncology, University of Toronto, Toronto, ON, Canada, [5]GINECO & Centre Francois Baclesse Caen, Caen, France, [6]Medical Oncology, Centre Oscar Lambret, Lille, France, [7]UCBG, UNICANCER, Paris, France, [8]Research & Develpment, UNICANCER, Paris, France, [9]Medical Oncology, Centre Georges-François Leclerc, Dijon, France, [10]Medical Oncology, Institut Curie, Paris, France, [11]Medical Oncology, Centre Georges-François Leclerc, Dijon, France, [12]Medical Oncology, Ospedale Policlinico San Martino, Genoa, Italy, [13]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [14]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France

Background: Obesity and unfavorable energy balance affect physical and psychological outcomes among BC survivors. There is little data describing the impact of weight loss on PROs in obese pts.

Methods: We used a prospective French nationwide longitudinal cohort (CANTO, NCT01993498) to select obese (Body Mass Index ≥ 30 kg/m^2) stage I-III BC pts diagnosed from 2012-14. Nurses assessed weight change from BC diagnosis (dx) to 3-6 months post treatment (surgery, chemo [CT] or radiotherapy [RT]), defined as weight gain (≥ 5%), stability (± 5%) or loss (≤ 5%). PROs were assessed by EORTC QLQ C30/BR23. Functional scores <60 and symptom scores ≥40 defined severe dysfunctions and symptoms, respectively (Giesinger, 2016). Multivariate logistic regression explored associations of weight change with severe PROs.

Results: We included 892 obese pts, 19% of CANTO population. Mean age was 59 y (range 27-87). 92% received RT, 54% CT and 84% endocrine therapy. Mean BMI at dx was 34.5 (range 30.0-59.0). 14% pts gained weight, 67% were stable and 19% lost weight post treatment. There was a significant differential reduction in physical activity in 39% pts who gained weight, 37% pts with stable weight, and 28% pts who lost weight (mean change [Standard Deviation] was -5 [77], -4 [66] and +4 [69] MET-hours/week, respectively [p=.036]). Prevalence of any severe dysfunction or symptom was 83% at dx and further increased over time, being highest in pts who gained weight. Weight loss was associated with lower odds of severe dysfunctions or symptoms vs weight gain, consistently across all PROs (Table).

Conclusions: The majority of obese pts report severe physical or psychological distress at BC dx and post treatment. A comprehensive approach to the care of obese BC pts should address the burden of morbidity caused by obesity and further post treatment weight gain. Weight loss may prevent physical and psychological deterioration, thus lifestyle interventions of purposeful weight loss should be encouraged.

Clinical trial identification: NCT01993498.

Legal entity responsible for the study: UNICANCER.

Funding: Has not received any funding.

Disclosure: A. Di Meglio: Recipient of the 2017 ESMO Clinical Research Fellowship Award. I. Vaz-Luis: Recipient of research grants from Susan Komen for the Cure and the "Association pour la recherche sur le cancer (ARC)". All other authors have declared no conflicts of interest.

1740P Patient reported outcomes: Web-monitoring versus nurse assessment to improve anticancer therapies

M. Korostelev[1], K. Sejean[1], C. Lepage[1], J. Stevens[2], B. Bonan[1], P. Beuzeboc[3], F. Scotté[3]

[1]Pharmacy, Hopital Foch, Suresnes, France, [2]Direction, Direct Medica, Boulogne, France, [3]Supportive Care in Cancer Unit, Oncology, Hopital Foch, Suresnes, France

Background: Patients treated in a chemotherapy day unit can benefit from "STAR", an innovative monitoring program to improve cancer management and reduce waiting-time as well as drug wastage. Two days before anticancer treatment, according to patient preference, a nurse (call) or the patient himself (web) completes a clinical data questionnaire. The aim of the study was to compare the reliability of those two methods of data collection.

Table: 1739P Prevalence of severe dysfunctions and symptoms at BC diagnosis and post treatment by weight change category among obese pts in CANTO (N = 892)

	Diagnosis	Post treatment			
	Overall	Overall	By weight change category (% pts)		
PRO Domain	-	-	Gain (14.0)	Stable (67.0)	Loss (19.0)
All domains combined ≥1 Function or Symptom ≥1 Function ≥1 Symptom	82.8 76.0 56.1	88.9 78.3 75.9	92.2 82.6 78.3	88.6 78.7 75.8	87.4 73.6 74.2
Global Health Status[a] % pts aOR (95% CI)	34.2 -	35.7 -	40.7 Ref	37.8 0.73 (0.44-1.21)	24.5 0.42 (0.23-0.80)
Physical Function[a] % pts aOR (95% CI)	10.9 -	20.4 -	23.7 Ref	20.8 0.59 (0.32-1.10)	16.5 0.43 (0.20-0.95)
Emotional Function[a] % pts aOR (95% CI)	34.0 -	29.5 -	36.5 Ref	29.7 0.67 (0.40-1.13)	23.4 0.53 (0.28-1.00)
Social Function[a] % pts aOR (95% CI)	6.2 -	14.4 -	22.6 Ref	13.8 0.56 (0.31-1.03)	10.3 0.42 (0.19-0.92)
Pain[a] % pts aOR (95% CI)	14.3 -	29.9 -	43.5 Ref	29.3 0.46 (0.28-0.75)	22.0 0.29 (0.15-0.55)
Dyspnea[a] % pts aOR (95% CI)	11.0 -	17.2 -	33.6 Ref	16.0 0.32 (0.18-0.56)	9.5 0.16 (0.07-0.35)
Body Image[b] % pts aOR (95% CI)	13.6 -	28.7 -	40.0 Ref	27.4 0.60 (0.35-1.02)	25.0 0.45 (0.23-0.87)
Systemic therapy side effects[b] % pts aOR (95% CI)	3.9* -	15.3 -	21.7 Ref	14.6 0.62 (0.33-1.18)	13.0 0.47 (0.21-1.04)

aOR= adjusted odds ratio; CI= Confidence Interval; [a]EORTC QLQ-C30 subscale; [b]EORTC QLQ-B23 subscale; *pts surveyed before start of treatment; All models adjusted for age, menopausal status, education, smoke, alcohol, physical activity, tumor stage, subtype, BC and axillary surgery, receipt of CT, RT, endocrine therapy, and level of the outcome at BC diagnosis.

Methods: Clinical information prospectively collected on STAR questionnaires during 11 months were compared using Mantel-Haenszel khi^2 (p-values) in the 2 groups (nurse call versus web self-questionnaire). Numbers of symptoms were classified into 3 categories: 0, 1 and at least 2 symptoms for each grade of severity (NCI-CTC AE, version 4.0).

Results: From May 2017 to April 2018, 622 (67.1%) of 928 patients admitted to daily hospital for a chemotherapy cycle were included in the STAR program. Monitoring was ensured by nurse phone calls for 477 patients (76.7%) versus 145 (23.3%) by web questionnaires. Patient's average age (66±11 years) and sex repartition (61% of men) were not different in the 2 groups. The overall rate of response was significantly better with nurse calls (84.8%) than with web questionnaires (78.2%) ($p < 0.0001$). Global incidence of grade 3 and grade 4 toxicities was similar in the two groups ($p = 0.1$ and 0.06 respectively) whereas web questionnaires mentioned significantly more grade 2 and grade 1 toxicities ($p < 0.0001$). When chemotherapy cycle was cancelled for a clinical reason, this information was similarly mentioned in the 2 groups ($p = 0.35$). Overall, global rate of delayed chemotherapy did not differ between the two groups.

Conclusions: Web questionnaires appear to be an interesting and reliable method for patient clinical monitoring. To take full advantage of STAR program, the importance of clinical evaluation should be reminded to patients to increase the rate of response. Web monitoring improvement in grade 1-2 toxicities screening should be explained by a better patient understanding and will be investigated in further studies.

Legal entity responsible for the study: Florian Scotté.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1741P Polymedication in elderly cancer patients treated with chemotherapy

A-L. Couderc[1], F. Correard[2], C. Tabele[2], E. Nouguerede[1], L. Greillier[3], F. Duffaud[4], P. Auquier[5], A. Daumas[1], P. Bertault-Peres[2], P. Villani[1], S. Honore[2]

[1]Department of Geriatric and Internal Medicine, Assistance Publique Hopitaux de Marseille, Marseille, France, [2]Pharmacy, Assistance Publique Hopitaux de Marseille, Marseille, France, [3]Department of Multidisciplinary Oncology and Therapeutic Innovations, Assistance Publique Hopitaux de Marseille, Marseille, France, [4]Department of Oncology, CHU La Timone Adultes, Marseille, France, [5]Public Health Research Unit EA 3279, Aix Marseille Université, Marseille, France

Background: Medication reconciliation (MedRec) including complementary and alternative medicine is considered as an important way to increase the safety of medication use. However, there are few studies in literature showing the impact of an oncogeriatric approach integrating MedRec program in elderly cancer patients (ECP). The objective is to measure the impact of a pharmacogeriatric approach (PGA) on ECP before treatment by chemotherapy.

Methods: A monocentric prospective study was implemented to evaluate the overall survival (OS), rate of readmission hospital (RRH) at 1stand 3rdmonth and Early Discontinuation of active treatment (ED). These variables were analyzed according to number of reviewed drugs in MedRec and geriatric tools of Comprehensive Geriatric Assessment (CGA).

Results: 144 patients were received in oncogeriatric consultations between 01/2017 and 10/2017 (mean age was 80.9 ± 5.5 years, 52.1 % were men, 48.6 % had metastatic tumors). Main cancers were lung (31.9 %), gastrointestinal (18.1 %), breast and gynecological (16.7 %). At 1st and 3rdmonth, death rates were 3 % and 12 %; RRH were 11.1 % and 16.3 %. Received treatment was analyzed and 62.5% received systemic treatment after oncogeriatric consultations. Concerning ED at 3rd month, 48 % had prematurely stopped it (because of cancer progression in 14.2 % and infections in 7 %) and 23.6 % reduced dose (because of chemotoxicity in 33 % and geriatric conclusions in 20 %). OS prognostic factors were malnutrition ($p = 0.03$) and metastatic status ($p = 0.05$), prognosis factors of early death at 1 month were lymphopenia ($p = 0.005$) and RRH ($p = 0.04$), and at 3 months: malnutrition ($p = 0.01$), ADL dependence ($p = 0.03$), and RRH ($p = 0.01$).

Conclusions: To our knowledge, this is the first study evaluating and describing the outcomes of PGA with MedRec and CGA in same time for the ECP. First month death rates and RRH are lower compared to literature in our study. RRH, ADL and nutritional disorder are OS prognostic factors. Full analyzes will be presented during the congress to show the real impact of PGA.

Legal entity responsible for the study: Assistance Publique Hôpitaux de Marseille.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1742P Geriatric oncology (GO): Long term follow-up of a prospective series of the GO unit at A.C. Camargo Cancer Center

A.L.A. Dettino[1], M.D.S. Donadio[1], A. Cabral[1], V.H.F.D. Jesus[1], M.F. Fanelli[2], S.M. Sanches[1]

[1]Oncologia Clinica, A.C. Camargo Cancer Center, Sao Paulo, Brazil, [2]Oncologia Clinica, Rede d'Or S Luiz, Sao Paulo, Brazil

Background: Ageing is a global phenomenon and has huge impact in healthcare. Still emerging in developing nations, there has been no major national innitiative focusing on oncologic geriatric patients (pts). The study describes a program to > 70y cancer pts in A C Camargo Cancer Center. We hypothesized that incorporating CGA into daily practice can improve individualized care.

Methods: Previous aims were to evaluate if: 1) CGA could be feasible in daily practice; 2) it could be useful as a tool in treatment/tx decision making; 3) analyse the impact of CGA in the selection of tx, with its ability to predict complications (such as dosis reduction, hospitalization, or tx discontinuation) in an Oncogeriatric Unit. The present study is to present the long term survival of those pts, candidates to receive systemic tx, who underwent CGA assessments, which included scales of: ADL (Katz, Lawton), mini-nutritional assessment, depression (GDS), comorbidities and polypharmacy. Patients were classified as fit, borderline or frail. Fit pts received mainly full treatment; frail/borderline pts, mainly modified tx or specific supportive care.

Results: From Oct 25/10-Dec/12/12, 638 pts were included to be prospectively evaluated - female 55%; cancers (%): breast 26, prostate 12, colorectal 12, hematologic 8. Katz A = 68%, Lawton 27=45%; polipharmacy (> =5): 48%; depression 29%, undernutrition: 21%. We have previously presented (ASCO 2014) that there was an association between the choice of oncologic treatment (original vs modified or with additional dose reduction) with Katz, Lawton, depression and nutrition scales ($p < =0.035$); as well as the ability to complete the individualized proposed treatment, which was correlated with Lawton ($p = 0.04$) scale. Hospitalization during chemotherapy was associated with comorbidities, altered Katz, Lawton and depression scales ($p < =0.038$). With 610 pts evaluable, median survival was 51.7 months.

Conclusions: We could find a high long term survival of 70+ cancer pts, showing CGA to be feasible and allowing long term survival follow-up. However, many pts have been lost to follow-up. How to better perform in pts' adherence and to reduce bias must be a concern in real world geriatric oncology.

Legal entity responsible for the study: Aldo L.A. Dettino; Grupo de Assistencia, Ensino e Pesquisa em Oncologia (GAEPO).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1743P Developing a predictive model for chemotherapy related toxicities in older Asian adults

S.L.A. Pang[1], F. Ho[2], Y.S. Ng[1], C. Cai[3], M. Wang[3], W.C. Yong[4], B.C. Tai[5]

[1]Haematology Oncology, National University Cancer Institute, Singapore, [2]Radiation Oncology, National University Cancer Institute, Singapore, [3]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, [4]Palliative Medicine, National University Cancer Institute, Singapore, [5]Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Background: Elderly patients (pts) are at increased risk of developing chemotherapy (CTx) related toxicities. There are several prediction tools including the Cancer and Aging Research Group (CARG) chemotoxicity calculator (CTC) but this has not been validated in the Asian population. The objective of our study is to identify predictors of G3-5 CTx toxicities and evaluate the utility of the CTC in older Asian adults.

Methods: We enrolled cancer pts aged ≥ 70 years, requiring outpatient treatment with chemotherapy at the National University Cancer Institute, Singapore. A comprehensive geriatric assessment was performed and baseline cancer characteristics, including the 11 variables in the CTC were collected prior to the initiation of CTx. Primary treating oncologists were asked to give an estimated likelihood of CTx related toxicities. Pts were then followed up to 3 months after completion of treatment and CTx toxicities were recorded.

Results: Amongst the 131 pts (mean age: 75 years; range: 70 – 89), their CA diagnoses include colorectal (CRC) (36; 27.5%), lung (27 ; 20.6%), non-CRC gastrointestinal (17; 13%) , breast (14 ; 10.7%), genitourinary (10 ;7.6%), head and neck (10 ; 7.6%), gynaecological (8; 6.1%) and other (9; 6.9%) cancers. 54 pts (41%) received CTx with curative intent, and 77 (59%) with palliative intent. The incidence of G3-5 toxicities was 58% (76). The most common toxicities were neutropenia (38 ; 29%) and anaemia (26; 20%) and there was 1 mortality from CTx related pneumonitis. In the multivariable analysis, the factors associated with the incidence of CTx related toxicities were i) Age >72 years, ii) GI/GU cancer, iii) Haemoglobin < 10g/dL (Female) ; <11g/dL (Male), iv) Limited ability to walk 1 block, iv) Limited social support and v) Disease interference with social activity. Based on this new model comprising the above 5 variables, the area under the receiver operating characteristic curve (ROC) is 0.776, whereas that for the CTC and oncologists' prediction of CTx related toxicities were 0.765 and 0.594 respectively.

Conclusions: Our new model for predicting CTx related toxicities appears to be comparable to the CTC. In our follow up study, we hope to further validate this model's utility in predicting CTx related toxicities in our elderly cancer population.

Legal entity responsible for the study: Angela Pang.

Funding: National Medical Research Council (Singapore)

Disclosure: All authors have declared no conflicts of interest.

1744P Palliative local therapy of advanced breast cancer

T. Letodiani[1], M. Shavdia[2], N. Shavdia[3], K. Chaava[2], N. Gegeshidze[2],

[1]Palliative Care, National Cancer Center of Georgia (NCCG), Tbilisi, Georgia, [2]Paliative Care, Tbilisi State Medical University, Tbilisi, Georgia, [3]Palliative Care, JSC 'Neo Medi' Tbilisi, Georgia

Background: Objective: Initial nidus tumor infiltration is often revealed in patients with advanced breast cancer. In such cases, all treatment is focused on improvement of the quality of life.

Methods: Special mixture of Linimentam Synthomycin 10% (25 gr) + Tegafur (Ftorafur) 800 mg was prepared for anti inflammatory and tumor therapy. The mixture was used in bandaging of breast tumor infiltration in 99 patients for 10 days (interval - 20 days). Tumor infiltration in 84 patients -15 cm, in 15 patients > 30 cm. In 3 cases double-sided process was observed. All the patients had low hematological indicator and KPS (40,0 %).

Results: After II course of treatment: significant improvement of dynamics of tumor infiltration in 49 (49,5%) patients (reduction of hyperemia, pain syndrome, itching, temperature, etc). After the III-IV courses: wound cleansing from purulent, formation of granulation areas and improvement of the quality of life in 10 patients (Tumor reduction and full epithelization in 10 (10,1%) patients enabling sanitation of mastectomy). Worsening of condition - in 18 (18.2%), stabilization in 71 (71.7%) patients. After the IV course of local therapy tumor infiltration was reduced by 9 cm in average (Maximum effect was seen in patients with infiltration of 15 cm) KPS average indicator improved from 40,0% to 53,4% ($p < 0,05$).

Conclusions: 1. Administration of Synthomycin 10% (25 gr) + Tegafur (Ftorafur) 800 mg for local chemotherapy and anti – inflammatory therapy of breast cancer tumor infiltration contributes to reduction of hyperemia, temperature reaction, itching, suppuration, size of nidus, pain syndrome and accordingly improvement of the quality of life (KPS has improved from 40,0% to 53,4%; 2. Practically there are no side effects upon a local chemotherapy of breast.

Legal entity responsible for the study: Tbilisi State Medical University (Georgia).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1745P General and dedicated cancer emergency room: Clinical and financial implications

N. Malavasi[1], C. Fiorani[1], L. Ferrara[1], R. Postiglione[1], L. Scarabelli[1], F. Cantile[1], A. Saviola[1], G. Longo[1], A. Luciani[2], S. Cascinu[1]

[1]Oncology and Hematology, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy, [2]General Emergency Room, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy

Background: Emergency department (ED) visits among cancer patients (pts) exceed those of the general population; acute oncology teams can influence strategy determining a reduction in ED accesses and hospitalizations. Local services may reflect number and type of admissions often referred to ED. Onco-Hemato Emergency Room (OHER) in Modena Hospital is a service completely dedicated to cancer pts needs integrated with Oncology Department since 2001.Medical team is composed by oncologists and hematologists, from Monday to Friday (08, 00-18, 00), Saturday (08, 00-12, 00). Otherwise pts must refer to ED. We tried to describe pts admitted to OHER between January, 1, 2007 and December, 31, 2017 by cancer types, reasons for visits and percentage of hospitalizations from OHER and ED with financial implications.

Methods: OHER data were obtained through the query of a relational database used to collect medical records, concerning all disease history including hospitalizations and planned evaluations. Pts were received regardless disease stage from suspected tumor to palliative care setting. ED term searches were conducted using a dedicated database.

Results: 28.680 admissions to OHER, of 11.239 pts, 5326 (47%) had a single access, the most recurrent one had 51 visits, 165 (0.6%) died there. According to the site of primary malignancy: digestive tract 24%, lung 16.5%, lymphoma 9%, acute and chronic leukemia 10%, breast 7.2%, colon-rectal 8.4%, urological 8%, myeloma 5%, head neck 4%, melanoma 1.4%, sarcoma 1.7%, hematologic 2.3%, thrombotic purpura 0.2%,other 2.3%. Most common reasons determining visits were worsening of disease (14.6%), pain (12%), therapy toxicities (8.6%), suspected tumor (5.6%), deferrable (7%). January was the most crowded month (2900, 10%), December the less one (1952, 6.8%), Monday (6926) the most haunted day of the week. Hospitalizations in Oncology Department were 6.781 (23%), 1.710 (5.8%) in others. 10.246 cancer pts acceded to ED in the same period (1.4% of all pts); 5961(58%) were hospitalized. Average long of stay was 10 days.

Conclusions: Acute oncology can play a key role in management of emergencies; despite true level of saving is difficult to quantify accurately, OHER lead to save 81430 bed days with hypothetic financial saving.

Legal entity responsible for the study: Medicina Oncologica Policlinico Modena.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1746P Comparing cancer patients' and support persons' preferences for the type of consultation and the format of information provided when making a treatment decision

A. Herrmann[1], R. Sanson-Fisher[1], A. Hall[1], L. Wall[2], N. Zdenkowski[3], A. Waller[1]

[1]School of Medicine and Public Health, University of Newcastle, Callaghan, Australia, [2]School of Psychology, University of Newcastle, Callaghan, Australia, [3]Department of Medical Oncology, Calvary Mater Newcastle, Waratah, Australia

Background: Cancer patients and their support persons often feel overwhelmed when being confronted with their diagnosis and treatment options. Such information is commonly provided during one consultation with their clinician. We compared cancer patients' and their support persons' preferences for: i) attending one 40-minute consultation or two 20-minute consultations when making a treatment decision; and ii) receiving additional information in written form only or in both written and online forms.

Methods: An Australian cross-sectional survey, using a discrete choice experiment (DCE), of 159 adult medical oncology patients, and 64 of their support persons. Participants were presented with four hypothetical scenarios and asked to indicate their most and least preferred option. They were told that both treatments would have the same impact on participants' life expectancy, and that there would be no difference between the scenarios in terms of when treatment would start.

Results: 147 patients and 59 support persons completed the DCE. The proportions of patients and support persons choosing each scenario did not differ statistically significantly from each other ($p > 0.05$). Of the four scenarios, most patients and support persons preferred to receive two consultations along with written and online information ($n = 65$, 44% and $n = 30$, 51% respectively). Significantly more participants preferred to receive two shorter consultations rather than one longer consultation when this was combined with written and online information ($p < 0.05$).

Conclusions: When making a cancer treatment decision, both patients and support persons seem to prefer to receive two shorter consultations combined with written and online information. Clinicians should consider offering this consultation style.

Legal entity responsible for the study: Anne Herrmann.

Funding: This study was funded by a Strategic Research Partnership Grant [CSR 11-02] from the Cancer Council New South Wales to the Newcastle Cancer Control Collaborative (New-3C), and by a Partnership Project [APP1059760] from the National Health & Medical Research Council (NHMRC). The authors also received funding support from the Hunter Cancer Research Alliance Implementation Science Flagship Program, the Hunter New England Local Health District, and the Australian Research Council. Infrastructure funding was provided by the University of Newcastle and Hunter Medical Research Institute.

Disclosure: All authors have declared no conflicts of interest.

1747P EXTEND: Safety and efficacy of exercise training in men receiving enzalutamide (ENZ) in combination with conventional androgen deprivation therapy (ADT) for hormone naïve prostate cancer (HSPC)

M.R. Harrison[1], P.G. Davis[2], M.G. Khouri[3], R.T. Gupta[4], A.J. Armstrong[1], M.A. McNamara[1], T. Zhang[1], M. Anand[5], K. Onyenwoke[5], H. Hood[5], S. Edwardson[6], D. Craig[6], Y. Wu[7], P. Healy[7], B. Coyne[8], L. Jones[9], D.J. George[1]

[1]Division of Medical Oncology, Duke Cancer Center, Durham, NC, USA, [2]Department of Kinesiology, UNCG, Greensboro, NC, USA, [3]Division of Cardiology, Duke Cancer Center, Durham, NC, USA, [4]Department of Radiology, Duke Cancer Center, Durham, NC, USA, [5]GU Oncology, Duke Cancer Center, Durham, NC, USA, [6]Health and Fitness Center, Duke University, Durham, NC, USA, [7]Biostatistics, Duke Cancer Center, Durham, NC, USA, [8]Cardiac Diagnostic Unit, Duke University Health System, Durham, NC, USA, [9]Exercise Oncology Research Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: ADT is associated with physical side effects and a decline in cardiorespiratory fitness that can be mitigated with exercise (EX). Addition of a more potent androgen receptor inhibitor such as ENZ might worsen these effects. In this pilot study, we

investigated whether an EX program could mitigate adverse changes from ADT + ENZ treatment.

Methods: Men starting ADT for M0 HSPC were treated with ADT + ENZ for 8 months and randomized to usual care (UC) or EX for 16 weeks. EX began 4 weeks prior to starting ADT + ENZ and consisted of 48 supervised exercise sessions delivered 3x/week between 55-80% of exercise capacity (VO_2peak) for aerobic training and 60-85% of one repetition maximum (1-RM) for resistance training. The primary endpoint was change in VO_2peak from baseline to 16 weeks. Secondary endpoints included 6 minute walk distance (6MWD), upper and lower body strength (1-RM), body composition (DXA), and patient reported outcomes (FACT-P, FACIT-Fatigue). The study was originally designed to recruit 56 subjects (N = 28/arm) but was halted early due to funding issues.

Results: 26 men (UC, N = 13; EX, N = 13) completed the protocol. Baseline age and BMI (mean ± standard deviation [SD]) were 65.0 ± 8.1 yr and 28.5 ± 4.6 kg/m2. Intention to treat analyses for mean 16-week change from baseline with a 95% confidence interval (CI) for each assessment by arm are presented in the table.

Table: 1747P

Endpoint	UC + ADT + ENZ (mean change [95% CI])	EX + ADT + ENZ (mean change [95% CI])
VO_2peak (ml kg^{-1} min^{-1})	-3.2 (-6.3, -0.2)	-0.9 (-2.4, 0.5)
6MWD (ft)	-32.0 (-71.2, 7.3)	+42.0 (5.6, 78.4)
1-RM Leg Press (lbs)	+6.7 (-46.7, 60.0)	+107.1 (43.2, 171.0)
1-RM Chest Press (lbs)	+4.9 (-11.0, 20.9)	+24.3 (9.2, 39.4)
1-RM Row (lbs)	+3.0 (-10.5, 16.5)	+14.9 (0.7, 29.0)
Fat Mass (g)	+2949 (565, 5333)	-122 (-1593, 1350)
Lean Mass (g)	-3088 (-5384, -792)	-2094 (-3549, -640)
FACT-P TOI	-11.6 (-20.3, -2.9)	-5.4 (-10.8, 0.1)
FACIT-F Score	-9.2 (-16.0, -2.4)	-5.0 (-8.0, -2.1)

Conclusions: Supervised aerobic and resistance EX resulted in less decline in VO_2peak, as well as improved function and strength in men treated with ADT + ENZ for M0 HSPC. EX was associated with less fat gain and muscle mass loss, less decline in QOL, and less increase in fatigue. Larger trials of EX in this setting are warranted.

Clinical trial identification: NCT02256111.

Legal entity responsible for the study: Duke University Health System.

Funding: Pfizer (Medivation), Astellas.

Disclosure: All authors have declared no conflicts of interest.

1748P Cancer care-related social media (SM) and internet usage differences between adolescents and young adults (AYA), adults and elderly patients with cancer

L. Eng[1], J. Bender[2], K. Hueniken[3], S. Kassirian[3], D. Yang[3], L. Mitchell[4], C.B. Paulo[5], A. Magony[3], E.C. Smith[3], M. Liang[3], M.C. Brown[3], W. Xu[3], S.M.H. Alibhai[6], G. Liu[3], A. Gupta[7]

[1]Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, ON, Canada, [2]Department of Epidemiology, Dalla Lana School of Public Health, Toronto, ON, Canada, [3]Department of Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, ON, Canada, [4]Adolescent and Young Adult Program, Hospital for Sick Chidlren, Toronto, ON, Canada, [5]Medical Oncology, Princess Margaret Cancer Center, Toronto, ON, Canada, [6]Geriatrics and General Internal Medicine, Toronto General Hospital, Toronto, ON, Canada, [7]Department of Hematology and Oncology, Hospital for Sick Chidlren, Toronto, ON, Canada

Background: Internet and SM provide important information and support to cancer patients. Evaluating age-related differences on how patients use these resources is important as it can impact decision-making. Here, we evaluated associations between patients' age, confidence in computer-use, and use of Internet/SM for cancer care.

Methods: Cancer patients completed a cross-sectional survey of cancer-related SM/Internet use and self-confidence using these resources. Multivariable logistic regression evaluated factors associated with Internet/SM use.

Results: Among 320 patients, 127 were AYA (age 18-39), 127 were adult (40-64) and 66 were elderly (65+). Most (>95%) had a smartphone/tablet/computer and used the Internet daily. Compared to AYA, non-AYA were less likely ($P < 0.001$) to own a data plan (77% vs 92%), have a SM account (72% vs 95%) or feel confident using computers (76% vs 98%). 75% used Internet and 43% used SM for cancer care information and support; 37% felt confident using online information for decision-making. AYA were more likely than non-AYA to use the Internet (aOR = 1.60, 95%CI [0.93-2.81], P = 0.09) and SM (aOR = 1.75 [1.04-2.95], P = 0.04) for cancer care. Adults were more likely than elderly patients to use the internet for cancer care (aOR = 3.10 [1.56-6.25], P = 0.001), while no difference was seen in their SM use for cancer care (P = 0.79). Confident computer users were more likely to use Internet (aOR = 5.36 [2.67-11.00], $P < 0.001$) and SM (aOR = 4.61 [1.98-12.14], $P < 0.001$) for cancer care and were more confident using this information in decision-making (aOR = 5.12 [1.92-17.81], $P < 0.001$). Age was not associated with self-confidence using online information for decision-making ($P > 0.10$).

Conclusions: Despite higher use of internet/SM for cancer care, AYA did not feel more self-confident evaluating online cancer information. Confidence in computer use was associated internet/SM usage and confidence evaluating online information. Patient education programs should focus on improving patients' confidence in using online resources so they can better evaluate online information for cancer care.

Legal entity responsible for the study: Princess Margaret Cancer Centre - University Health Network.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1749P Ultrasound-guided femoro-popliteal block in lower limb sarcoma and cutaneous malignancy patients: Is it the time to abandon spinal anaesthesia for foot and ankle surgeries?

N. Moda

Department of Anesthesia, Critical Care and Pain Medicine, IMS & SUM Hospital SOA University, Bhubaneswar, India

Background: Ultrasound-guided regional anaesthesia has recently become very popular. The aim of this study was to compare the efficiency of Ultrasound-guided femoro-popliteal block (US-FPB) against spinal anaesthesia (SA) for foot and ankle surgeries in lower limb cancer (sarcoma and skin cancer) patients and to further define its role in intra-operative anaesthesia and post-operative analgesia.

Methods: This randomized controlled trial included 52 adult lower limb cancer patients. They were randomized into two groups. Patients from group A (experimental) received Ultrasound-guided femoro-popliteal block, while a spinal anesthesia (SA) was given in group B patients. In both the groups, Bupivacaine (0.5%) was used as local anaesthetic drug. The statistical analysis was done using student's t-test and p value <0.05 was considered significant.

Results: 25 patients from the first and 24 patients from the second group completed the study. Using modified Bromage score, levels of anaesthesia were found to be sufficient in both the groups without any statistically significant differences (p value=0.67). Average duration of postoperative analgesia was 12.3 hours and 2.7 hours in group A and B, respectively (p value<0.001).

Conclusions: Both US-FPB and SA provided sufficient and comparable anaesthesia for ankle and foot fractures. However, post-operative analgesia was significantly longer in US-FPB group with subsequent much less requirement of post-operative analgesics. Better and longer post-operative analgesia in US-FPB group also resulted in shorter rehabilitation periods and decreased time-gaps for beginning of joint movements.

Legal entity responsible for the study: Nupur Moda.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1750P Assessment of socio-economic, physical and mental health status of long-term cancer survivors

A. Gallego Martínez, B. Martínez, I. Ghanem, E. Espinosa, B. Castelo, M.P. Zamora Aunon, A. Pinto Marin, L. Ruiz-Giménez, A. Redondo, J. Feliu Batlle

Medical Oncology, Hospital Universitario La Paz, Madrid, Spain

Background: Long-term survival rates for many types of cancer have substantially improved in past decades. In order to improve follow-up and comprehensive care of this population a specific medical office was started up three years ago at our institution. This is the health and socio-economic analysis of the long-term cancer survivors in our area.

Methods: A 54-item questionnaire was developed based on QLACS (Quality of Life in Adult Cancer Survivors) and SF-36 Health Survey. 347 patients completed the questionnaire from January 2015 to December 2016. A medical questionnarie (63-item) was also completed for each patient by oncologists responsible for the medical office. The information was collected in a database and processed with SPSS 18.

Results: Median age at the time of diagnosis was 56.8 years and median time from cancer diagnosis to questionnarie completion was 7.1 years. 53.9% were women and 46.1% men. At the time of diagnosis 72% were married/committed relationship, 27.9% had university studies and 32.8% were retired. 35.4% had hipercolesterolemia and 3.2% anxiety/depression syndrome. Colon and breast carcinomas accounted for 49.9% of all cases and 67.1% were diagnosed in stages I and II. 91.8% underwent surgery, 59.6% received chemotherapy and 32.3% radiotherapy. After the diagnosis and treatment of cancer relationship status of patients scarcely changed, 19.9% more of the patients retired, 17.9% of those who kept their

employment status decreased their income, though only 9 patients reduced their working hours. Despite 24.3% made healthy dietary modifications, 25.4% gained al least 5 kg over their recommended weight and the anual incidence rate of hipercolesterolemia was 5.8%. 34.9% patients more had anxiety/depression syndrome and 68.9% reduced their sexual activity with significant differences between colon and breast cancer (OR:3.3; p = 0.007). 78.7% were satisfied with the information received by their oncologist about their cancer.

Conclusions: Long-term cancer survivors are patiens with major health and socio-economic issues who need a multidisciplinaty follow-up. Despite their median age, more than half had cardiovascular risk factors, sexual difficulties or were retired and more than one-third had anxiety/depression syndrome.

Legal entity responsible for the study: Medical Oncology Department, La Paz University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1751P Usability testing of EirV3-a computer-based tool for patient reported outcome measures in cancer

H. Krogstad[1], S.M. Sundt-Hansen[2], M.J. Hjermstad[3], L.Å. Hågensen[4], S. Kaasa[3], J.H. Loge[5], S.X. Raj[1], A. Steinsbekk[6], K. Sand[1]

[1]European Palliative Care Research Centre (PRC) and Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Cancer Clinic, Norwegian University of Science and Technology and St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [2]Department of Medicine, St.Olavs hospital, Trondheim University Hospital, Trondheim, Norway, [3]European Palliative Care Research Centre, Institute of Clinical Medicine and Department of Oncology, University of Oslo and Oslo University Hospital, Oslo, Norway, [4]Coordination Unit Orkdal Region, Orkdal Region, Orkanger, Norway, [5]Institute of Basic Medical Sciences, Faculty of Medicine and Department of Oncology, University of Oslo and Oslo University Hospital, Oslo, Norway, [6]Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

Background: Eir Version 3 (V3) is an electronic tool for registration administration of patient reported outcome measures (Eir-Patient) that immediately presents patient scores on the physiciań s computer (Eir-Doctor). Perceived usability is an important determinant for successful implementation.The objective was to assess the number, type, and severity of usability issues of the Eir-Patient and Eir-Doctor modules respectively, when used by cancer patients and physicians in three different settings: 1) outpatient clinics, 2) at home, and 3) at the general practitioner's office.

Methods: A usability evaluation using observations, think-aloud sessions, individual and focus group interviews in patients and their physicians was conducted. Identified usability issues were graded on a severity scale from 1 (irritant) to 4 (unusable).

Results: Overall, 73 Eir registrations were performed by 37 patients, and used by 17 physicians in clinical consultations. All patients were able to complete the Eir-Patient symptom registration, which was perceived easy. Seventy-two usability issues were identified. None of them were graded as unusable. 62% of the identified usability issues in Eir-Patient were graded as irritant (grade 1), 18% and 20% as moderate or severe (grade 2-3), none as unusable. For the Eir-Doctor module, 46% of the identified usability issues were graded as irritant, 36% as moderate and 18% as severe. Observations of physician consultations showed that Eir-Doctor was intuitive and easy to use.

Conclusions: Patients and physicians found EirV3 easy to use. Results indicate that EirV3 is usable for a heterogeneous population of cancer patients, in different settings. In the subsequent Eir-version, issues in the severe and moderate categories have been changed, to optimize the usability and feasibility of using real time PROMs in clinical practice.

Legal entity responsible for the study: Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, NTNU.

Funding: Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, and Regional Research Funds in Norway, Mid-Norway.

Disclosure: S. Kaasa, J.H. Loge: Eir Solutions AS was established in 2015 with Kaasa, Loge and NTNU Technology Transfer AS/Andersen as shareholders. No income, dividend or financial benefits are related to the work presented here, nor in relation to Eir in any way. All other authors have declared no conflicts of interest.

1752P Monitoring quality of life in Dutch women with breast cancer: The Care Notebook study

R.T. Lugtenberg[1], M.J. Fischer[2], F. de Jongh[2], K. Inoue[3], A. Matsuda[4], S.R.S. Ramai[5], J.W. Nortier[1], H. Putter[6], K. Yamaoka[7], K. Kubota[8], K. Kobayashi[9], A.A. Kaptein[2], J.R. Kroep[1]

[1]Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [2]Medical Psychology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [3]Division of Breast Oncology, Saitama Cancer Center, Ina, Japan, [4]Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan, [5]Pulmonology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [6]Medical Statistics, Leiden University Medical Center (LUMC), Leiden, Netherlands, [7]Graduate School of Public Health, Teikyo University, Tokyo, Japan, [8]Division of Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan, [9]Respiratory Medicine, Saitama Medical University International Medical Centre, Saitama, Japan

Background: For many patients the diagnosis and treatment of cancer are associated with negative consequences for their physical, psychological and social well-being. However, patients' needs for care cannot be addressed unless they are recognized by healthcare providers (HCP). The use of quality of life (QoL) assessments with feedback to clinicians might facilitate the discussion of QoL-items, resulting in improved QoL.

Methods: Women with stage I-IIIB breast cancer treated with chemotherapy were included in this randomised study. All respondents completed questionnaires regarding QoL, illness perceptions, self-efficacy, satisfaction with communication, and distress at three moments. Women in the experimental arm completed 'the Care Notebook' (CNB) questionnaire, assessing QoL, distress and care needs before every hospital visit. Results were automatically stored and presented in patients' medical files. From the 2nd visit onwards, patients and HCPs received a copy of the latest QoL overview before the consultation. Women in the control arm received care as usual. Audio-recordings were used to investigate effects on communication and patient management.

Results: presented here are drawn from a collaborative study between Japan and the Netherlands. From July 2012 to May 2016, 60 out of 113 Dutch patients were randomized to the experimental arm. In the experimental condition, more QoL-items 'were discussed (0.7 items each visit, p=.04), compared with the control condition, especially regarding disease-specific and psychosocial issues (p<.01). There were no differences in patient management, QoL, illness perceptions or distress. Patients in the experimental arm had higher scores on satisfaction with communication (p<.05). All patients perceived high self-efficacy in interacting with HCP. Patients in the intervention condition perceived the tool as user-friendly and a valuable addition to regular care.

Conclusions: Use of the QoL-monitor 'The Care Notebook' resulted in more frequent discussion of psychosocial and disease-specific issues, associated with high levels of patients' satisfaction. However, patient management and patients' QoL were unaffected by the intervention.

Legal entity responsible for the study: Leiden University Medical Center.

Funding: This study was supported by a grant of the Dutch Pink Ribbon Foundation and from Pfizer, Japan.

Disclosure: All authors have declared no conflicts of interest.

1754P Prognostic factors for critically ill patients with solid cancer tumours admitted to a medical intensive care unit

C. Baylot[1], A. Francopoulo[2], A. Quivy[1], O. Guisset[3], G. Hilbert[4], E. Frison[2], A. Ravaud[1], A. Daste[5]

[1]Department of Medical Oncology, CHU Bordeaux Hopital St. André, Bordeaux, France, [2]Medical Information Department, CHU Bordeaux, Bordeaux, France, [3]Department of Medical Intensive Care Unit, CHU Bordeaux Hopital St. André, Bordeaux, France, [4]Department of Medical Intensive Care Unit, CHU Bordeaux, Hôpital Pellegrin, Bordeaux, France, [5]Gironde, CHU Bordeaux Hopital St. André, Bordeaux, France

Background: The decision to transfer patients (pts) with solid cancer tumours to an intensive care unit (ICU) is still controversial and difficult. Few studies have assessed the outcome for these patients. The aim of this study was to identify 30-day prognostic factors/mortality for pts with solid cancer tumours admitted to an ICU.

Methods: We conducted a retrospective cohort study of all consecutive pts with solid cancer tumours admitted to ICUs at Bordeaux University Hospital, between January 2010 and December 2015. The study end point was 30-day mortality. Secondary end points were to describe the characteristics and outcomes for pts, and ethical practices.

Results: We included 235 patients with solid tumours. Most of them were in a metastatic setting (60%).The most common causes for ICU admission were sepsis (56%) and/or respiratory failure (52%). ICU, 30-day, 90-day mortality rates were 24%, 36% and 50% respectively. After ICU stay, 44% of pts had restarted an anti-tumoral treatment. In multivariate analysis and after excluding SAPS 2 score, two or more organ failures (p = .005) and being under non-curative care (p = 0.028) were independent prognostic factors of 30-day mortality. A support person was designated in 81% of cases, advance directives expressed in 2% and collective decision reported in 21%. Limitation of life-sustaining therapy was decided for 23% and 43% of pts before admission and during the ICU stay, respectively.

Conclusions: The number of organ failures is a rapidly assessable variable that can help oncologists and intensive care specialists in their decision. A support person is often designated but advance directives are still unusual.

Legal entity responsible for the study: CHU Bordeaux.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1755P A pilot study of exercise intervention in patients with metastatic cancer: Feasibility, safety, and patient reported outcome

J-H. Park[1], E.Y. Kim[2], K.D. Park[3], S.M. Kang[4], H. Ahn[1], Y.S. Kim[1], I. Park[1], S.J. Sym[1], D.B. Shin[1]

[1]Medical Oncology, Gachon University Gil Medical Center, Incheon, Republic of Korea, [2]Radiology, Gachon University Gil Medical Center, Incheon, Republic of Korea, [3]Rehabilitation Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea, [4]Pulmonology and Allergy, Gachon University Gil Medical Center, Incheon, Republic of Korea

Background: Skeletal muscle loss is a central component of cancer cachexia syndrome and is a poor prognostic factor in patients with cancer. We investigated prevalence of sarcopenia and the feasibility of exercise intervention in patients with newly diagnosed advanced solid cancer.

Methods: Between July 2017 and February 2018, consecutive patients with newly diagnosed advanced solid cancer were enrolled to our prospective cohort. Sarcopenia was defined as the third lumbar vertebra(L3) muscle index of less than 55 cm^2/m^2 for men and of less than 39 cm^2/m^2 for women. Patients were recruited to participate in a 12-week, combined resistance and aerobic exercise program consisted of supervised, hospital-based (2x/week) and home-based training (3x/week), during the first-line palliative chemotherapy. The primary endpoint were feasibility and safety of the exercise intervention. Pre- and post- exercise intervention skeletal muscle mass by bioelectrical impedance analysis(BIA) and patients' quality of life questionnaires were measured and compared.

Results: Among 76 patients enrolled in the prospective cohort, sarcopenia was present in 58 (76.3%) patients (94.3% in men, 34.8% in women). Nineteen patients was enrolled in the exercise program, however 5 patients withdrew consent before commencement. Reasons for withdrawal were health concern (n = 2), distance to the hospital (n = 1) and unspecified (n = 2). The completion rate of the 12-week exercise program was 78.6% (11/14). Disease progression (n = 2) was the main reason for early discontinuation. The adherence rate of the supervised exercise session was 78.1% (207/265) and there was no adverse event associated with the exercise training. Among participants in the exercise program, there was no significant change in skeletal muscle index from baseline to post-intervention (mean, $9.4\pm1.3kg/m^2$ vs $9.4\pm1.2kg/m^2$, p = 0.982). FACIT-fatigue scale was non-significantly improved after the exercise intervention (mean, 35.2 ± 10.4 vs 38.2 ± 9.8, p = 0.635).

Conclusions: Exercise interventions appear to be feasible and safe in patients with advanced solid cancer and might have a role of preventing skeletal muscle loss without fatigue exacerbation during palliative chemotherapy.

Legal entity responsible for the study: Gachon University Gil Medical Center.

Funding: National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (grant no. HA17C0045).

Disclosure: All authors have declared no conflicts of interest.

1756P A prospective analysis of 30-day mortality following palliative chemotherapy at an Australian tertiary cancer centre

J.A. McCracken[1], A. Dabscheck[1], M. Coperchini[1], I. Hornung[2], A. Jalali[2], G. Akers[2], A. Karahalios[3], L. Lipton[2]

[1]Palliative Care, Western Health, St Albans, Australia, [2]Medical Oncology, Western Health, St Albans, Australia, [3]Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Australia

Background: 30 day mortality for patients receiving palliative intent chemotherapy has been suggsted by the 2008 NCEPOD as a measure of quality of cancer care. This has to a number of global audits, with rates ranging from 8-43%. This world first prospective study aimed to benchmark an Australian tertiary cancer centre, and identify factors associated with 30 day mortality.

Methods: A Prospective cohort study of all patients with a diagnosis of malignancy referred for palliative intent intravenous chemotherapy to the Western Health Chemotherapy Day Unit from the 8th December 2014 to 8th December 2015. The primary outcome was death within 30 days of receiving palliative intent chemotherapy.

Results: A total of 314 patients were enrolled in the study. The average age was 63 years, 45% were female, and 60% were born overseas. 98 patients died during the audit period. Of these, 21 (6.6%) died within 30 days of commencing palliative intent chemotherapy, and 60 (18.8%) died more than 30 days after receiving chemotherapy. Of the 34 patients that were referred, but did not start chemotherapy, 17 (52%) died. Multivariable logistic regression found that patients who had been referred to palliative care and received chemotherapy were more likely to die within 30 days, although this did not reach statistical significance. There was no difference in mortality rate by gender, age, tumour type, number of lines of previous chemothearpy, or patient performance status. Patient's who commenced chemotherapy were more likely to die in hospital (n = 44, 74%), as those who were referred but did not commence chemotherapy were more likely to die at home (n = 9, 50%). 199 patients ceased chemtoehrapy during the study period, with the most common reason being progression of disease (n = 78, 39.2%), and toxicity (n = 60, 30.2%).

Conclusions: This prospective cohort study demonstrated taht 6.6% of patients died within 30 days of administration of palliative intent chemotherapy. Multivariate analysis did not identify any pre-specified variables that were significantly associated with 30 day mortality. in our study, the strongest predictor of 30 day mortality was referral to outpatient palliative care.

Legal entity responsible for the study: Western Health.

Funding: Western Central Melbourne Integrated Cancer Service.

Disclosure: All authors have declared no conflicts of interest.

1757P Characterisation of oncologic patient visits at the ED at an Austrian tertiary care center

B. Pauzenberger[1], T. Fuereder[2], A. Laggner[3], C.C. Zielinski[2], C. Minichsdorfer[2]

[1]Clinical Division of Oncology, Department of Medicine I, Medizinische Universitaet Wien, Vienna, Austria, [2]Clinical Division of Oncology, Department of Medicine I & Comprehensive Cancer Center, Medizinische Universitaet Wien, Vienna, Austria, [3]Department of Emergency Medicine, Medizinische Universitaet Wien, Vienna, Austria

Background: Oncologic patients with tumor or therapy associated complications often seek out the ED as first contact point. Next to the rare classic oncologic emergencies, other causes are supposed to be more frequent. However, little is known about other reasons of patients with cancer to consult the ED.

Methods: The study is a retrospective data analysis of emergency visits of patients with active cancer or adjuvant therapy, who were taken by ambulance to the ED. From 1.1.2017–31.7.2017 data from all patient contacts were collected. The medical history of adult patients were searched for diagnosis of active malignant disease or adjuvant therapy, to be eligible for this study.

Results: From a total of 1029 patient contacts 743 met the inclusion criteria. 425 male contacts (57%) and 318 female contacts (43%) were recorded. The median age was 67 years. The vast majority of patients (648, 87%) were in a palliative setting. 339 patients (46%) were under active treatment and 111 patient contacts (15%) were treatment associated. 384 patient contacts (52%) were tumor related. The most common malignancies were lung cancer (141, 19%), pancreatobilliary cancer (73, 10%), colorectal cancer (67, 9%) and breast cancer (54, 7%). The most frequently reasons for ED consultations were detorriation of general condition (140, 19%), pain (130, 18%), dyspnea (106, 14%) and fever (97, 13%). The most common diagnosis were infections (142, 19%) with pneumonia as the leading cause (61, 8%). Followed by pain (130, 18%), with cancer pain beeing the most common complication (52, 7%) and tumor progression (103, 14%). Data regarding OS until the date of censorship (28.2.18), 3 month mortality (3MM) and factors possibly influencing 3MM are yet immature, but will be added at time of presentation.

Conclusions: The majority of cancer patients seeking help at the ED are in a palliative setting. Cancer associated complications pose the most frequent cause for ED consultation. Lung cancer, pancreatobiliary and colorectal cancer present the most common malignancies related to ED visits. The results of the study may help to optimize the supportive treatment of cancer patients and may help to inform both oncological patients and primary care units about frequent complications associated with the diagnosis of cancer.

Legal entity responsible for the study: Medical University of Vienna.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1758P High proportion of prostate cancer survivors continue to experience a negative impact on quality of life long after diagnosis: Patient reported outcomes for an Australian population-based sample

Q. Tran[1], A.C. Ward[2], K. Lisy[3], J.F. Bishop[4], M. Jefford[5]

[1]Cancer Care Centre, St Stephen's Hospital, Urraween, Australia, [2]Biostatistics, The Social Research Centre, Melbourne, Australia, [3]Department of Cancer Experiences Research, Peter MacCallum Cancer Centre, Melbourne, Australia, [4]Department of Medical Oncology, Victorian Comprehensive Cancer Centre, Melbourne, Australia, [5]Department of Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia

Background: Prostate cancer is a leading cause of cancer-related burden of disease in Australia. Despite careful patient selection and advances in therapy, men may experience complications beyond completion of treatment. There is a lack of robust population-based data regarding the quality of life (QoL) of prostate cancer survivors. We aimed to determine the feasibility of collecting health and quality of life (QoL) data

from an Australian population-based sample of prostate cancer survivors, using standard measures.

Methods: A cross-sectional survey was mailed to a representative group of patients approximately 1, 3 or 5 years post cancer diagnosis. Eligible participants were 18 years or older, had prostate cancer, and registered with the Victorian Cancer Registry. QoL was assessed using the EQ-5D-5L, Functional Assessment of Cancer Therapy-Prostate (FACT-P) and the Social Difficulties Inventory (SDI-21). The results were compared to an English dataset that used similar methods.

Results: 494 of 1078 eligible participations returned the survey (RR 45.8%). The majority reported their prostate cancer had responded fully to treatment (69.9%). QoL was similar between the Australian and English data, and at 1, 3 and 5 years post diagnosis. Symptoms were commonly reported; from FACT-P: erectile dysfunction 84%; problems with satisfaction with present comfort level 74%; poor appetite 61%; aches and pains that bother me 61%; and from the EQ-5D-5L: anxiety 32%. Improved QoL and improved social wellbeing was associated with full response to treatment (EQ-5D-5L, $p \leq 0.001$; SDI-21, $p \leq 0.01$). Reduced QoL was associated with not having a care plan (EQ-5D-5L, $p \leq 0.01$) and having another medical condition (EQ-5D-5L, $p \leq 0.001$; SDI-21, $p \leq 0.01$).

Conclusions: The method of assessment is feasible in the Australian setting. A high proportion of men experience difficulties that continue to impact their QoL long after diagnosis. This highlights an unmet need and that a process to identify and respond to these issues is needed. Care plans may assist.

Legal entity responsible for the study: Victorian Comprehensive Cancer Centre.

Funding: Victorian Comprehensive Cancer Centre.

Disclosure: All authors have declared no conflicts of interest.

1759P A systematic approach to smoking cessation in regional cancer centres in Ontario, Canada

W.K. Evans[1], E. Cameron[2], M. Haque[2], N. Schwartz[2], S. Khan[2], R. Truscott[2]

[1]Oncology, McMaster University, Hamilton, ON, Canada, [2]Population Health and Prevention, Cancer Care Ontario, Toronto, ON, Canada

Background: Cancer patients who continue to smoke gain less benefit from treatments, experience greater toxicities, are at increased risk of cancer recurrence and second primaries, experience poorer quality of life and decreased survival. Despite awareness of the negative health benefits of continued smoking after a diagnosis of cancer, a systematic approach to help newly diagnosed cancer patients in cancer centres to quit smoking is uncommon.

Methods: In 2012, Cancer Care Ontario established a framework to implement smoking cessation (SC) in all 14 regional cancer centres (RCCs) in the province of Ontario, Canada. The Framework included: use of the 5A's (ask, advise, assess, assist, arrange), recruitment of regional champions to promote the program, and data collection to document that new ambulatory cancer patients were screened for smoking status, advised on the health benefits of cessation and recommended a referral for cessation support. Screening rates became a performance metric to drive implementation and were reviewed quarterly with provincial and regional leaders. During fiscal 2014/15, just over 50% of patients were screened for smoking status. Recent efforts to improve performance include the transition to the 3A's (ask, advise, act) model, using proportion of smokers accepting a referral for SC services as a performance metric, and use of an "opt-out" approach to referrals where tobacco users are automatically referred to cessation services. An environmental scan and site visits resulted in RCC site-specific improvement plans.

Results: The majority of RCCs are exceeding the screening target of 70% (5 centres with proportions $> 80\%$) but the proportion of smokers accepting a referral remains low. The opt-out referral approach is anticipated to increase referral rates and preliminary data are encouraging for centres that have transitioned to the opt-out approach.

Conclusions: To improve program efficiency and impact, Cancer Care Ontario's provincial smoking cessation initiative has transitioned from a 5 to 3 A's model and introduced an opt-out referral process. Front-line staff are adopting the simplified approach and early results show a promising increase in the number of smokers accepting referrals for SC services.

Legal entity responsible for the study: Cancer Care Ontario.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1760P A longitudinal study of a new point-of-care nerve conduction device for quantitative assessment of chemotherapy-induced peripheral neurotoxicity

A. Matsuoka[1], O. Maeda[1], A. Mitsuma[1], K. Uehara[2], G. Nakayama[3], M. Nagino[2], Y. Kodera[3], Y. Ando[1]

[1]Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan, [2]Surgical Oncology, Nagoya University Hospital, Nagoya, Japan, [3]Gastroenterological Surgery, Nagoya University, Graduate School of Medicine, Nagoya, Japan

Background: Chemotherapy-induced peripheral neurotoxicity (CIPN) exacerbates cumulatively and dose-dependently. Assessment of CIPN usually depends on subjective grading scales, such as the Common Terminology Criteria for Adverse Events (CTCAE). We previously validated a newly developed point-of-care nerve conduction device (POCD) for the quantitative assessment of CIPN (Cancer Sci 2016). The aim of the present study was to prospectively assess CIPN using this POCD.

Methods: Patients scheduled to receive 8 cycles of adjuvant CapeOX therapy (capecitabine and oxaliplatin) for colorectal cancer were enrolled. Sural nerve amplitude potentials (SNAP, μV), a quantitative measure of the axonal degeneration, and sural nerve conduction velocity (SNCV, m/s), that of the degree of demyelination, were recorded using a portable and automated POCD (DPN-Check®, Neurometrix Inc., Waltham, MA, USA) at baseline, each cycle of chemotherapy, and within 1 month after the end of chemotherapy. The severity of CIPN was evaluated according to the CTCAE. The total sum of SNAP/SNCV was calculated for each patient, and compared according to each CTCAE grade.

Results: A total of 39 patients (M/F: 22/17; median age 61 years, range 36-76; worst CTCAE G1/G2/G3: 25/10/4) were enrolled. Mean SNAP/SNCV at baseline, each cycle of chemotherapy, and within 1 month after the end of chemotherapy are shown in the table. SNAP decreased significantly during each cycle of chemotherapy (repeated ANOVA, $P < 0.001$), whereas SNCV remained relatively unchanged. The mean total sum of SNAP was 112.6±36.8 G1, 69.8±19.2 G2, and 44.8±12.8 G3. The mean total sum of SNCV was 451.1±34.9 G1, 454.2±24.7 G2, and 429.8±30.1 G3. The total SNAP differed significantly among each CTCAE grade (ANOVA, $P < 0.001$), whereas the total SNCV did not.

Conclusions: This POCD demonstrates SNAP-dominant neuropathy in patients who receive oxaliplatin, indicating axonal degeneration as a mechanism of CIPN.

Clinical trial identification: UMIN000017868.

Legal entity responsible for the study: Nagoya University Hospital.

Funding: Novartis Pharma K.K.

Disclosure: Y. Ando: Honoraria: Yakult Honsha Co., Ltd, Chugai Pharmaceutical Co., Ltd, Mochida Pharmaceutical Co., Ltd.; Research funding: Yakult Honsha Co., Ltd, Chugai Pharmaceutical Co., Ltd, Mochida Pharmaceutical Co., Ltd, Nippon Kayaku Co. Ltd. All other authors have declared no conflicts of interest.

1761P Risk of health-related quality of life events and pulmonary toxicities in recurrent ovarian cancer patients treated with poly adenosine diphosphate ribose polymerase (PARP) inhibitors maintenance

K.Z. Thein[1], A. Sultan[1], M.H. Zaw[2], M.M. Han[3], N.H. Yu[4], H.P. Igid[1], C. Jones[1], N. D'Cunha[1], S. Awasthi[1], F. Hardwicke[1]

[1]Hematology Oncology, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [2]Internal Medicine, The Brooklyn Hospital Center, Brooklyn, NY, USA, [3]Oncologic Emergency, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]Internal Medicine, Kingsbrook Jewish Medical Center, Brooklyn, NY, USA

Background: Pain and fatigue are the major determinants of health-related quality of life (HRQOL) in cancer patients undergoing chemotherapy. Ovarian cancer is the seventh most common cause of cancer in women worldwide. PARP inhibitors maintenance has shown to improve survival in recurrent ovarian cancer patients with notable toxicities. We undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of HRQOL events and pulmonary toxicities.

Methods: We conducted a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018. Phase III RCTs that mention HRQOL events and pulmonary toxicities as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Fixed effects model was applied.

Table: 1760P

	baseline	2nd	3rd	4th	5th	6th	7th	8th	afterwards
SNAP (μV)	15.2±8.9	12.7±5.3	12.8±6.7	11.9±5.1	9.8±4.1	9.2±2.9	8.4±3.9	7.7±3.7	7.4±4.1
SNCV (m/s)	52.7±5.6	52.7±4.4	53.7±5.1	52.5±5.9	50.4±5.2	48.0±5.8	47.3±4.1	46.3±4.4	46.1±4.7

Results: Three phase III RCTs with a total of 1401 patients with recurrent ovarian cancer were eligible. The study arms used olaparib or niraparib or rucaparib while the control arms utilized placebo. The randomization ratio was 2:1 in all studies. The RR of all-grade side effects were as follows: fatigue, 1.54 (95% CI: 1.37 – 1.73, P < 0.001); back pain, 0.93 (95% CI: 0.70 – 1.24, P = 0.64); arthralgia, 1.05 (95% CI: 0.79 – 1.40, P = 0.69); headache, 1.75 (95% CI: 1.34 – 2.29, P < 0.001); decreased appetite, 1.76 (95% CI: 1.36 – 2.28, P < 0.001); cough, 1.87 (95% CI: 1.33 – 2.63, P < 0.001); dyspnea, 2.39 (95% CI: 1.64 – 3.48, P < 0.001); and upper respiratory infections (URI), 1.71 (95% CI: 1.16 – 2.53, P = 0.007). The RR of high-grade side effects were as follows: fatigue, 3.94 (95% CI: 1.90 – 8.17, P < 0.001); back pain, 0.49 (95% CI: 0.10 – 2.48, P = 0.39); arthralgia, 2.00 (95% CI: 0.22 – 17.82, P = 0.53); headache, 1.00 (95% CI: 0.18 – 5.47, P = 0.99); decreased appetite, 1.16 (95% CI: 0.17 – 7.82, P = 0.87); and dyspnea, 1.28 (95% CI: 0.30 – 5.48, P = 0.73).

Conclusions: Our study showed that the risk of developing any-grade headache, decreased appetite, cough, dyspnea and URI as well as all grades of fatigue with PARP inhibitors was high. Prompt intervention with good supportive care is required.

Legal entity responsible for the study: Kyaw Zin Thein, Texas Tech University Health Sciences Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1762P Chemotherapy-induced peripheral neurotoxicity (CIPN): What are patients telling us?

G. Cavaletti

School of Medicine and Surgery, Università degli Studi di Milano Bicocca, Monza, Italy

Background: This is a secondary analysis of the original CI-PeriNomS study dataset to formally test in CIPN patients: a) which is the correlation between patients' perception of activity limitation and actual neurological impairment, and b) how the responses to simple questions regarding daily activities potentially related to sensory and/or motor impairment are interpreted by the treating oncologist.

Methods: For the purposes of the current study we have analyzed data on the presence (frequency) of CIPN-associated peripheral nerve damage, without taking into account its severity. Comparison was performed between the oncologists' responses and the scores obtained in strength and vibration detection threshold using the Total Neuropathy Score (clinical, TNSc) criteria compared to patients answers to 8 tasks scored as "impossible" to be performed by at least 5% of the patients.

Results: The distribution of the scores attributed by oncologists to each daily life maximum limitation ("impossible") allowed categorizing the responses into 3 groups: Group 1 included the limitations that the oncologists attributed mainly to motor impairment (item median motor score = 7, item median sensory score 2-3), Group 2 consisted of limitations mainly attributed to sensory impairment (item median sensory score = 8, item median motor score = 1-2) and Group 3 included limitations with uncertain motor and sensory impairment (item median sensory score = 4-6, item median motor score = 5). We demonstrate that the interpretation of patients' report provided by the panel of oncologist is poorly consistent with the actual neurological impairment, and that activity limitations capture more than simple impairments and reflect a broader impact than impairment measures.

Conclusions: These observations form a critical basis for further research on the core set of outcome measures needed for future trials in CIPN and at the same time suggest a careful use of available PROs alone as main endpoints in CIPN trials. Presented on behalf of the CI-PeriNoms study group.

Legal entity responsible for the study: CI-PeriNoms study group.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1763P Malnutrition in cancer patients: Is late diagnosis a missed opportunity to improve care?

C. Tlemsani[1], G. Zalcman[2], R. Bernard[3], A. Zerouali[3], F. Goldwasser[4]

[1]APHP, Hôpital Cochin, Paris, France, [2]Oncology, Hôpital Bichat, Paris, France, [3]Baxter Healthcare, Guyancourt, France, [4]Oncology, Hôpital Cochin, Paris, France

Background: Malnutrition (MN) related metabolic defects, through the tumor or its treatment, can negatively impact on cancer patients' outcomes. Yet, MN is often undiagnosed and untreated. This study investigated diagnoses of MN and hospital resource use in patients with gastro-intestinal (GI) system cancers.

Methods: The study used the French Hospital database PMSI MCO. We identified 644,720 GI cancer patients (colon-rectal-anal, liver/biliary tract, pancreas, stomach, esophagus) with a first related hospital stay (no stay 2 years pre-index) between 2013 and 2016. Patients were grouped into: no MN diagnosis, MN diagnosis at first hospitalization and MN diagnosis after first hospitalization. Resource use (number and duration of hospitalizations) was analyzed by patient group, GI cancer category and by presence/absence of metastases. Propensity score matching for key characteristics, such as age, gender and comorbidities was used to adjust for differences between groups.

Results: MN diagnoses at first hospitalization occurred in 10% of patients, 13% were diagnosed after first hospitalization and 77% had no diagnosis of MN during the study period. Patients without MN had on average 5.2 hospitalizations of 13 days. Compared to MN diagnosed at first hospitalization, hospital stays were twice as frequent and longer when MN was diagnosed after 1st cancer hospitalization (6.8 vs. 13.9 stays and 38 vs. 53 days, respectively). After propensity score matching, a significantly higher frequency of hospitalizations in those with a late compared to early diagnosis of MN remained. Differences in frequency and duration of hospitalizations increased linearly with a later MN diagnosis (1, 3, 6 months after first hospitalization), with the strongest association in patients without metastases.

Conclusions: The data suggests that an earlier diagnosis of MN should help to reduce frequency and length of hospitalizations, particularly in patients without metastases, potentially improving patients' clinical outcomes and reducing health economic costs. Further research is warranted to understand the potential of early nutritional therapy in improving cancer patients' outcomes and in reducing resource use.

Editorial acknowledgement: Medical writing support for this abstract was provided by Anne-Kathrin Fett, IQVIA, Frankfurt, Germany.

Legal entity responsible for the study: Baxter Healthcare SA, Zurich, Switzerland.

Funding: Baxter Healthcare SA, Zürich, Switzerland. This work is supported by a public grant overseen by the French National Research Agency (ANR) as part of the "Investissements d'Avenir" program (reference: ANR-10-EQPX-17 - Centre d'accès sécurisé aux données – CASD).

Disclosure: G. Zalcman: Consultant and/or on advisory panel: Baxter Healthcare Corporation; Personal fees: BMS, MSD, AstraZeneca for advisory board; Investigator in clinical trials: BMS, Roche, Takeda, Boerhinger, AstraZeneca, Pfizer; Reimbursement for congress attendance: Pfizer (ASCO 2015), Roche (ASCO 2017), Abbvie (ASCO 2018), AstraZeneca (ESMO 2017, WCLC 2018). R. Bernard, A. Zerouali: Employee, holds stock: Baxter Healthcare Corporation. F. Goldwasser: Consultant and/or on advisory panel: Baxter Healthcare Corporation, Fresenius Kabi. All other authors have declared no conflicts of interest.

1764P A survey on acceptable nomenclature in addressing patient needs among the delegates of a national conference on supportive medicine

R.D. Arora

Palliative Medicine, All India Institute of Medical Sciences, New Delhi, India

Background: The scope and ambit of services offered in an integrated inpatient palliative medicine unit located in tertiary cancer centre is explored through various questions pertaining to multiple domains encompassing clinical management of advanced cancer patients. The survey tests the attitudes of the respondents while laying the foundation of building and sustaining a novel model where Supportive cancer care services, Pain management and Palliative medicine interventions (including End of life care) are offered as part of a continuum.

Methods: The survey was carried out among the registered delegates of the annual national conference of the Indian Association of Palliative Care.

Results: 48 percent (84/175) felt that Palliative medicine and Supportive oncology are mutually exclusive domains in patient management. 40 percent (71/175) agreed that the terms Palliative medicine and Palliative care are different entities in patient management. 47 percent (96/203) agreed that the term Palliative medicine should be substituted by Supportive medicine while only 22 percent (38/172) agreed that using the term Supportive oncology would be justified in place of Palliative medicine. 34 percent (59/169) felt that substitution of the term Palliative medicine by Supportive oncology might remove the stigma associated with the referral of the patient to avail these services.

Conclusions: These results reflect the multiplicity of views which underlie existing divergent schools of thought in this nascent subspeciality. An indigenous academic model based on the premise of closeknit integration of supportive care and medical oncology which dispels the myth of pure palliation as a segregated entity is the need of the hour. The services offered should reflect the understanding that recognition and management of supportive care needs of cancer patients is of utmost important in making the model economically viable and socially sustainable.

Legal entity responsible for the study: Rahul D. Arora.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1765P A survey on purview of palliative medicine services among the delegates of a national conference on supportive medicine

R.D. Arora

Palliative Medicine, All India Institute of Medical Sciences, New Delhi, India

Background: The provision of personalized, symptom oriented, patient centered care at an early stage in the patient's trajectory of illness is the philosophy that underlies supportive care.

Methods: A questionnaire based on clinical scenarios encountered in the integrated inpatient palliative medicine unit was carried out among the registered delegates of the annual Indian association of Palliative care conference.

Results: Interventional pain procedures (65.49 percent) and counseling regarding goals of care and provision of palliative sedation (57.75 percent) were considered the main indications for an inpatient palliative medicine unit admission. A majority (66.89 percent) agreed that the duration of inpatient stay should be defined by the stage of the illness. 48.9 percent agreed that pulse oximetry should be available for all inpatients. Acute kidney injury and dyselectrolytemia were considered valid indications for an ICU admission. 36.9 percent felt that use of non-invasive ventilation strategies, antibiotic stewardship, management of sepsis and dyselectrolytemia should be duties of a palliative medicine professional in the ICU. 48.3 percent, 65.31 percent and 50.34 percent of individuals reported that the timing of intervention, healthcare professional involved and subset of patients involved were the differences between supportive oncology and palliative medicine.

Table: 1765P Purview of early palliative medicine

1.	Management of complex psychiatric symptoms	34.87 %
2.	Management of chemotherapy related complications	40.79 %
3.	Counselling regarding goals of care	80.92 %
4.	Assessment of quality of life	73.68 %
5.	Interventional pain management techniques	50.66 %

Conclusions: There is an overlap in nature of supportive medicine services provided by a medical oncology and palliative/supportive medicine team. A practical, cost effective and resource intensive solution lies in building a workforce of health care professionals from palliative/supportive medicine who are well trained in supportive oncology. Inpatient admission is integral to sustain a cost effective model of delivery of supportive medicine services, however a consensus on the guidelines which govern the establishment and functioning of such a unit need to be developed.

Legal entity responsible for the study: Rahul D. Arora.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1766P Sexual functioning and depression among Egyptian breast cancer patients following surgery and neoadjuvant/adjuvant chemotherapy

S.A. Al Hassanin[1], S. Alsirafy[2]

[1]Clinical Oncology Department, Faculty of Medicine, Menoufia University, Shebin El Kom, Egypt, [2]Palliative Medicine Unit, Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt

Background: Breast cancer and its treatment may have a negative impact of the sexual wellbeing of patients and psychological morbidity may further add to this impact. Little is known about the sexuality of Egyptian patients with breast cancer. This may be due to barriers related to health care professionals, patients and their families and the culture. Aim: To evaluate sexual functioning among Egyptian breast cancer patients following treatment and to determine the relation between their sexual wellbeing and anxiety and depression and other possible factors.

Methods: This prospective cross-sectional observational study included married breast cancer patient from 20 to 50 years of age who underwent surgery and received neoadjuvant/adjuvant chemotherapy. The Female Sexual Function Index (FSFI) was used to assess their sexual wellbeing. FSFI total score cutoff value of 26.55 was used to determine sexual dysfunction. The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression. In addition, demographic and clinical data were collected.

Results: Thirty-six out of 38 patients (94.7%) invited to participate in the study signed an informed consent and completed the FSFI questionnaire. The mean FSFI total score was 23.1 ± 7.4 and 61% of patients had sexual dysfunction. The HADS depression scale was >7 (borderline-abnormal/abnormal) in 12 (33%) patients and the HADS anxiety scale was >7 in 25 (69%). Patients with borderline-abnormal/abnormal HADS depression score had a significantly lower FSFI total score compared to those with normal HADS depression score (20 vs. 25, respectively; $p = 0.029$). The HADS anxiety score did not correlate significantly with the FSFI scores.

Conclusions: Unlike the common belief, the majority of Egyptian female breast cancer patients included in this study was willing to discuss their sexual wellbeing. The results suggest that a significant proportion of Egyptian patients who completed treatment for breast cancer experience sexual dysfunction and psychological morbidity and that sexual dysfunction correlate significantly with depression among them.

Legal entity responsible for the study: Clinical Oncology Department, Faculty of Medicine, Menoufia University, Shebin Elkom, Egypt.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1767P Supportive care: Patient expectations, availability and uptake

H. Simon[1], J. Viguier[1], G.M. Ganem[1], C. Touboul[1], C. Lhomel[1], H. Naman[1], J.F. Morère[1], F. Eisinger[1],

[1]Medical Oncology, CHRU Brest Hôpital Morvan, Brest, France, [2]Medical Oncology, CHRU Bretonneau, Tours, France, [3]Medical Oncology, Clinique Victor Hugo, Le Mans, France, [4]Statistics, Kantar Health, Paris, France, [5]Medical, Roche, Boulogne-Billancourt, France, [6]Oncology, Centre Azuréen Cancérologie, Mougins, France, [7]Oncology, Hôpital Paul Brousse, Villejuif, France, [8]Département d'Anticipation et de Suivi du Cancer DASC, Institute Paoli Calmettes, Marseille, France

Background: Integrative oncology uses complementary approaches alongside conventional medical therapy to improve quality of life, improve outcomes and reduce the risk of recurrence. The Calista2 survey sought to identify, understand, and rank cancer patients' expectations and utilization of supportive care and activities. Accessibility of such supportive care was also assessed.

Methods: The 82 physicians who accepted to take part in the survey recruited 666 patients. Inclusion criteria were: patients already on specific therapy for breast cancer (BC), colorectal cancer (CC) or lung cancer (LC). Patient questionnaires were self-reported. Questions covered drug management of pain, fatigue, adverse effects of treatments (AE), and sleep disorders, social and psychological support, physical activities, and complementary and alternative medicines. Questionnaires were collected between September 2016 and October 2017. This analysis focuses on the patients' expectations, the supportive care or activity made available to patients, and how they were used.

Results: After exclusion of non-valid patient questionnaires, 467 were analyzed. All cancer localizations combined, patients rated the medical management of adverse events (AE) and pain as highly important (>7/10). Of the 18 items considered, physical activity and management of fatigue were rated as moderately important (5-7/10). The different types of supportive care or activity provided included predominantly the management of adverse events (AE, 81%) and pain (72%), psychological support (56%), and diet/nutrition (49%). Patients primarily used drug management of AE (72%) and pain (61%), diet/nutrition (34%), and self-image improvement techniques (31%). There is a lack of availability of complementary medicine, fatigue management, and relaxation techniques according to 28%, 27% and 24% of patients, respectively.

Conclusions: In our sample, the complementary approaches currently available practically satisfied patient requirements with regards to management of AE and pain. However, these findings also highlight the need for greater access to fatigue management, complementary medicine, and relaxation techniques.

Editorial acknowledgement: Medical writing assistance was provided by Potentiel d'Action (France).

Legal entity responsible for the study: Kantar Health.

Funding: Roche.

Disclosure: H. Simon, G.M. Ganem, H. Naman, J.F. Morère, F. Eisinger: Honorarium: Roche. C. Lhomel: Employee: Roche. All other authors have declared no conflicts of interest.

1768P Novel approach for counselling of young cancer patients

U., Seifart[1], T. Langer[2], I-K. Na[3], J. Schulze[4], M.R.F. Freund[4]

[1]Rehabilitation, Clinic Sonnenblick, Marburg, Germany, [2]Department for Pediatric Oncology and Hematology, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany, [3]Medical Department, Division of Hematology, Oncology and Tumor Immunology, Charité – University Hospital Berlin, Berlin, Germany, [4]Project Young Cancer Portal, German Foundation for Young Adults with Cancer, Berlin, Germany

Background: About 80% of cancer patients between the age of 18 to 39 survive their disease. They have to cope with different problems than children or older adults. They suffer from short- and long-term social burden as well as from physical disorders associated with the disease or cancer treatment. The objective of this project is to consult patients on options for social support to avert financial problems and to provide medical help to reduce disease- or therapy-associated disorders. The consultation takes place in collaboration with the attending physicians.

Methods: The Young Cancer Portal of the German Foundation for Young Adults with Cancer is a nation-wide, open-access service for young patients. The advisory process rests on an independent softwaredatabase. Patients are initially asked to register with their personal information and to raise their first questions. A questionnaire captures their current situation regarding the disease status and daily life. Expert advice is given in writing, by phone, or in person by a regionally assigned oncologist with extra training. In addition, a special access offers the exchange of expertise of for medical professionals. The protected database allows an anonymous collection and systematic analysis of the data by the foundation.

Results: The module for social law questions started on Nov 24, 2015, the module for endocrinological ques-tions on Sep 22, 2016, and the module on immune defects in Aug 2017. Thus far, 495 people have registered and 345 patients have been advised. Female patients represent 72% of the pool, male patients 28%. The average median age is 30.5 years (ranges from 18 to 52).

Conclusions: The Young Cancer Portal is unique throughout Germany and offers a new way for expert-patient-communication with high acceptance by long-term survivors. The portals basic structure is appropriate for a enables the modular addition of topics. Modules for long-term effects and integrative oncology will be established.

Legal entity responsible for the study: German Foundation for Young Adults with Cancer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1769P Health-related quality of life priorities in adolescents and young adults (AYA) with cancer: Discrepancies with health care professionals' perceptions

S.E.J. Kaal[1], J.B. Prins[2], R. Jansen[1], E. Manten-Horst[3], P. Servaes[2], W.T.A. van der Graaf[4], O. Husson[4]

[1]Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [2]Medical Psychology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [3]Dutch AYA Young & Cancer Platform, IKNL, Utrecht, Netherlands, [4]Division of Clinical Studies, Royal Marsden Hospital Institute of Cancer Research, Sutton, UK

Background: Health-related quality of life (HRQoL) measurement among adolescents and young adults (AYA) with cancer is instrumental to identify areas of need and to organize age-specific psychosocial care. Health care professionals (HCP) are not always aware of what matters most to patients. The aims of the current study were to determine top 10 HRQoL priorities relevant to AYA cancer patients and HCP and to determine discrepancies between items prioritized by AYA and HCP.

Methods: Patients aged 18 to 35 years at time of cancer diagnosis and who had been seen by one of the members of the multidisciplinary AYA team of Radboud university medical center in the Netherlands, and Dutch HCP involved in AYA oncology were invited to complete the Quality of Life for Cancer Survivors questionnaire.

Results: 83 AYA cancer patients and 34 HCP completed the questionnaire. Patients scored significantly lower on negatively formulated HRQoL issues (e.g. fatigue, coping difficulties, feeling isolated) and significantly higher on positive formulated issues (e.g. support from others, overall physical health, happiness). Most important HRQoL items scored by AYA patients were: perceived support from others, distress about initial cancer diagnosis, distress for family, overall quality of life and happiness. HCP perceived distress about initial cancer diagnosis, distress for family, cancer treatment distress, interference of illness with employment/study and fatigue as most important HRQoL items. Patients and HCP had a congruence on 5 out of 10 HRQoL items where distress about initial cancer diagnosis, distress for family and cancer treatment distress were the main overlapping issues. There was a incongruence on fatigue, sexuality and concerns about fertility as these items only appeared in the top 10 HRQoL items rated by HCP and not in the top 10 for AYA patients.

Conclusions: AYA cancer patients perceived most HRQoL items as less problematic in comparison to HCP, in particular regarding physical symptoms, psychological and social HRQoL issues. The discrepancy between patients and HCP illustrates the importance of patient participation, i.e. involving patients in organizing and prioritizing their own (psychosocial) care.

Legal entity responsible for the study: Radboud University Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1770P What information and features do young and older adults with cancer want in their hospital-based social media cancer resource?

C.B. Paulo[1], L. Eng[1], L. Mitchell[2], I. Geist[1], S. Kassirian[1], A. Magony[1], E.C. Smith[1], C. Brown[1], M. Liang[1], K. Hueniken[1], D. Yang[1], W. Xu[1], G. Liu[1], A. Gupta[3], J. Bender[4]

[1]Department of Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, ON, Canada, [2]Adolescent and Young Adult Program, Hospital for Sick Children, Toronto, ON, Canada, [3]Department of Hematology and Oncology, Hospital for Sick Children, Toronto, ON, Canada, [4]Department of Epidemiology, Dalla Lana School of Public Health, Toronto, ON, Canada

Background: Social media is increasingly used by patients for cancer information and psychosocial support. Certain information/features may be more desired in a new hospital-based social media cancer resource; these may vary between adolescent-young adult (AYA; age <40) and non-AYA (age 40+).

Methods: Using age specific sampling, cancer patients across all disease sites completed a cross-sectional survey of demographics, health status, and social media/online resource use for cancer education. Clinical information was abstracted.

Results: Of 127 AYA cancer patients and 193 non-AYA (older adult) patients, 100% (AYA) and 92% (non-AYA) stated they use the internet ($p < 0.001$); 95% AYA and 72% non-AYA used social media ($p < 0.001$). When asked about attitudes towards social media, 64% AYA and 50% non-AYA believed they could judge social media information quality; 18% AYA and 18% non-AYA recommended use of current social media resources. When asked what types of features they would want in an online resource for their cancer care, both AYA and non-AYA most frequently reported wanting to view their own personal health records (82% AYA/63% non-AYA), followed by an online library of cancer resources (73% AYA/56% non-AYA), ability to communicate with healthcare professionals (73% AYA/55% non-AYA), and appointment reminders (72% AYA/58% non-AYA). The most frequently desired information for both groups were treatment options (61% AYA/56% non-AYA), causes/risk factors/symptoms (65% AYA/56% non-AYA), and prognosis/outcomes (52% AYA/46% non-AYA). The largest difference in information preference between the two age groups were in wellness programs (62% AYA/39% non-AYA) and work return (42% AYA/20% non-AYA) ($p < 0.001$).

Conclusions: There is significant agreement between AYA and non-AYA patients in the most desired information and features they want in a social media resource, though AYA patients wanted a greater number of features. Patients' desired information suggested a patient preference for more autonomy and insight into their disease, regardless of age. There is a lack of satisfaction with current social media resources. A single set of informational tools can therefore be developed for all adults.

Legal entity responsible for the study: Princess Margaret Hospital, University Health Network.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1771P Hypothyroidism in cancer patients received multikinase inhibitors: Risk factors and outcomes

S. Hansuranant[1], H. Nimitphong[2], O. Pattanaprateep[3], R. Phraewphiphat[4], D. Muntham[5], T. Reungwetwattana[1]

[1]Medical Oncology, Ramathibodi Hospital, Bangkok, Thailand, [2]Endocrinology, Ramathibodi Hospital, Bangkok, Thailand, [3]Section for Clinical Epidemiology and Biostatistics, Ramathibodi Hospital, Bangkok, Thailand, [4]Section for Data Health for Informatics Section, Ramathibodi Hospital, Bangkok, Thailand, [5]Department of Mathematic, Rajamangala University of Technology Suvarnabhumi, Nonthaburi, Thailand

Background: Hypothyroidism was a known and common side effect from multikinase inhibitors notably in sunitinib, pazopanib and sorafenib. The goal of this study was to explore risk factors in developing hypothyroid and whether the occurrence of this endocrine adverse event (AE) leading to better survival outcomes.

Methods: Seventy-one renal cell carcinoma (RCC) patients and 136 hepatocellular carcinoma (HCC) patients were retrospectively analyzed. Data relating to the treatment course and development of hypothyroid were collected, extracted and presented in separate cohort.

Results: The incidence of hypothyroidism was 47.8% in RCC patients treated with either sunitinib or pazopanib. For HCC patients whom received sorafenib, the incidence of hypothyroidism was 31.8%. We found no factor significantly associated with hypothyroidism in RCC patients. HCC patients whom had duration of treatment of less than 3 months tend to develop hypothyroidism. There was no significant association between the development of hypothyroid and PFS or OS in RCC patients. In HCC group, euthyroid patients had statistically significant longer mPFS [7.6 vs. 2.2 months; HR = 6.38; 95%CI 1.87-21.8; $p = 0.003$] and mOS (16.9 vs. 5.2 months; HR = 22.96; 95%CI 4.45-118; $p = 0.<001$) than the hypothyroid group.

Conclusions: Hypothyroid is the most common endocrine AE of multikinase inhibitors. There are no significant clinical factors associated with the development of hypothyroid. This AE might serve as a good predictive marker for multikinase inhibitors treatment in HCC patients and their survival outcomes. The larger cohort is needed to confirm this evidence.

Legal entity responsible for the study: Faculty of Medicine Ramathibodi Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1772P Immune related adverse events across cancer types: Incidence, risk factors and survival

D.H. Owen[1], J. Burkart[1], S. Patel[1], L. Wei[2], G. Tinoco[1], D. Liebner[1], K. He[1], P.G. Shields[1], E.M. Bertino[1], C.J. Presley[1], A. Johns[1], E. Folefac[1], T. Olencki[1], D.P. Carbone[1], C. Verschraegen[1], G.A. Otterson[1], K.L. Kendra[1]

[1]Division of Medical Oncology, Department of Internal Medicine, The Ohio State University James Cancer Hospital, Columbus, OH, USA, [2]Center for Biostatistics, The Ohio State University James Cancer Hospital, Columbus, OH, USA

Background: Immune checkpoint inhibitors (ICI) have transformed oncology practice, however serious immune-related adverse events (irAE) occur and are poorly understood. A correlation between irAE and clinical benefit has been suggested in melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The incidence of irAEs has been described in clinical trials but risks factors remain undefined. This study reports the incidence and risks factors of irAE in patients (pts) with multiple cancers treated with any ICI, as well as overall survival.

Methods: A retrospective study of pts with any malignancy treated with ICI (alone or in combination) between January 2010 and June 2017 was carried out at The Ohio State University. Grade >= 2 irAEs were abstracted based on the treating physician diagnosis. Overall survival (OS) was calculated from the date of initiation of ICI to death from any cause or date of last follow-up. The associations between irAE incidence

and categorical outcomes were studied using chi-square or Fisher's exact test. The Wilcoxon test was used for continuous outcomes. Survival outcomes were studied using log-rank test or cox regression model.

Results: Of 1,113 pts identified, 417 pts had complete irAE data: 156 pts with melanoma, 117 pts with NSCLC, 33 pts with RCC, and 111 pts with other cancers. irAEs occurred in 120/417 pts (28.78%). Gender, age at treatment, and smoking history were not associated with irAE. Incidence of pneumonitis and colitis were 3.84% and 6%, respectively. Pneumonitis was more common in NSCLC ($p = 0.004$), and colitis was more common in melanoma ($p = 0.016$). Rates of thyroid, hepatic, and neurologic irAE were 5.29%, 4.08%, and 0.84%. irAEs were associated with length of therapy ($p = 0.021$), and were more common in 29 pts treated with combination ICI ($p < 0.001$). For 366 pts with metastatic disease, irAEs were associated with longer survival: median OS 21.1 months vs 9.2 months (HR = 0.48, 95% CI: 0.35 - 0.66, $p < 0.001$). Thyroid toxicity (HR = 0.25, 95% CI: 0.10 – 0.29, $p = 0.002$) and hepatitis (HR = 0.32, 95% CI: 0.12 – 0.85, $p = 0.023$) were associated with longer OS.

Conclusions: Increased awareness of irAE patterns across different cancer and treatment types will allow for rapid identification and treatment of irAE.

Legal entity responsible for the study: The Ohio State University.

Funding: Has not received any funding.

Disclosure: G. Tinoco: Advisory board: Blueprint. E.M. Bertino: Advisory board: Takeda, Boehringer Ingelheim. D.P. Carbone: Research funding: BMS; Paid advisory boards: Merck, BMS, AZ, Genentech. All other authors have declared no conflicts of interest.

1773P Effect of yoga on chemo-radiotherapy induced diabetes and hypertension (CRID-H) among cervical cancer patients at a regional cancer institute in south India

N.K. Nelson[1], I.A. Khaleel[1], M. ROY[2], H.B. Govardhan[2], N. Jasti[2], S. Suresh[2], R. Kashyap[2], L. Lokanath[2]

[1]Radiation Oncology, Kidwai Cancer Institute, Bangalore, India, [2]Radiation Oncology, Kidwai Memorial Institute of Oncology, Bangalore, India

Background: Prior studies suggest the benefits of yoga in maintaining Diabetes and Hypertension. In this study we aim to evaluate the effect of yoga on Chemo-Radiotherapy induced Diabetes and Hypertension (CRID-H) in cervical cancer patients.

Methods: 60 cervical cancer subjects (stage II - IV) undergoing chemo-radiation therapy were randomized into yoga ($n = 30$) and control group ($n = 30$). Yoga group was given loosening, breathing, chanting and meditation for 5 days/ week for 6 weeks. Weekly assessment of Random Blood Sugar and blood pressure was recorded from baseline to discharge. Appropriate statistical analysis was conducted.

Results: 6 yoga and 6 non-yoga patients were found to be known case of hypertension and on medications. During the course of chemo-radiation 4 yoga and 6 non-yoga patients developed hypertension. The systolic pressure among the yoga group remained constant with a mean difference of just 11.3mm of Hg while non-yoga group recorded 37.2mm of Hg Comparative analysis between the two groups show Systolic BP attained significance of $p = 0.3$ and Diastolic BP, $p = 0.11$. Diastolic BP in non-hypertensive patients of yoga group ($p = 0.01$) achieved good significance while hypertensive patients ($p = 0.14$) and all patients ($p = 0.11$) the results incline towards significance. Thus, yoga is effective to maintain BP among non-hypertensive patients and attain moderate control in hypertensive ones. RBS data reveals 5 yoga and 6 non-yoga subjects had pre-existing diabetes. 4 yoga and 6 non-yoga subjects developed diabetes with chemo-radiation by the 3rd week of treatment. Good significance was achieved between the two groups as a whole ($p = 0.02$). The difference was highly significant at $p = 0.009$ among pre-existing diabetic patients.

Conclusions: Adjuvant yoga therapy helps to control CRID-H in cervical cancer efficiently. The control achieved in RBS is highly significant. Considerable effect in hypertension was also observed. The above direction can be employed in future studies with larger sample size. Acknowledgement- Ministry of AYUSH, Government of India.

Legal entity responsible for the study: Ministry of Ayush, Government of India.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1774P Fatigue prevalence and adherence to treatment: A real-world data survey and mathematical model application

D.A. Vorobiof, E. Malki, I. Deutsch, M. Bivasbenita

Medical Oncology, Sandton Oncology Centre, Sandton, South Africa

Background: Fatigue is a common symptom reported by cancer patients (pts) and has been previously documented to affect patient's quality of life.

Methods: A real-world data survey was designed to evaluate, from the pts perspective, the fatigue effect and treatment adherenceA survey was created in a digital format. This was sent randomly and replied anonymously by users of the Belong app a dedicated social network for cancer pts and their caregivers. Belong leveraged both push notifications as well as DPROs (Digital patients reported outcome feature) which appeared on user's apps dashboards for their increased engagement.

Results: 505 replies were received from pts (85%) and caregivers (15%). The data was then extracted from the digital platform and analysed. A statistical mathematical predictive model was utilized. A machine learning analytical model was programmed to obtain the results. The most common diagnoses were Breast Cancer (all stages, 34.5%), lung (10.1%) and colorectal cancer (7.7%). 67.1% of the pts were on active treatment at the time of the survey and 11.5% finished the treatment less than 6 months before. 66% of the pts experienced daily fatigue (described as mild, moderate and severe) and 17.2% experienced it weekly. As a direct result of fatigue, 10.1% of all pts reported that their ongoing treatments were delayed, stopped or changed (poor adherence). 137 (27%) of the total number of replies (mainly advanced breast and lung cancers pts) reported severe fatigue and 19% of them confirmed poor treatment adherence. However, better adherence was seen in the subgroup of pts which experienced mild to moderate fatigue.

Conclusions: This survey describes the prevalence and adverse impact of severe fatigue present in certain cancer pts subgroups (advanced breast and lung cancers) which can alter significantly their adherence to planned treatments. Uniquely, while poor treatment adherence was observed in some cancer diagnosis, most of patients who experienced mild to moderate fatigue maintained their treatment schedule. Effective strategies and efforts should aim to solve this common side effect and its deleterious consequences.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1775P A survey on attitude towards euthanasia among delegates of a national conference on supportive medicine

R.D. Arora

Palliative Medicine, All India Institute of Medical Sciences, New Delhi, India

Background: There is a widespread belief that Euthanasia and good palliative medicine are mutually exclusive. It is important to explore whether the philosophy of palliative medicine which lays an emphasis on a good death also recognizes the individual's right to seek death as a means to end suffering.

Methods: A survey exploring the attitude and opinion of respondents on the extent of involvement of Palliative/Supportive medicine professionals in the provision of Euthanasia was conducted among the registered delegates of Indian association of Palliative Care conference 2018.

Results: 55.66 percent (85/153) of the respondents agreed that the debate on Euthanasia was within the purview of Palliative Medicine, while 52.71 percent (78/148) agreed that the provision of Euthanasia was within End of Life care. 61.27 percent (87/152) of the respondents believe that a set of multidisciplinary experts should be introduced to initiate the discussion on Euthanasia in a terminally ill patient when the same is expressly demanded by the patient or family members. A majority (37.68 percent - 52/138) disagreed with the use of the terms Passive and Active euthanasia. A majority of the respondents (51.74 percent - 74/143) also strongly disagreed with the use of the term physician assisted suicide. 42.46 percent (62/146) of the individuals agreed that the right to a good death and Euthanasia were mutually exclusive. 40.13 percent (61/152) agreed that they do not recognize the right to Euthanasia.

Conclusions: The right to seek Euthanasia as a means of a respectable death is a debatable subject which should be approached carefully keeping in mind the distinct socio-politicocultural thread which runs through the moral fiber of each society. The involvement of experts from multiple subspecialities (as suggested by the highest court of law in India) while ignoring the pivotal role of the palliative medicine professional in establishing a framework of guidelines surrounding Euthanasia does not seem to be justified. The importance of having the tenets of law firmly on their side should not be underestimated by Palliative/supportive medicine professionals who are bound by duty to take the lead in the discourse surrounding End of life care.

Legal entity responsible for the study: Rahul D. Arora.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1776P Acute toxicity of concurrent radiochemotherapy for locally advanced head and neck cancer: A prospective study

E. Dewaele[1], P.J. van Dam[2], B. De Laere[2], C. Verschueren[3], P.M.C. Specenier[3]

[1]Oncology, Sint Trudo Ziekenhuis, Sint-Truiden, Belgium, [2]Oncology, University of Antwerp, CORE, Antwerp, Belgium, [3]Oncology, Antwerp University Hospital, Edegem, Belgium

Background: Concurrent chemoradiation (CCRT) is the standard treatment for patients with inoperable locoregionally advanced squamous cell carcinoma of the head and neck (HNSCC). CCRT can be associated with severe acute toxicity. Usually only the maximum grade of a limited selection of adverse events (AEs) is reported, without mentioning the evolution of toxicity over time. By the lack of the time factor, the global burden of toxicity experienced by the patient is not adequately reflected.

Methods: Adverse events (AEs) were prospectively scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 scoring system by 2 dedicated medical oncologists. AEs were evaluated at predefined time point from the start of CCRT up to 21 weeks after the start of CCRT. The cumulative toxicity load was measured by calculating the area under the curve (AUC) from AE score versus time functions. The AUC for each AE was obtained by multiplying the time and grade of each AE during that time. Mean AUC's per patient category (i.e. HPV status, tobacco use, localisation of primary tumour and the use of ICT) were compared by Kruskal-Wallis testing.

Results: Forty patients (31 men), mean age 62.15 years, were included. The primary tumour site was located in 42.5% at the oropharynx and 45% were p16-positive. The AEs, with exception of xerostomia, typically developed in the second and third week of CCRT, with the intensity and frequency increasing during the treatment. Two weeks after ending CCRT (week 9), the side effects decreased. AEs were recorded in 85% (radiation dermatitis), 97% (orofacial pain), 89.7% (stomatitis), and 97.5% (anorexia) of patients. Significant different mean AUCs were seen for hoarseness (non-oropharynx group, $p = 0.027$), alopecia (the use of ICT, $p = 0.00014$), sensory PNP (the use of ICT, $p = 0.00016$), diarrhea (the use of ICT, $p = 0.021$), nausea (p16 positive, $p = 0.047$), and hoarseness (p16 negative, $p = 0.015$). For tobacco use no significant differences were seen.

Conclusions: This prospective trial recorded the maximum intensity and frequency of the different AEs, but also the evolution over time and the global AE load. More prospective trials with a larger number of patients are required to confirm the results.

Legal entity responsible for the study: University Hospital Antwerp.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1778P Chemotherapy effect on daytime sleepiness and contributing factors in older adults with cancer

S. Sadighi[1], B. Saberzadeh-Ardestani[2], B. Khosravi[2], J. Zebardast[2]

[1]Medical Oncology, Cancer Research Centre of Cancer Institute of Iran, Teheran, Iran, [2]Medicine, Tehran University of Medical Sciences, Tehran, Iran

Background: Excessive daytime sleepiness has been related with several functional and psychological disabilities. The objective of this study was to determine the prevalence of excessive daytime sleepiness (EDS) among older Iranian patients with cancer and to analyze the effect of chemotherapy treatment on patients' sleep problems. The relationship between sleep disturbances and physical activity, psychological factors, and demographic data were also explored.

Methods: This cross-sectional study, carried out in Cancer Institute of Iran, consisted of interviews with patients older than 60 years with a solid tumor; once prior to receiving chemotherapy and the second time after two cycles of chemotherapy. Questionnaires consisted of Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scales (HADS), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), and Eastern Cooperative Oncology Group performance status. Medical data were also gathered from hospital records. Logistic regression was used to identify predictors of excessive daytime sleepiness after chemotherapy.

Results: From the cases, 56.8% were female ($n = 42$). Mean participants' age was 68.26 ($SD = 6.77$) and 78.4% had advanced tumors. Bivariate analysis did not show any significant association between education, tumor stage, and the number of comorbidities and daytime sleepiness after receiving chemotherapy. The results showed a significant association between EDS and receiving chemotherapy. Initially EDS rate was reported as 8.1% which increased to 21.6% after chemotherapy ($P < 0.001$). Anxiety before chemotherapy and number of regions of recurrence, were identified as independent predictors of daytime sleepiness.

Conclusions: Given that, EDS prevalence increases with chemotherapy treatment, and this can affect patients' quality of life and treatment outcomes, caregivers should bear in mind that older patients with cancer, especially those with anxiety and cancer recurrence, need special attention before decision making over starting chemotherapy in order to prevent and manage EDS in the course of chemotherapy.

Clinical trial identification: Research Deputy of TUMS proposal number: 22704.

Legal entity responsible for the study: Research Deputy of TUMS.

Funding: Research Deputy of TUMS.

Disclosure: All authors have declared no conflicts of interest.

1779P Group pre-chemotherapy education: Improving patient experience through education and empowerment

K. McIntyre, R. Blackwood, V. Riley, L. Carballo, H. Plant, T. Marler-Hausen

Chemotherapy Daycare, University College Hospital London, London, UK

Background: Patients are not always adequately prepared to start chemotherapy. Information given may not be consistent and little education is given on how patients can be empowered to support themselves to manage side effects of treatment. A pre-chemotherapy education session delivered in a group setting was developed to improve and standardise the information given to patients prior to starting treatment and to reduce the amount of time delivering one to one pre-chemotherapy sessions.

Methods: The project was led by senior cancer nurses who identified four themes that became the focus of the education session; safety, patient experience, process and patient empowerment. The education session was piloted for gynaecology patients before expanding to all new referrals. We collected both qualitative and quantitative data pre and post the sessions using a 0-10 rating scale to evaluate how informed, how worried and how confident patients felt about their prospective treatment.

Results: Since April 2017 we have had a total of 211 attendees, inc relatives which is approx 25% of new patient referrals to Chemotherapy Daycare. When asked about how informed patients felt about their treatment plan they had an average score of 6.7[SD2.5] before the session, increasing by 28% to 8.6[SD1.6] afterwards. When asked about how worried patients felt about their treatment they had an average score of 6.3[SD2.7], decreasing by 19% to 5.1[SD2.8] afterwards. When asked how confident patients felt, they had an average score of 6[SD2.4], increasing by 16% to 7[SD2.3] afterwards. Analysis of the qualitative data showed positive feedback but also highlighted problems with patients understanding the process to treatment.

Conclusions: The education session is a useful way of providing information to patients and improves their confidence. Patients on average become less worried after attending the session although some patients felt more worried, likely to be because they were confronted with the reality of their situation. The main challenges were to engage the clinical teams as this was a change in practice. In response to concerns around travelling distance and numerous appointments we are developing a patient education video for patients to watch at their convenience.

Legal entity responsible for the study: Tom Marler-Hausen.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1780P Clinical and psychometric validation of the BreSAS questionnaire for symptom assessment among breast cancer survivors

R. Giusti[1], E. Scarpi[2], K. Cannita[3], R.R. Silva[4], M. Filetti[1], M. Mazzotta[1], R. Rossi[5], V. Cocciolone[3], T. Sidoni[3], M. Tudini[4], C. Ficorella[3], A. Botticelli[1], P. Marchetti[1], G. Porzio[3], L. Verna[3]

[1]Medical Oncology Unit, Azienda Ospedaliero Universitaria Sant' Andrea, Rome, Italy, [2]Biostatistics and Clinical Trials Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [3]Medical Oncology Unit, S. Salvatore Hospital, University of L'Aquila, L'Aquila, Italy, [4]Medical Oncology Unit, Ospedale E. Profili U.O. Oncologia Medica, Fabriano, Italy, [5]Palliative Care Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

Background: Today a large number of breast cancer (BC) patients survive many years post diagnosis. The large number of women surviving many years post BC diagnosis has heightened interest in studying long-term effects of cancer on quality of life. A number of cancer-specific health-related quality of life (QoL) measures have been developed but these measures may not be appropriate for use with long-term survivors. With this study we want to evaluate the reliability, clinical and psychometric validity of the BreSAS Questionnaire (BQ) among BC survivors.

Methods: The BQ is a quick, simple 10 items module for the assessment of long-term physical, psychological, sexual and cognitive effects that may influence quality of life (pain, anxiety, depression, fatigue, irritability, quality of sleep, impaired concentration, hot flashes, vaginal itching, other). The total BreSAS score ranks from 0-100, with a low score indicating a better QoL. Patients were not stratified into predetermined clinically distinct groups. QoL data were collected alongside standard outcomes in patients undergoing treatment for BC. Patients complete the BQ, the FACT-ES questionnaire, case report forms for clinical and socio-demographic data at different time points during follow up visits. Reliability, and clinical and psychometric validity of the questionnaires are assessed by correlation analyses, exploration of known group comparisons, and responsiveness to clinical changes.

Results: From September 2015 to February 2016, 149 patients from three Italian oncology units were enrolled. Baseline questionnaires were returned from all and the majority of patients ($n = 134$ - 89%) completed the BQ and FACT-ES in less than 15 min. For reliability, Cronbach's alpha coefficients for each scale were greater than 0.70 in all analyzed symptoms. Convergent validity of BQ showed by Pearson's r demonstrated a high correlation between intensity of symptoms and QoL, especially for pain and depression. No data were provided about reproducibility with test-retest study.

Conclusions: The BQ demonstrates sufficient validity and reliability to support its use to assess patient-reported outcomes and symptom assessment during planned follow-up clinical visits among BC survivors.

Legal entity responsible for the study: Giampiero Porzio.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1781P Association of phase angle and chemotherapy toxicity among Mexican patients with non-metastatic breast cancer

M.T. Nieto Coronel[1], C.H. Arce- Salinas[2], A. Peña-Ruiz[2], M.A. Espinoza Cuevas[3], J. Santamaria-Galicia[2]

[1]Medical Oncology, Hospital de Clinicas Universitario, La Paz, Bolivia, [2]Medical Oncology, Instituto Nacional de Cancerologia, Mexico City, Mexico, [3]Nutrition, Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, Mexico City, Mexico

Background: Chemotherapy is the cornerstone of the treatment of patients with non-metastatic breast cancer; however, its toxicity may be limiting. It has been reported that some degree of toxicity is present in 98% of patients. To date, no predictors of this toxicity have been identified. Bioimpedance and Phase Angle (PA) are non-invasive procedures to evaluate nutritional status. The aim of this study was to associate the PA with chemotherapy toxicity during (neo)adjuvant (neoCT) treatment of breast cancer.

Methods: 172 patients were prospectively evaluated, 31 were excluded because they had metastatic disease or had received endocrine therapy. Only chemotherapy candidates were enrolled, patient selection criteria were PS 0-1, adequate liver, hematologic and renal function tests. The chemotherapy regimen consisted in AC-T at standard doses and schedules +/- cisplatin in triple-negative tumors. Toxicity was evaluated per NCI CTC v4.0. In all patients bioimpedance by SECA mBCA 514 and Inbody 720 were registered. Statistical analysis was done with SPSS v20.0.

Results: 141 were analyzed, median age was 50 years old, 53.2% of them received neoCT and 46.8% adjuvant CT. Regarding comorbid status, 10.6% had diabetes, 14.0% had hypertension, most of the patients were obese or over weight, median BMI was 27.7kg/m^2 (13.79-39.84 kg/m^2), median waist circumference was 97.30cm (72-135 kg/m^2), overall metabolic syndrome per ATPIII criteria was found in 34.1% of all patients. 54.3% were diagnosed in early stage (I-IIb), 24.2% were HER2-positive, 46.8% were HR-positive and 29.1% were triple negative. Any grade of toxicity was present in 98.6%, 9.9% required hospitalization and in 2.1% toxicity led to death, most common side effects were gastrointestinal 85.8%, fatigue 70.9%, peripheral neuropathy 50.4% and hematologic 48.9%. PA average was 4.8° (2.8-6.26°). We found a correlation between PA and any grade of toxicity ($p = 0.022$). Patients with low PA had more G3-5 toxicity ($p = 0.045$). and more peripheral neuropathy ($p = 0.045$).

Conclusions: PA helps us to assess nutritional status and it seems to be useful as a toxicity predictor. However, external validation is necessary to confirm this benefit.

Legal entity responsible for the study: Maria Tereza Nieto Coronel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1782P Hepatitis screening for patients to undergo chemotherapy in Cyprus

P. Kountourakis, A. Agathocleous, E. Kakouri, Y. Marcou, G. Orphanos, F. Kyriacou, D. Papamichael, H.C. Charalambous

Medical Oncology, Bank of Cyprus Oncology Centre, Nicosia, Cyprus

Background: Cancer patients undergoing chemotherapy who have Hepatitis B (HBV) infection may be at elevated risk of liver failure from HBV reactivation, resulting in treatment interruptions/delays, hospitalization, even liver transplantation and death. There is conflicting guidance regarding screening for HBV infection, given that the US Center for Disease Control recommends universal screening for all patients receiving cytotoxic or immunosuppressive therapies, whilst ASCO suggests a selective approach.

Methods: A screening initiative was set up from November 2010, with the aim of identifying patients with chronic infection and referring them for chemoprophylaxis to prevent re-activation. Patients prior to receiving chemotherapy, were offered HBV and HCV testing after being given information leaflets explaining the rationale and implications. Testing included HBsAg surface antigen, HBcAb core antibody, and for those –ve HBsAg and +ve HBcAb, viral load for HBV was recommended. HCV Abs were also tested. Patients HBsAg +ve, or HBcAb +ve and detectable viral load were referred for consideration of antiviral therapy, as were patients with +ve HCV Abs. Patients with Hepatocellular cancer and known Hepatitis infections were excluded from this analysis.

Results: 1353 patients were screened between November 2010 and May 2015. With about 2.2% being positive for HBsAg, 14.8% for HBcAb and 1.2% for HepCAb, however with significant differences for gender and ethnicity. HepBcAb+ve: males 17.19% (99/576), females 12.78% (86/673). HepCAb +ve: Greek Cypriot 0.83% (9/1085), Turkish Cypriot 0% (0/49), Greeks 13.33% (2/15). Further data will be provided on the poster. In a sub-study for HepBcAb +ve but HepBsAg -ve, viral load was negative in 55 and positive in 3 patients. Of interest is that during this period two patients were diagnosed with Hepatitis re-activation, that were not part of this study; both patients had to stop chemotherapy and start anti-viral therapy.

Conclusions: This study confirms the low percentage of Hepatitis B and C infection in the Cyprus population, and that hepatitis re-activation although rare, is a real complication of chemotherapy. Patients born outside Cyprus have a higher incidence of HBV and HCV infections. The results are going to be used to set up local guidelines.

Legal entity responsible for the study: Haris C. Charalambous.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1783P Hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) screening prior to chemotherapy initiation among patients with solid tumors

S.H. Giordano[1], Z. Duan[2], H. Zhao[2], J. Hwang[3], M. Chavez MacGregor[1]

[1]Breast Medical Oncology, Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Internal Medicine Department, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: Cancer patients with HVB, HCV and HIV receiving systemic therapy are at risk of reactivation. It is relevant to determine the serologic status of patients at high risk. The CDC has broad screening recommendations for HBV, HCV and HIV. ASCO recommends HBV screening in patients with risk factors, before starting anti-CD20 therapy or stem-cell transplantation. In this population-based study we determine the rates of screening in a large cohort of elderly patients with solid tumors.

Methods: Patients with solid tumors (>66 yo) diagnosed between 2007-2013 and treated with systemic anticancer therapy were identified in the SEER-Medicare database. HBV, HCV and HIV testing was identified using HCPCS codes, the screening period was defined as testing within the first year of cancer diagnosis and no later than 30 days after the first dose of systemic anticancer therapy. Descriptive statistics and logistic regression were used.

Results: A total of 70,488 patients were included. The rates of HBV, HCV and HIV screening were 4.13%, 2.05% and 0.73%, respectively. The median time from cancer diagnosis to screening were 26, 24 and 22 days for HBV, HCV and HIV respectively. Screening rates varied according to cancer type. The highest HBV screening rates were in pancreas (18.9%), melanoma (4.7%) and prostate cancer (5.7%). For HCV, melanoma (7.6%), prostate (3.6%) and anal/penile/vagina/vulvar cancers (2.9%). For HIV, the highest rates were in patients with anal/penile/vagina/vulvar cancers (6.7%), melanoma (2.7%), cervix/endometrial cancers (1.5%). Screening rates increased over time, in addition, males, younger patients and those living in urban areas had higher screening rates (all $p < 0.001$). Asians had the highest screening rates of HBV and HCV while African Americans had the highest HIV screening rate.

Conclusions: HBV, HCV and HIV screening rates were very low among elderly cancer patients receiving systemic anticancer therapy. There was significant variability in the screening rates according to cancer site and patient characteristics. Guidance is needed to select patients that can benefit from screening in order to avoid potential complications.

Legal entity responsible for the study: Mariana Chavez MacGregor.

Funding: CIPRIT.

Disclosure: All authors have declared no conflicts of interest.

1784P Rapid identification of bloodstream infection pathogens

N.I. Panova[1], O.I. Kit[1], O.Y. Kutsevalova[1], I.B. Lysenko[1], V.V. Dmitrieva[1], D.A. Rozenko[1], Y.A. Gevorkyan[1], E.E. Pak[1], O.V. Kozyuk[1], E.A. Kapuza[1], O.N. Shatokhina[1], N.V. Nikolaeva[1], E.A. Kalabanova[1], I.S. Mitashok[1], L.Y. Vladimirova[1],

[1]Laboratory of Microbiology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [2]Department of Surgical Oncology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [3]Department of Hematology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [4]Department of Anesthesiology and Reanimation, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, Medical Department, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Background: Sepsis remains the leading cause of death in cancer patients. Biomarkers allow an objective and reliable possibility of rapid prediction of the septic process. The purpose of the study was to assess the prognostic significance of a rapid and accessible verification of the sepsis pathogens with biomarkers – procalcitonin and Platelia Candida Ag Plus

Methods: The study included 440 patients with clinical manifestations of the inflammatory response in intensive care units, oncological and oncohematological departments. Levels of procalcitonin and Platelia Candida Ag Plus were determined by ELISA together with the blood sterility testing using the BacT/ALERT 3D analyzer.

Results: The most common pathogens (78%) were bacteria (K. pneumoniae. E. coli, less often other members of the Enterobacteriaceae family, P. aeruginosa, A. baumannii, E. faecalis, E. Faecium, etc.); yeasts of Candida spp. – 22%; mixed pathogens – 7.5%, comprising 37.5% bacteria and 62.5% bacterial-fungal pathogens. Positive blood cultures were found in 106 (24.1%) patients. The results of a blood culture took on average 3 days. The use of two biomarkers allowed predicting a pathogen in the first hours after the blood collection. An increase in the levels of one biomarker in 137 (31.1%) patients with negative blood cultures indicated the presence of bacterial, fungal or bacterial-fungal infections. The blood culture examination together with determination of biomarkers improved verification of sepsis pathogens in 243 (55.2%) patients with clinical manifestations of sepsis and hastened preliminary results and empirical therapy.

Conclusions: The study of the blood culture and determination of levels of the biomarkers allowed the prediction of pathogens in 243 (55.2%) patients with clinical manifestations of sepsis. 197 (44.8%) patients with negative blood cultures and normal levels of biomarkers required additional tests.

Legal entity responsible for the study: Ministry of Health of the Russian Federation.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1785P Pathogens and characteristics of candidemia in hospitals of Rostov-on-Don: Multicenter study in Russia

O.Y. Kutsevalova[1], O.I. Kit[2], N.I. Panova[1], I.B. Lysenko[3], V.V. Dmitrieva[1], D.A. Rozenko[4], E.A. Kalabanova[5], I.S. Mitashok[5], G. Klyasova[6], Y.V. Shatokhin[7], I.V. Snezhko[7], D.V. Martynov[7], V.N. Malygin[7], O.V. Korosteleva[8], A.A. Matsuga[8], K.S. Aslanyan[9], L.Y. Vladimirova[5]

[1]Laboratory of Microbiology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [2]Department of Surgical Oncology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [3]Department of Hematology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [4]Department of Anesthesiology and Reanimation, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [5]Medical Department, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, [6]Hematology, National Research Center for Hematology, Moscow, Russian Federation, [7]Rostov State Medical University, Rostov-on-Don, Russian Federation, [8]Hospital, Rostov-on-Don, Russian Federation, [9]Rostov Regional Children's Hospital, Rostov-on-Don, Russian Federation

Background: Invasive candidiasis is a serious nosocomial infection developing generally in patients at risk; it is characterized by a severe clinical course and high (10-49%) additive mortality. It develops predominantly in immunocompromised, especially cancer, patients and patients in intensive care units. The purpose of the study was to analyze the etiology of invasive candidiasis and in vitro activity of caspofungin and azoles for isolates of Candida fungi.

Methods: Isolates were obtained in hospital departments in Rostov-on-Don and Rostov region in 2013-2016. Candida fungi were identified using MALDI-TOF MS; interpretation was performed according to CLSI 2012, M27-S4 criteria. Sensitivity testing was performed using the Sensititre system (Trek Diagnostic Systems, England).

Results: 92 Candida isolates were obtained from blood culture: C. albicans - 31.5% (29) and non-albicans - 68.5% (63), including C. tropicalis 30.2% (19), C. parapsilosis 28.6% (18), C. glabrata 19.0% (12), C. krusei 15.9% (10) and C. guilliermondii 6.3% (4). Fungal-bacterial associations were found in 5 cases; such combinations worsened the patient's condition and complicated the treatment. The table demonstrates comparative activities of caspofungin, fluconasole and voriconasole (susceptible – S, intermediate – I, resistant – R) in % to Candida spp.

Table: 1785P

Species	n	Caspofungin S/ I/ R (%)	Fluconazole S/ I/ R (%)	Voriconazole S/ I/ R (%)
C. albicans	29	100/ 0/ 0	82/ 3/ 15	90/ 6/ 4
C. parapsilosis	18	98/ 0/ 2	82/ 4/ 14	88/ 11/ 1
C. tropicalis	19	100/ 0/ 0	90/ 5/ 5	100/ 0/ 0
C. glabrata	12	95/ 5/ 0	86/ 9/ 5	N/A
C. krusei	10	83/ 4/ 13	N/A	100/ 0/ 0

Conclusions: Candida non albicans prevailed among invasive candidiasis pathogens (68.5%), which could be associated with the use of azole antifungal agents for the prophylaxis and empirical therapy. Dominating isolates showed decreased activity to caspofungin and azoles. Acquired resistance to azoles was noted for C. parapsilosis and C. albicans. Special attention should be paid to C. glabrata characterized by high lethality and high resistance rates. The results demonstrate the advisability of microbiological monitoring of invasive candidiasis pathogens.

Legal entity responsible for the study: Ministry of Health of the Russian Federation.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1786P Antiviral prophylaxis cannot reduce the risk of hepatitis B reactivation during chemotherapy for non-HCC solid tumor patients with lower HBV DNA titer: A retrospective cohort study

Q. Gin[1], A. Zhou[2], L. Yang[2], D. Zhong[3]

[1]Medical Oncology, Tianjin Medical University General Hospital, Tianjin, China, [2]Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [3]Medical Respiratory, Tianjin Medical University General Hospital, Tianjin, China

Background: The high-risk factors related to HBV reactivation during chemotherapy include lymphoma, hematopoietic stem cell transplantation (HSCT), treatment regimen containing rituximab, a high HBV viral load before chemotherapy and baseline prechemotherapy HBeAg positivity. However, the role of antiviral prophylaxis in preventing HBV reactivation in patients with non- hepatocellular carcinoma (HCC) solid tumor and lower HBV DNA titer is unclear.

Methods: Between January 2011 and March 2018, all HBsAg seropositive patients with solid tumor receiving cytotoxic chemotherapy were retrospectively evaluated. The titer of HBV DNA and liver function were routinely examined before chemotherapy. The patients whose titer of HBV DNA was under 100 IU/ml were eligible. HBV reactivation, hepatotoxicity and disruption of chemotherapy attributed to HBV reactivation were compared according to antiviral prophylaxis.

Results: Of 170 consecutive patients eligible for, 102 were treated without antiviral prophylaxis and 68 received antiviral prophylaxis. 55 patients were treated with entecavir, 7 for lamivudine and 6 for adefovir. The two groups were comparable in most clinical baseline characteristic including gender distribution, age, tumor types, tumor stage, the use of prednisone and/or anthracyclines. There was no significant difference between the two groups ($P = 0.587$). Patients without antiviral prophylaxis had a similar prevalence of HBV reactivation (6.8% vs 4.4%, $P = 0.741$) and severe hepatitis attributable to reactivation (4.9% vs 4.4%, $P = 0.882$). No patients died ultimately from fulminant hepatitis. Furthermore, no significant difference in disruption of chemotherapy was noted between patients with or without antiviral prophylaxis (3.9% vs 4.4%, $P = 0.875$).

Conclusions: For patients with non-HCC solid tumors and the titer of HBV DNA less than 100IU/ml before chemotherapy, antiviral prophylaxis failed to further reduce the reactivation of HBV. For such patients, regular monitoring of HBV viral load maybe more reasonable and cost-effective optimal choice.

Legal entity responsible for the study: Clinical Research Ethics Comittee of Tianjin Medical University General Hospital and National Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1787P Prospective observational study to evaluate the persistence of treatment with denosumab (dmab) in patients (pts) with bone metastases (BM) from solid tumors (ST) in routine clinical practice: Final analysis

F. Haslbauer[1], A.L. Petzer[2], M. Safanda[3], A. Tomova[4], M. Porubska[5], Z. Bajory[6], D. Niepel[7], C. Jäger[8], D. Kalinin[9], R. Greil[10]

[1]Oncology, Krankenhaus Voecklabruck, Voecklabruck, Austria, [2]Department of Internal Medicine I - Oncology, Hematology and Gastroenterology, Ordensklinikum Linz Barmherzige Schwestern/Elisabethinen, Linz, Austria, [3]Department of Clinical Oncology, Nemocnice Na Homolce, Prague, Czech Republic, [4]1st Internal Dept, Complex Cancer Center, Plovdiv, Bulgaria, [5]Department of Internal Medicine, St. Elisabeth Cancer Institute, Bratislava, Slovak Republic, [6]Department of Urology, University of Szeged, Szeged, Hungary, [7]Global Medical Affairs, Amgen (Europe) GmbH, Zug, Switzerland, [8]Medical Affairs, Amgen, Vienna, Austria, [9]Biostatistics, Quartesian, Kharkov, Ukraine, [10]Department of Internal Medicine III, Salzburger Landeskliniken - Universitätsklinikum Salzburg, Paracelsus Medizinische Privatuniversität, Salzburg Cancer Research Institute, Salzburg, Austria

Background: Persistence with dmab therapy may impact clinical efficacy in preventing skeletal-related events (SREs), but is undetermined in real-world.

Methods: Single-arm, prospective, observational, non-interventional study in pts with BM from ST (breast, prostate, lung, other) treated with dmab in real-world in Austria, Czech Republic, Hungary, Slovakia, and Bulgaria between 10/2012 and 05/2017. Primary objective: persistence at 24 weeks (wks) (=6 dmab subcutaneous injections; permissible intervals: 4±1 wks). Secondary objectives: persistence at 48 wks, time to non-persistence, calcium (Ca) / vitamin D supplementation, (serious) adverse drug reactions ([S]ADRs) incl. non-adjudicated osteonecrosis of the jaw (ONJ) rate.

Results: 598 patients were included, 451 completed 24 wks, 387 completed 48 wks of study, 211 discontinued before 48 wks due to death (n = 80), loss to follow-up (n = 35), informed consent withdrawal (n = 7), dmab discontinuation (n = 56, [S]ADRs [n = 5]), other reasons (n = 28). 10.9% (n = 65) had previous SREs. Persistence with dmab and safety are shown in the table. Persistence at 24/48 wks was 62.6/40.1% overall, 69.5/45.5% for breast, 69.3/46.6% for prostate, 26.1/10.9% for

lung, and 40.7/21.1% for other cancers. Median (IQR) duration of dmab exposure was 309 days (168.0, 319.0) and 11 doses (6.0, 12.0). The most frequent reason for non-persistence was the violation of one time window. Overall, analgesics use trended towards weaker analgesics over time, with ~60% of pts not requiring any analgesics. Serum Ca remained within the normal range of 2.2 to 2.7 mmol/L throughout the study. ~70% of pts received Ca and vitamin D supplements at baseline, increasing to ~80% at dose 2 and steadily decreasing thereafter.

Table: 1787P

	N = 598
Persistence, % (95% CI)	
At 24 wks	62.6 (58.4, 66.7)
At 48 wks	40.1 (35.9, 44.4)
KM-median (95% CI) time to non-persistence, days	274.0 (232.0, 316.0)
ADRs, n (%)	61 (10.2)
SADRs, n (%)	8 (1.3)
ONJ	3 (0.7)
Incidence of ONJ per pt-year (95% CI)	0.012 (0.004, 0.029)

Conclusions: Persistence (Diel, ESMO 2015) and ONJ rate (Stopeck, JCO 2010, Fizazi, Lancet 2011, Henry, JCO 2011) were comparable with previous reports.

Editorial acknowledgement: Margit Hemetsberger, Hemetsberger Medical Services, Vienna, Austria.

Legal entity responsible for the study: Amgen.

Funding: Amgen.

Disclosure: A.L. Petzer: Speakers honoraria, advisory board: Amgen. D. Niepel, C. Jäger: Employee, stocks: Amgen. R. Greil: Research grants: Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, BMS; Consulting fees: Celgene, Roche, BMS, Takeda, Abbie, AstraZeneca, Novartis. All other authors have declared no conflicts of interest.

1788P A multicenter retrospective investigation on the efficacy of perioperative oral management in cancer patients

S-I. Yamada[1], S. Soutome[2], T. Hasegawa[3], I. Toujou[4], H. Nakahara[5], M. Kawakami[6], M. Hirose[7], S. Fujita[4], T. Komori[3], T. Kirita[6], Y. Shibuya[7], M. Umeda[2], H. Kurita[1]

[1]Department of Dentistry and Oral Surgery, Shinshu University, School of Medicine, Matsumoto, Japan, [2]Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, [4]Department of Oral and Maxillofacial Surgery, Wakayama Medical University, Wakayama, Japan, [5]Department of Dentistry and Oral Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, [6]Department of Oral and Maxillofacial Surgery, Nara Medical University, Kashihara, Japan, [7]Department of Oral and Maxillofacial Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Background: Patients suffer from various oral complications in cancer treatments. Oral bacteria associate with the onset of dental focal infections and the progression of oral mucositis. Moreover, dental focal infections frequently associate with the onset of bacteremia, sepsis, and pneumonia systemically. The oral function degeneracy with these complications may become obstacle in cancer treatments. In Japan, the comprehensive oral management, including oral care and removal of dental focal infections, are performed in cancer patients. The aim of present study was to investigate the incidence of dental/oral complications in the cancer patients who underwent perioperative oral managements (POMs) based on large number of case series with a multicenter retrospective analysis.

Methods: In cancer patients who underwent POMs, medical records were reviewed and the incidence of oral complications and the efficacy of oral management were investigated retrospectively. This study protocol was approved by the Committee on Medical Research of Shinshu University (♯3639).

Results: Two thousand seven hundred and forty-four cancer patients underwent POMs (1,684 males and 1080 females, mean age 65.9±13.0 years) were investigated in this study. Among 2,744 patients, 2,097 patients (76.4%) started POMs before the initiation of cancer treatment, in which 2,130 patients (77.6%) underwent only oral care, and 391 patients (14.2%) invasive treatment such as tooth extraction. The incidence of dental focal infections during the period of cancer treatment was 8.2%. Acute periodontitis including alveolar abscess was most frequently seen (112 patients, 4.1%). The incidence of grade 2 and 3 oral mucositis was 2.8%. And the fever of unknown origin was seen in 113 patients (4.1%). Among them, dental focal infections were proved to be associated in 7 cases (6.2%). These incidences were thought to be lower than those of previously reports.

Conclusions: The efficacy of oral management in cancer patients might be suggested based on the analysis of large number of patients in this study. However, the further investigation is needed to establish the adequate oral management guideline in cancer patients.

Legal entity responsible for the study: The Committee on Medical Research of Shinshu University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1790P Correlation between fatigue evaluated with a visual analog scale (VAS) and quality of life (QoL) in cancer patients treated with biosimilar epoetin alfa for chemotherapy-induced anemia (CIA): The CIROCO study

J. Desrame[1], J. Loup Mouysset[2], T. Altwegg[3], L. Zelek[4], N. Baize[5]

[1]Institut Privé de Cancérologie, Hôpital Privé Jean Mermoz, Lyon, France, [2]Department of Medical Oncology, Clinique Rambot Provençale, Aix-en-Provence, France, [3]Oncology, Institut de Cancérologie de Bourgogne, Dijon, France, [4]Oncology Department, Hôpital Avicenne, Bobigny, France, [5]Oncology, Centre Hospitalier Universitaire d'Angers, Angers, France

Background: Anemia often occurs in cancer patients receiving chemotherapy. QoL can be affected by symptoms of anemia, fatigue being the most common. Evaluation of QoL with validated tools (eg EORTC QLQ C30) is time-consuming. Correlation between fatigue assessed with a VAS and QoL is unclear. Aim: To determine the correlation between fatigue assessed by a VAS and QoL in cancer patients treated with biosimilar epoetin alfa (Sandoz) for CIA.

Methods: CIROCO is a non-interventional, prospective, multicenter study of adult patients (Full Analysis Set [FAS] population, n = 538) with ≥2 cycles of chemotherapy planned after study inclusion, with CIA and receiving biosimilar epoetin alfa. Data were collected on day of inclusion (T0), and after 2–3 (follow-up; T1) and 4–6 chemotherapy cycles (end of follow-up; T2). Patients and physicians separately assessed fatigue using a VAS (range 0–10); patients assessed QoL with the EORTC QLQ C30 questionnaire.

Results: Data are reported for a subgroup of patients with solid tumors (FAS population, n = 434). Mean (SD) hemoglobin (Hb) at baseline was 9.7 (±0.8) g/dL. Mean (SD) increase in Hb was 1.2 (±1.4) g/dL between T0 and T1 and 0.4 (±1.5) g/dL between T1 and T2. In the safety population (n = 464), 151 (32.5%) had adverse events (AEs; n = 320), 64 patients (13.8%) had serious AEs (n = 144) and 14 patients (3%) experienced AEs considered related to study treatment (n = 25). In the FAS population, between T0 and T2, mean (SD) change in fatigue VAS score (patient-reported) was +5.2 (±92.6) % and mean (SD) change in QoL was 29.9 (±98.0) %. The Pearson correlation coefficient for fatigue VAS score and QoL was –0.4993 ($p < 0.0001$) at T0, –0.5726 ($p < 0.0001$) at T1, and –0.5681 ($p < 0.0001$) at T2. Using fatigue VAS, physician assessment of fatigue was consistent with patient perceptions at T0 (5.0±2.1 vs 5.3±2.2), T1 (4.3±2.2 vs 4.8±2.3) and T2 (4.2±2.3 vs 4.7±2.3).

Conclusions: Biosimilar epoetin alfa was effective in this study, with improvements observed in Hb and QoL. A correlation was observed between reduced fatigue assessed with a VAS and improved QoL.

Editorial acknowledgement: Tony Reardon, Spirit Medical Communications Ltd.

Legal entity responsible for the study: Sandoz SAS.

Funding: Sandoz SAS.

Disclosure: N. Baize: Steering Committee member: CIROCO study. All other authors have declared no conflicts of interest.

1791P Quality of life, late effects, and related clinical factors among Korean colorectal cancer survivors

J.S. Park[1], T.I. Kim[2]

[1]Cancer Prevention Center, Yonsei Cancer Center, Yonsei University, Seoul, Republic of Korea, [2]Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

Background: Colorectal cancer (CRC) is one of the most common cancers worldwide, and the third most common cancer in Korea. Although the number of Korean CRC survivors is estimated over 220,000, we have insufficient survivorship care program to improve survival and quality of life (QoL) of CRC survivors.

Methods: We started to build a prospective cohort on October, 2016, and collected clinicopathological and social factors from 265 Korean CRC survivors in Cancer Prevention Center, Yonsei Cancer Center, Seoul, Republic of Korea. Health-related QoL (HRQOL) was assessed using EORTC-QLQ C30, CR29, ELD14, CIPN20, and EQ-VAS in 189 CRC survivors.

Results: Median duration of cancer survivorship was 70.7 months (range, 0.7-209.8), and 80 patients (42.3%) was long term CRC survivor (who live with cancer more than 5 years). In terms of HRQOL, median scale was 63.4 (standard deviation [SD], ±21.2) for global health, 81.7 (±15.3) for function, and 19.1 (±14.7) for symptom in all CRC survivors. Symptom scale was higher in the long-term survivors (21.8 vs. 17.1; P = 0.040), and in female patients (21.4 vs. 15.3; P = 0.006). Higher stage of disease (III or IV) was related to higher symptom scale (21.6 vs. 17.2; P = 0.042), and lower

functional scale (78.2 vs. 84.3; P = 0.005). Frequently reported late effects were fatigue, insomnia, flatulence, bloated feeling, defecation problem, urinary frequency, sexual dysfunction in male, and sensory neuropathy. Insomnia (P = 0.018), sexual dysfunction in male (P = 0.003), and sensory neuropathy (P = 0.043) were significantly correlated with lower HRQOL scales. In the patients who were treated with oxaliplatin (n = 41), chemotherapy-induced neuropathy is related to worse global health (hazard ratio [HR], -3.29; 95% confidence interval [CI], -8.34- -2.0; P = 0.002).

Conclusions: Various late effects are found in CRC survivors, and late effects may worsen the HRQOL of Korean CRC survivors. We are developing personalized and integrative management programs for CRC survivors.

Legal entity responsible for the study: Yonsei University College of Medicine, Ministry of Health & Welfare, Republic of Korea.

Funding: This study was supported by a grant from the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (1631020).

Disclosure: All authors have declared no conflicts of interest.

1792P Comparison of palonosetron and granisetron in triplet antiemetic therapy in nonmetastatic breast cancer patients receiving high emetogenic chemotherapy. A multicenter, prospective, and observational study

M. Araz[1], M. Karaağaç[2], L. Korkmaz[2], L. Koral[3], F. İnci[4], I. Beypinar[1], M. Uysal[1], M. Artac[2]

[1]Medical Oncology, Afyon Kocatepe University School of Medicine, Afyonkarahisar, Turkey, [2]Medical Oncology, Necmettin Erbakan University, Konya, Turkey, [3]Medical Oncology, Çanakkale Onsekiz Mart University, Çanakkale, Turkey, [4]Medical Oncology, Karabük State Hospital, Karabük, Turkey

Background: In the literature, there have been only two head to head trials investigating first and second generation 5HT3 receptor antagonists in triplet antiemetic regimens in cancer patients receiving high emetogenic chemotherapy (HEC). In these two Japanese studies, granisetron(G) was compared with 0.75 mg palonosetron(P). However, P is approved as 0.25 mg in Turkey and most other countries. Therefore, we aimed to investigate the efficacy of 0.25 mg of P and G in triplet antiemetic regimen for HEC.

Methods: This study was carried out between April 2017 and December 2017 at four different cancer center in Turkey. Patients with nonmetastatic breast cancer who received HEC (doxorubicin or epirubicin plus cyclophosphamide (AC/EC)) were enrolled in this study. The prophylactic triplet antiemetic regimens were used during the first cycle of HEC as intravenous dexamethasone and P (0.25 mg) or G (3mg) as well as oral aprepitant(125 mg on day 1 and 80 mg/day on days 2–3). The choice of P or G was left to the doctor's preference. The primary endpoint was complete response rate (CCR) in acute and delayed chemotherapy-induced nausea and vomiting (CINV). MASCC Antiemesis Tool was used to assess the CINV.

Results: A total of 118 female patients were included in the study. None of them had alcohol consumption story. The mean age of the patients was 51 years. Patients received AC (83%), EC (3%), and dose-dense AC (14%) as adjuvant (88%) or neoadjuvant (12%). The majority of patients received P (59%) containing antiemetic treatment. The dexamethasone dose used in the majority was 8 mg (%80). The CCRs on vomiting were high in two arms and not statistically different with P and G (acute 87% vs. 96%, p = 0.089; delayed 90% vs. 92%, p = 0.508), respectively. Nevertheless, the CCRs of either acute or delayed nausea were lower than compared with vomiting (acute 50% vs. 53%, p = 0.475; delayed 41% vs 31%, p = 0.186), respectively.

Conclusions: To best our knowledge, this is the first study that compared 0.25 mg P and G in triplet antiemetic regimens in cancer patients receiving HEC. There were no differences between P and G, in terms of CCRs of acute and delayed CINV.

Legal entity responsible for the study: Murat Araz.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1793P Painkiller-related dizziness in malignant tumors: A systematic review

R. Spiegel[1], S.I. Rothschild[2], R. Sutter[3], R. Kalla[4]

[1]BG Unfallklinik, Anästhesie, Intensivmedizin und Schmerztherapie, Berufsgenossenschaftliche Unfallklinik Tübingen, Tübingen, Germany, [2]Onkologie, Universitätsspital Basel, Basel, Switzerland, [3]Medizinische Intensivstationen und Neurologische Klinik, Universitätsspital Basel, Basel, Switzerland, [4]Neurologische Klinik, Inselspital (University Hospital Bern), Bern, Switzerland

Background: To our knowledge, there is no systematic review on painkiller-related dizziness, which often occurs.

Methods: Papers from core clinical journals on PubMed-database resulted in 340 articles on dizziness in malignant tumors until 31st Dec 2017. Eight studies with level of evidence (LoE) 1 focused on dizziness as a side effect of painkillers.

Results: In a meta-analysis on codeine, dizziness was reported in 18.06 % of patients (LoE 1a) [1]. In randomized controlled trials (LoE 1b), oxycodone-associated dizziness was only seen in controlled release (8.3 %) and not in immediate release oxycodone [2]. In a systematic review (LoE 1a) [3], controlled release oxycodone was associated with 11.9 % of dizziness reports. A meta-analysis on immediate release morphine and transmucosal fentanyl (7 % dizziness) favoured transmucosal fentanyl for breakthrough cancer pain, but did not differentiate between the painkillers for dizziness [4]. Effective analgesia with rare (1.8 to 7.5 %) events of dizziness was reported for intranasal fentanyl spray (LoE 1b) [5]. For long-acting analgesia, a systematic review favoured transdermal fentanyl over sustained release oral morphine (LoE 1a) [6]. A randomized controlled trial in bone metastases favoured the combination of two nonsteroidal anti-inflammatory drugs (NSAIDs) plus morphine (10.3 % dizziness reports) over one NSAID plus morphine (> 25 %), presumably due to lower morphine need in two NSAIDs (LoE 1b) [7]. Finally, both hydromorphone and morphine had at least 15 % of dizziness reports in a systematic review (LoE 1a) [8].

Conclusions: There is level of evidence 1a to 1b that immediate release oxycodone, transmucosal or intranasal fentanyl are associated with the lowest incidence of dizziness. For long-acting analgesia, transdermal fentanyl is a promising option. References: 1. Straube C, et al. Cochrane Database Syst Rev. 2014;9:CD006601. 2. Salzman RT, et al. J Pain Symptom Manage. 1999;18:271-9. 3. Ma H, et al. Medicine (Baltimore). 2016;95:e3341. 4. Coluzzi PH, et al. Pain. 2001;91:123-30. 5. Kress HG, et al. Clin Ther. 2009;31:1177-91. 6. Yang Q, et al. J Exp Clin Cancer Res. 2010;29:67. 7. Liu Z, et al. Int J Clin Oncol. 2017;22:980-5. 8. Bao YJ, et al. Cochrane Database Syst Rev. 2016;10:CD011108. Equal contribution: S.R., R.S., R.K.

Legal entity responsible for the study: Rainer Spiegel.

Funding: Has not received any funding.

Disclosure: S.I. Rothschild: Honoraria for advisory boards to institution: Abbvie, AstraZeneca, Boehringer Ingelheim, BMS, Eisai, Eli Lilly, Merck, MSD, Novartis, Pfizer, Roche, Takeda; Research support: AstraZeneca, Boehringer Ingelheim, BMS, Eisai. R. Sutter: Research grants: Swiss National Foundation (No 320030_169379), Research Fund of the University of Basel, Scientific Society Basel, Gottfried Julia Bangerter-Rhyner Foundation; Personal grants: UCB-pharma, Destin Pharma GmbH; Stocks: Novartis, Roche. R. Kalla: Supported by the Swiss National Science Foundation (Grant #320030_173081). All other authors have declared no conflicts of interest.

1794P Prevalence, risk factors and management of opioid-induced constipation in cancer pain: A nationwide, cross-sectional study in Korea

S.Y. Lee[1], Y.S. Hong[2], K.T. Lee[3], S.H. Shin[4], M.Y. Choi[5], S.J. Sym[6], H-S. Oh[7], S.N. Lee[8], E-K. Song[9]

[1]Medical Department, Mundipharma Korea Ltd, Seoul, Republic of Korea, [2]Medical Oncology, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Republic of Korea, [3]Medical Oncology, Soon Chun Hyang University Hospital Cheonan, Cheonan, Republic of Korea, [4]Hematology-Oncology, Kosin University Gospel Hospital, Busan, Republic of Korea, [5]Medical Oncology, Inje University Busan Paik Hospital, Busan, Republic of Korea, [6]Medical Oncology, Gachon University Gil Medical Center, Incheon, Republic of Korea, [7]Medical Oncology, GangNeung Asan Hospital, Republic of Korea, [8]Medical Oncology, Ewha Womans University School of Medicine, Seoul, Republic of Korea, [9]Medical Oncology, Chonbuk National University Medical School, Jeonju, Republic of Korea

Background: As opioid therapy is the mainstay treatment for moderate-to-severe cancer pain, a thorough investigation of opioid-induced constipation (OIC) is important due to high prevalence in cancer pain patients undergoing opioid therapy. This study aimed to investigate the prevalence, risk factors and management of opioid-induced constipation among cancer pain patients in Korea.

Methods: A cross-sectional analysis of cancer patients with pain from 30 teaching hospitals was performed, with data extracted from patient charts and questionnaires. Clinical characteristics, prevalence and management for AEs were assessed.

Results: Among 2,395 patients, the most common opioid-related AE was constipation (29.69%). The impact of overall AEs on patients' daily activities was the highest for constipation (69.80%, ≥3). Route of opioid administration was not associated with increased opioid-induced constipation. However, OIC occurrence was dependent to opioid dose. Although approximately half of patients used laxatives prophylactically, 18.50% of those patients experienced constipation. In particular, opioid-use duration, use of laxatives, dose and GI surgery history were significantly associated with constipation.

Conclusions: This study evaluated opioid-induced constipation in cancer pain patients in Korea. As evidenced by the negative impact on patients' daily activities, proper management of OIC is critical as OIC persists although with the use of laxatives. Use of prophylactic laxatives was an important effector as the occurrence of constipation was lower in patients using laxatives prophylactically compared with those using laxatives for constipation treatment. Patients may also benefit from more specific and innovative therapy such as agonist/antagonist combination as stated in EFIC guideline.

Editorial acknowledgement: Medical writing and editorial support was provided by Geraldine Toh of Tech Observer Asia Pacific. This support was funded by Mundipharma Korea Ltd.

Legal entity responsible for the study: Mundipharma Korea Ltd.

Funding: Mundipharma Korea Ltd.

Disclosure: All authors have declared no conflicts of interest.

1795P Bald is beautiful: No more. The stigma of alopecia during chemotherapy: Brindisi oncology department experience

D. Loparco, L. Orlando, M. Caloro, P. Fedele, P. Schiavone, A. Quaranta, C. Caliolo, M. Cinefra, P. Ferrara, L.L. Falcone, V. Capone, C. Destro, A. Morleo, A. Ricco, V. Bonuso, G. Lotti, M. D'amico, P. Rizzo, A. Marino, S. Cinieri

UOC Oncologia Medica, Ospedale A. Perrino, Brindisi, Italy

Background: The cancer treatments (T) bring with it body image challenges, causing low self-esteem and contributing to worsen the quality of life. Chemotherapy (CT)-induced hair loss (HL) is one of the most emotionally distressing side effects of several breast cancer (BC) T. The DigniCap system (DCS), using the scalp cooling system, has been shown to reduce CT-induced alopecia (A) in a multicenter prospective trial. The purpose of this prospective observational study was to describe our experience.

Methods: Two DCS device are available at the Brindisi Oncology Dpt. From February 2016 and May 2018, 86 consecutive early stage BC pts who received anthracycline and/or taxane-based T were enrolled. A nurse and a psychologist were dedicated for these pts. Success of scalp cooling was defined according to the Dean's scale: G0= no HL; G1 < 25% HL; G2=25–50% HL; G3=50–75% HL; G4 >75% HL.

Results: A total of 86 women were included in the following T cohorts: n = 37 (43%) received 4 courses of EC (IV) on day 1, with 21 days between cycles) followed by 12 courses of weekly Paclitaxel (P); n = 39 (45%) received only 4 courses of EC and n = 10 pts (12%) P and concurrent weeklyTrastuzumab for 12 consecutive doses. Median age was 48 years (range 31-74). Overall success (G0-G2) was observed in 61 pts (71%). Full preservation of the hair (G0) was observed in 16 pts (19%), G1 in 31 pts (36%) and G2 in 14 pts (16%) (tab 1). Most frequent scalp cooling-related symptoms were: coldness (n = 70, 81%) and headache (n = 60, 70%). Overall, 11% (n = 9) of pts discontinued DCS because of unsatisfactory hair preservation (n = 5, 6%) and cold discomfort (n = 2; 2.5%). Furthermore, we observed a hair growth when DCS was continued for pts with A G3 – G4.

Table: 1795P

ALOPECIA H/L	G0	G1	G2	G3	G4
N (%)	16 (19%)	31(36%)	14(16%)	20 (23%)	5 (6%)

Tab 1: A/HL

Conclusions: Our results reinforced previous evidences, showing that DCS is a good chance to prevent A during CT with anthracycline and/or taxane-based regimen and supported the wider use to all women with early stage BC.

Legal entity responsible for the study: Saverio Cinieri.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1796P A large multi-center, randomized, double-blind, crossover study in healthy volunteers to compare pharmacokinetics and pharmacodynamics of a proposed biosimilar pegfilgrastim with EU and US reference pegfilgrastim: Methodological approach

R. Nakov[1], S. Schussler[2], S. Schier-Mumzhiu[3], A. Skerjanec[4], A. Bellon[4], J. Wang[5], A. Krendyukov[6], G. Otto[3]

[1]Hematology, Hexal AG, Holzkirchen, Germany, [2]Clinical Research, Sandoz Inc., Princeton, NJ, USA, [3]Clinical Research, Hexal AG, Holzkirchen, Germany, [4]Clinical Pharmacology, Hexal AG, Holzkirchen, Germany, [5]Biostatistics, Sandoz Inc., Princeton, NJ, USA, [6]Medical Oncology/Hematology, Hexal AG, Holzkirchen, Germany

Background: Biosimilar development applies a totality of evidence approach, in which Phase I (pharmacokinetic [PK]/pharmacodynamics [PD]) studies have a pivotal role. Phase I studies are particularly important in biosimilar pegfilgrastim development due to high inter-subject variability (ISV) mainly linked to target-mediated clearance.[1] A pivotal Phase I study confirmed that Sandoz proposed biosimilar pegfilgrastim (LA-EP2006) and EU-reference biologic have matching PK/PD profiles.[2] For FDA approval of LA-EP2006, a bridging study is necessary to confirm that PK/PD properties of LA-EP2006 match EU and US reference pegfilgrastim. This Phase I bridging study is ongoing and here we present the methodology.

Methods: To meet FDA requirements of LA-EP2006, EU and US reference pegfilgrastim PK/PD similarity, and to address ISV, a three-way crossover design was chosen following FDA advice. The study was sufficiently powered (90%) to achieve confidence intervals within margins 0.8–1.25 in co-primary endpoints pairwise comparisons.

Results: Due to historically known high intra- and inter-subject variabilities with reference biologic (CV: 45% and ~80%, respectively)[3] in $AUC_{0\text{-}inf}$, a randomized, double-blind, single-dose, 3-treatment, 6-sequence crossover, Phase I study in healthy volunteers is suitable to demonstrate similarity of PK/PD, safety and immunogenicity between LA-EP2006, EU and US reference pegfilgrastim. Multiple centers, regions, contract research organizations and medicine batches are required, which further amplifies operational complexity of study conduct and scientific standards. The study is ongoing in 5 US and 1 Dutch study sites.

Conclusions: Phase I methodology applying a 3-way crossover design addresses known high ISV with pegfilgrastim and establishes the scientific bridge between proposed biosimilar and reference US and EU biologics. References 1. Yang et al. Clin Pharmacokinet 2011;50:295–306. 2. Nakov et al. Poster presented at SABCS 2017 (P3-14-10). 3. Yang et al. Cancer Chemother Pharmacol 2015;75:1199–206.

Editorial acknowledgement: Caroline McGown, Spirit Medical Communications.

Legal entity responsible for the study: Hexal AG, Holzkirchen, Germany.

Funding: Hexal AG, Holzkirchen, Germany.

Disclosure: R. Nakov, S. Schier-Mumzhiu, A. Skerjanec, A. Bellon, A. Krendyukov, G. Otto: Employee: Hexal AG. S. Schussler, J. Wang: Employee: Sandoz Inc.

1797P Quality of life in breast cancer Tunisian women: A monocentric survey

S. Labidi, C. Bousrih, M. Saadi, H. El Benna, M. Nesrine, N. Daoud, H. Boussen

Department of Medical Oncology, Abderrahman Mami Hospital, Ariana, Tunisia

Background: Quality of life (QoL) has become an integral part of breast cancer (BC) management and been considered an important endpoint of clinical trials. Our objective was to report the results of the first Tunisian study assessing the QoL in BC and to identify the specific demographic characteristics.

Methods: One hundred and ten patients with BC from the department of Medical oncology of the Abderrahman Mami hospital were enrolled in the study in April, 2018. EORTC QLQ-BR23 (European Organization for Research and Treatment of Cancer) Questionnaire was used to assess specifically functional and symptoms scales/items of BC patients. Functional scales consisted of body image (BRBI), sexual functioning (BRSEF), enjoyment (BRSEE) and future perspective (BRFU). Symptom scales / items included systemic therapy side effects (BRST), breast (BRBS), arm (BRAS) symptoms and upset by hair loss (BRHL). A high score for a functional scale represents a healthy level of functioning and a high score for a symptom scale / item represents a high level of symptomatology.

Results: Median age was 52 years (range, 27-75 years) and 70.9% were above the age of 40. Fifty six of patients were menopausal and 19.1% had metastatic disease. Most of women were married (68.2 %), housekeepers (46.4%) and living in urban area (61.8%). Radical surgery was performed in 45.5% of cases and 59.1% of patients were receiving chemotherapy. We identified low scores of BRSEE (47.91, ± 31.44) and BRFU (51.81, ± 37.12) and high scores of BRBS (30.50, ±25.6) and BRAS (26.74 ±24.08) indicating a poorer QoL. Whereas, BRBI (74.33±26.07), BRSEF (77.42±27.79), BRST (40.6 ±20.16) and BRHL (38.46, ± 42.66) were not associated with poorer QoL. Marital status had significant positive effect on body image (Married women: 70.83 vs 70, p = 0.03), sexual functioning (98.14 vs 70.88, p = 0.011) and future perspective (60.80 vs 22.22, p = 0.00). Systemic therapy side effects were significantly higher among patients having chemotherapy (41.53 vs 32.53, p = 0.031). Arm symptoms were as well significantly more reported in patients aged above 40 (35.41 vs 26.78, p = 0.022) and menopausal (33.33 vs 24.80, p = 0.039).

Conclusions: Our study demonstrates the impact of demographic factors in QoL, which need to be systematically assessed by clinicians in breast cancer care.

Legal entity responsible for the study: Soumaya Labidi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1798P Anticancer therapy within the last 30 days of life in a regional cancer centre

M. Nguyen

Medical Oncology, Goulburn Valley Health, Shepparton, Australia

Background: Anticancer therapy within the last 30 days of life is an important indicator of quality end of life care. The decision to cease treatment is complex with several patient, family and clinician driven factors. Similarly, the development of novel anticancer therapies create opportunities for more treatment options. This is reflected in trends toward more aggressive treatment near the end of life. Other institutions in Australia have reported treatment rates within the last 30 days of life of between 10 - 26%.

Methods: Deaths between 1 January 2015 and 30 June 2018 of patients who attended the oncology department were analysed through a retrospective review of medical records.

Results: 122 of 444 deaths (27%) occurred in patients who had received anticancer therapy within the last 30 days of life. The majority (96%) were treated with palliative intent. Palliative care service referral status was low (50%) and tended to be later in those who received treatment within the last 30 days of life. Treatment within the last 30 days of life was associated with other indicators of aggressiveness of care including more emergency presentations, hospitalisations and ICU admissions.

Conclusions: A significant number of patients received anticancer therapy within the last 30 days of life. This emphasises difficulties in disease prognostication, the conflict between treatment cessation and trialling other tempting treatment options and the need for referral to palliative care services.

Legal entity responsible for the study: Goulburn Valley Health.
Funding: Has not received any funding.
Disclosure: The author has declared no conflicts of interest.

1799P Febrile neutropenia management and concordance of institutional protocol with clinical practice

A.F. Oliveira, L. Bretes, I. Furtado, B.E. Gosalbez Pequeno, J.G. Magalhaes
Medical Oncology, Centro Hospitalar Universitário Algarve, Faro, Portugal

Background: Febrile Neutropenia (NF) is an oncologic emergency defined as fever (oral temperature greater than 38.3 °C) and neutrophil count <500. It is one of the most common complications due to chemotherapy. NF is responsible for a considerable morbidity since 20% to 30% of the patients present complications that require hospitalization, with global hospital mortality around 10%. The objective of this study is to evaluate the initial approach to patients with NF in Oncology Day Unit (ODU), Service of Unplanned Care (SUC) and Emergency (ER) and compare the procedures performed in these patients with the protocol at our institution, which is based on guidelines (ESMO/NCCN).

Methods: Retrospective, unicentric study, with the consultation of the clinical records of the patients who presented at ODU, SUC, ER and hospitalized in the Oncology ward with FN and cancer, during a period of 3 months in 2017. Patients were diagnosed by the attending physician with fever and N < 500 or with fever and N < 1000 and> 500, with a drop expected in the next 7 days.

Results: There were 21 episodes, all with solid tumors. The most frequent sites were lung (23%), breast (19%) and colon (17%). 61% of the patients had stage IV cancer. About half developed FN after 1st cycle of chemotherapy. 52% were male, with a mean age of 66.2 years (36-86). In terms of infectious site, the most frequent were fever without a focus (42%) followed by respiratory, skin and urinary tract infections. The MASCC was described in 20% of the cases. The first antibiotic therapy was performed in the SUC in 30% of the cases, in the ER in 65% and in the ODU in 10%. The hospitalization was performed in 11 patients with a median of 13 days of hospitalization. 8 patients underwent outpatient therapy, 3 of whom were subsequently hospitalized for FN. 60% of the patients were treated with G-CSF (N < 500). There were no deaths. The total agreement between clinical practice and the institutional protocol was 17/21 (81%).

Conclusions: Not all patients initiated antibiotic therapy at SUC. The description of the MASCC in the clinical record would be ideal for arguing the therapeutic decision. We have found the overuse of G-CSF. This analysis served to investigate and improve our approach in FN. Protocols can improve the consistency and quality of care.

Legal entity responsible for the study: Centro Hospitalar Universitário Algarve.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1800P Salient features of an indigenous integrated inpatient model of delivery of supportive medicine services: A narrative review

R.D. Arora
Palliative Medicine, All India Institute of Medical Sciences, New Delhi, India

Background: The multiplicity of existing models has the potential to act as a deterrant to the development of an economically feasible and self-sustaining model of delivery of supportive medicine services. A uniformity in guidelines governing the delivery of these services is urgently needed.

Methods: The department recently submitted an application for recognition as an ESMO Designated Centre for Integrated Oncology and Palliative Medicine. This paper tries to highlight the features unique to this model and builds upon the argument that the western model cannot be transplanted to the Indian setting.

Results: The following salient features were identified. The department encourages cancer directed therapy where feasible and prides itself as being ahead of the times in proposing a model which incorporates various aspects of disease-directed therapy, supportive care and palliative care (including quality end of life care provision) as a continuum. A larger role for the palliative medicine professional with direct involvement in critical areas of supportive oncology, procedures such as therapeutic paracentesis, pigtail insertion and interventional pain management techniques is envisaged. We have been able to cut down significantly on the time spent for the patient in obtaining an expert liaison with specialists from other super-specialities. A weekly clinico-radiological conference is held where important cases are discussed with radiologists. The fact that advanced cancer patients (who are not recieving any cancer directed therapy) are being treated alongside those receiving active anticancer treatment has also been instrumental in creating an environment where there is no discrimination and stigma attached to the term palliation.

Conclusions: This model of delivery of supportive medicine services can act as a benchmark on which other regional centres can be modelled. The close involvement of professionals from disciplines such as anaesthesiology and radiology could be one of the important reasons in ensuring that this model has been successful in pushing the boundaries and managing patient issues which were traditionally considered outside the scope and ambit of palliative medicine.

Legal entity responsible for the study: Rahul D. Arora.
Funding: Has not received any funding
Disclosure: The author has declared no conflicts of interest.

1801P Novel online drug-drug interaction resource reveals clinically relevant interactions in > 20% of the searches

N.A.G. Lankheet[1], K.R.M. Ferrier[1], S.E. Gibbons[2], D.M. Burger[1], K. McAllister[2], J.L.M. Martin[2], S.H. Khoo[2], N. van Erp[1], F.G. Jansman[3]
[1]Pharmacy, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, [2]Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK, [3]Clinical Pharmacy, Deventer Ziekenhuis, Deventer, Netherlands

Background: Patients with cancer are at risk to endure a drug-drug interaction (DDI) with their oncolytic drugs. To facilitate the safe prescription and use of oncolytics, the freely available website www.cancer-druginteractions.org was introduced. Hereby we present the results of the use of this online DDI resource since the launch in June 1st, 2017.

Methods: For the most frequently used co-medications (>400) in cancer patients DDI potential was reviewed based on registration documents and scientific literature. A simple "traffic light" system was used to warn for the interaction potential. Background information and level of evidence is provided in the summary for each interaction. Since the launch of the website the demographic use, the number of unique visitors and the number and severity of the interactions consulted are monitored every 3 months.

Results: 34 targeted oncolytics used for ten different malignancies have been added to the website. These represent 24 targeted oral oncolytics and 10 monoclonal antibodies (MoABs). Between June 1st, 2017 and March 31st, 2018 a total of 11,295 searches has been performed by 3,428 unique visitors from 35 countries. 78% of the searches were performed for oral oncolytics and 22% for MoABs. 20.8% of the searches showed a potential interaction which requires action of the prescriber. The table gives an overview of the searches performed. Frequently checked co-medications were for example coumarins, PPIs, dexamethasone, metamizole and aspirin. Currently, a user-friendly app is under development which will be launched in October 2018.

Table: 1801P Overview of DDI queries

Interaction classification 'traffic light' (%)	
Green No clinically significant interaction	63.3
Yellow Interaction of weak/moderate intensity; no a priori dosage adjustment required	15.9
Amber Potential interaction which may require dosage adjustment or close monitoring	14.3
Red Do not co-administer	6.5
Countries consulted the website (%)	
United Kingdom	68
The Netherlands	16
Other European countries (top 3: Spain, France, Switzerland)	7
USA and Canada	3
Asia-Pacific (top 3: Australia, India, Hong Kong)	2
Other	4

Conclusions: Thus far, the DDI checker is being used all over the world. More than 20% of the performed searches showed a clinically relevant interaction. The freely available website, and the soon to be launched app, will facilitate health care professionals' awareness of potential DDIs between oncolytics and frequently used co-medications and this supports safe prescription.

Legal entity responsible for the study: Radboudumc and University of Liverpool.
Funding: Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Ipsen, Janssen, Pfizer, Roche, Sanofi.
Disclosure: S.H. Khoo: Advisory board: Merck, ViiV; Corporate sponsored research: ViiV, Gilead, Merck, Janssen; Other: Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Gilead, Ipsen, Janssen, Pfizer, Roche, Sanofi. N. van Erp: Research funding: Novartis, Astellas, Janssen Cilag, AstraZeneca, GSK, Boehringer Ingelheim, Gilead, Roche, Pfizer, Sanofi. F.G. Jansman: Advisory board: Amgen, Servies. All other authors have declared no conflicts of interest.

1802P The concordance with antiemetic guideline for pediatric, adolescent and young adult patients with cancer using a large-scale administrative database

S. Bun[1], S. Kunisawa[1], N. Sasaki[1], K. Fushimi[2], K. Matsumoto[3], A. Yamatani[4], Y. Imanaka[1]

[1]Healthcare Economics and Quality Management, Kyoto University, Kyoto, Japan, [2]Health Policy and Informatics Section, Tokyo Medical and Dental University Graduate School, Tokyo, Japan, [3]Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan, [4]Pharmacy, National Center for Child Health and Development, Tokyo, Japan

Background: In the field of adult patients, the risk factors for discordance with antiemetic guideline (GL) are reported to be hematological malignancy, older age, and the use of low emetic risk chemotherapy. However, there are scarce reports in the field of pediatric or adolescent and young adult (AYA) patients. Therefore, we assessed the concordance with antiemetic GL in the field of pediatric and AYA patients who received chemotherapy.

Methods: Using the Diagnosis Procedure Combination system in Japan, we identified patients with cancer aged 30 years or younger from July 2010 to March 2016. Patients' data included age, gender, diagnosis, anticancer drugs, and antiemetic drugs. We assessed the concordance with antiemetic GL of ASCO in patients of each emetic risk category. Furthermore, we assessed the risk factors for discordance with antiemetic GL, using logistic regression.

Results: A total of 21,106 patients who underwent chemotherapy were included. We classified patients into the following 6 age categories: 0-2 yo (n = 2,480), 3-5 yo (n = 1,983), 6-11 yo (n = 2,782), 12-17yo (n = 3,495), 18-23 yo (n = 3,941) and 24-29 yo (n = 6,425). The median age was 16 (0-29) years old. The rate of concordance with GL in each emetic risk category was 18.2% in high risk (18 yo >, n = 2,531), 51.1% in high risk (18 yo ≤, n = 4130), 32.1% in moderate risk (n = 7,188), 52.0% in low risk (n = 5,806), and 51.6% in minimum risk (n = 1,451). In multivariate analysis, risk factors for discordance with antiemetic GL were high emetic risk chemotherapy, lower age (0-2 yo), hematological malignancies, and brain tumor.

Table: 1802P Risk factors for discordance with antiemetic guideline

		Odd ratio	95% CI	P Value
Age category	0-2 yo	1.71	1.55-1.89	<0.05
	3-5 yo	1.16	1.04-1.29	<0.05
	6-11 yo	1.12	1.02-1.24	<0.05
	12-17yo	1.49	1.37-1.63	<0.05
	18-23 yo	1.13	1.04-1.23	<0.05
Emetic risk category	High	2.27	2.0-2.55	<0.05
	Moderate	1.43	1.27-1.60	<0.05
	Low	0.98	0.87-1.11	0.79
Disease	non-malignancy	0.75	0.52-1.11	0.15
	Brain tumor	1.46	1.31-1.62	<0.05
	Hematorogical malignancy	1.28	1.20-1.37	<0.05
	Breast cancer	0.53	0.42-0.67	<0.05
	Ovarian/Cervical cancer	0.39	0.34-0.44	<0.05

Conclusions: Our study identified substantial room for improvement in antiemetic practice and risk factors for discordance with antiemetic GL in pediatric and AYA patients. These identified risks are different from those in adult patients. Further investigation of the causes of this discordance is warranted, especially considering the unique background of this field.

Legal entity responsible for the study: Kyoto University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1803P Effectiveness of surgical glove compression therapy as a prophylactic method against nab-paclitaxel induced peripheral neuropathy

S. Tsuyuki[1], K. Yamagami[2], H. Yoshibayashi[3], T. Sugie[4], Y. Mizuno[5], S. Tanaka[6], H. Kato[7], T. Okuno[8], N. Ogura[9], H. Yamashiro[10], H. Takuwa[11], Y. Kikawa[12], T. Hashimoto[13], T. Kato[14], S. Takahara[15], A. Yamauchi[16], T. Inamoto[17]

[1]Breast Surgery, Osaka Red Cross Hospital, Osaka, Japan, [2]Department of Breast Surgery, Shinko Hospital, Kobe, Japan, [3]Department of Breast Surgery, Japanese Red Cross Wakayama Medical Cente, Wakayama, Japan, [4]Department of Breast Surgery, Kansai Medical University Hospital, Osaka, Japan, [5]Breast surgery, Yokkaichi Municipal Hospital, Yokkaichi, Japan, [6]Breast Surgery, National Hospital Organization Osaka-Minami Medical Center, Kawachinagano, Japan, [7]Department of Breast Surgery, Kobe City Medical Center General Hospital, Kobe, Japan, [8]Department of Breast Surgery, Kobe City Nishi-Kobe Medical Center, Kobe, Japan, [9]Department of Breast Surgery, Kansai Electric Power Hospital, Osaka, Japan, [10]Breast Surgery, Tenri Hospital, Tenri, Japan, [11]Breast Surgery, Shiga General Hospital, Moriyama, Japan, [12]Breast Surgery, Kobe minimally invasive cancer center, Kobe, Japan, [13]Breast surgery, Hashimoto Clinic, Kobe, Japan, [14]Breast Surgery, Yamato Takada Municipal Hospital, Yamatotakada, Japan, [15]Breast Surgery, Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan, [16]Breast Surgery, Nara Prefecture General Medical Center, Nara, Japan, [17]Health Care, Tenri Health Care University, Tenri, Japan

Background: No effective prophylactic managements are established for chemotherapy-induced peripheral neuropathy (CIPN). We developed a new, feasible method to prevent CIPN, using compression therapy with surgical gloves (SGs), called SG compression therapy, and recently reported that this method significantly reduced the overall occurrence of grade 2 or higher nanoparticle albumin-bound-paclitaxel (nab-PTX)-induced peripheral neuropathy (PN) from 76.1% to 21.4%, as SGs decreased the microvascular flow to each fingertip (Breast Cancer Res Treat. 2016; 160:61-67). To avoid the major disadvantages of PN for the non-SG-wearing patients by a randomized controlled trial, we investigated the efficacy and safety of SG compression therapy for nab-PTX induced PN in a multicenter single-armed confirmatory study, comparing to the incidence of 44.1% grade 2 or higher PN found in known literature, which we considered as a control group.

Methods: Primary breast cancer patients who received 260 mg/m^2 of nab-PTX were eligible for this study. Patients wore two SGs of the same size, i.e., one size smaller than the size that fit their both hands, for 90 minutes. PN was evaluated at each treatment cycle using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and the Patient Neurotoxicity Questionnaire (PNQ). The temperature of each fingertip was measured by using thermography.

Results: Between October 2016 to June 2017, 61 patients were enrolled, and 58 were evaluated. The incidence of sensory PN of CTCAE grade 2 or higher was as low as 13.8% following SG compression therapy. The occurrence rate of grade 4 or higher PNQ responses, which indicate interference with activities of daily living, was also as low as 10.3%. A goodness-of-fit test using a chi-square test proved that the overall incidence of 13.8% grade 2 or higher PN obtained in this study is equal to 13% of the hypothesis-predicted value. All patients completed this study because they tolerated the compression from the SGs. SG compression therapy significantly reduced the temperature of each fingertip by 1.3–2.3 °C compared to that before chemotherapy.

Conclusions: This study demonstrated that SG compression therapy is effective and safe for reducing CIPN.

Clinical trial identification: University Hospital Medical Information Network (UMIN) Number: 000024836.

Legal entity responsible for the study: Kamigata Breast Cancer Study Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1804P Effect of oral magnesium supplementation on the kinetics of magnesium wasting induced by EGFR targeted antibody therapy for colorectal carcinoma (MAGNET trial)

H. Piessevaux[1], W. Demey[2], A. Bols[3], J. Janssens[4], M. Polus[5], H. Rezaei Kalantari[6], S. Laurent[7], A. Demols[8], Y. Humblet[9], G. Deboever[10], K. Kargar Samani[11], M. Ferrante[12], E. Monsaert[13], T. Rondou[14], J-L. van Laethem[8], S. Tejpar[15]

[1]Hepato-Gastroenterology Department, Cliniques Universitaires St. Luc, Brussels, Belgium, [2]Medical Oncology Department, A.Z. Klina, Brasschaat, Belgium, [3]Oncology Department, AZ St. Jan Av, Brugge, Belgium, [4]Gastroenterology, A.Z. Turnhout, Turnhout, Belgium, [5]Gastroenterology Department, Centre Hospitalier Uuniversitaire Sart Tilman, Liège, Belgium, [6]Oncology Department, CHR Verviers, Verviers, Belgium, [7]Gastroenterology, UZ Gent, Gent, Belgium, [8]Gastroenterology Department, Erasme University Hospital-(Universite Libre de Bruxelles), Brussels, Belgium, [9]Medical Oncology, Cliniques Universitaires St. Luc, Brussels, Belgium, [10]Gastroenterology Department, AZ Damiaan, Oostende, Belgium, [11]Oncology Department, CHWAPI, Tournai, Belgium, [12]Gastroenterology, A.Z. Sint Maarten, Mechelen, Belgium, [13]Gastroenterology Department, AZ Maria Middelares, Gent, Belgium, [14]Gastroenterology Department, St-Jozef Kliniek, Bornem, Belgium, [15]Gastroenterology Department, University Hospitals Leuven, Leuven, Belgium

Background: Progressive decrease of serum magnesium levels occurs in virtually all patients treated with anti-EGFR antibodies. This is supposedly linked to an inhibition of renal TRPM6 activity. This Mg loss may ultimately require stopping the anti-cancer treatment. In patients with congenital TRPM6 deficiency, high dose oral Mg supplementation allows to maintain acceptable serum Mg levels but may induce significant diarrhea. We hypothesized that oral Mg gluconate substitution may prevent and/or treat Mg wasting due to anti-EGFR treatment in colorectal cancer (CRC).

Methods: We performed a prospective randomized multi-centre trial in patients treated with anti-EGFR antibodies for CRC evaluating the efficacy and tolerability of oral Mg gluconate for prevention and/or treatment of Mg wasting. Upon initiation of anti-EGFR treatment, patients were randomized to no intervention (arm A) or Mg gluconate 3 g bid (arm B). After occurrence of hypomagnesaemia grade 1, Mg gluconate 3 g bid was initiated in arm A, whereas the dosage was increased to 3g 6 times daily in arm B. The co-primary outcome variables were the slope of the serum Mg levels since baseline and the mean number of bowel movements per day. An a priori statistical analysis plan estimated the need to screen 180 patients ($\beta = 0.90$) to demonstrate an effect on serum Mg slopes.

Results: After excluding 7 patients during screening, 89 were randomized to arm A (no intervention) and 84 to arm B (Mg supplementation). In an ITT approach, the mean serum Mg slope was significantly ($p = 0.015$) steeper in arm A: -0.0045 (95%CI: -0.0062 to -0.0034) vs. -0.0021 (95%CI: -0.0037 to -0.0009) mg/dl/day in arm B. Hypomagnesaemia occurred in 12 and 4 patients respectively ($p = 0.05$). This lead to insufficient number of patients to draw conclusions for the second part of the trial. The mean number of bowel movements was not different across arms. Oral Mg supplementation was not associated to significant adverse events.

Conclusions: This prospective randomized trial demonstrated that oral Mg gluconate 3 g bid. significantly decreased Mg wasting during anti-EGFR treatment in colorectal cancer, thereby delaying the occurrence of hypomagnesemia. This treatment was well tolerated.

Clinical trial identification: EudraCT: 2007-001131-61.

Legal entity responsible for the study: Belgian Group of Digestive Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1805TiP Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV)

A. Mersiades[1], A. Tognela[2], P.S. Haber[3], M. Stockler[1], N. Lintzeris[3], J. Simes[1], I. McGregor[4], I. Olver[5], D.J. Allsop[4], C. Gedye[6], A. Kirby[1], R.L. Morton[1], K. Briscoe[7], P. Fox[8], M. Aghmesheh[9], N. Wong[1], A. Bhardwaj[1], A.D. Tran[1], C. Hahn[10], P. Grimison[10]

[1]NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia, [2]Department of Medical Oncology, Macarthur Cancer Therapy Centre, Sydney, Australia, [3]Sydney Medical School, University of Sydney, Sydney, Australia, [4]Lambert Initiative for Cannabinoid Therapeutics, University of Sydney, Sydney, Australia, [5]Sansom Institute for Health Research, University of South Australia, Adelaide, Australia, [6]Department of Medical Oncology, Calvary Mater Newcastle, Newcastle, Australia, [7]Department of Medical Oncology, Mid-North Coast Cancer Institute, Coffs Harbour, Australia, [8]Department of Medical Oncology, Central West Cancer Care Centre, Orange Health Service, Orange, Australia, [9]Department of Medical Oncology, Illawarra Cancer Care Centre, Illawarra Shoalhaven Local Health District, Wollongong, Australia, [10]Department of Medical Oncology, Chris O'Brien Lifehouse, Sydney, Australia

Background: Up to half of patients receiving chemotherapy of moderate or high emetic risk experience CINV despite optimal anti-emetic prophylaxis. Limited evidence suggests cannabinoid medicine in the form of tetrahydrocannabinol (THC) may reduce CINV, and addition of cannabidiol (CBD) may improve efficacy and tolerance. The aim of this multi-centre, randomised, placebo-controlled, phase II/III trial is to determine efficacy and cost-effectiveness of addition of an oral cannabinoid-rich THC/CBD cannabis extract for control of CINV.

Trial design: The target population is adult patients experiencing CINV during moderate and highly emetogenic chemotherapy regimens despite appropriate anti-emetic therapy, who are scheduled to receive at least 2 more consecutive cycles (A, B and, where applicable, C). Treatment consists of oral THC 2.5mg/CBD 2.5mg (Tilray TN-TC11M) capsules or placebo TDS days -1 to 5, in addition to guideline-consistent anti-emetics, including rescue medications. Patients will start with 1 tablet PO TDS and can dose-titrate to a maximum of 4 tables PO TDS based on nausea control and side-effects. In the pilot trial ($N = 80$), subjects are randomised for cycle A, cross-over for cycle B, and nominate preferred treatment for cycle C. The planned definitive trial ($N = 250$) will randomise subjects to investigational product or placebo for cycles A, B and C in a parallel design. The primary end-point is the proportion of patients gaining a complete response (no emesis and no use of rescue medications) (0 – 120h), with additional end-points of (i) complete response, (ii) no emesis, (iii) no significant nausea and (iv) no use of rescue medication during the a) acute, b) delayed, and c) overall phases of cycle A, B and C, (iv) adverse events, (v) quality of life, and (vi) cost-effectiveness. As of 09/05/2018, 52 of 80 patients have been recruited to the pilot study, with expected recruitment completion in 3rd quarter 2018. Funding: NSW Department of Health. Acknowledgements: Trial participants, investigators and research staff. Drug supply by Tilray.

Clinical trial identification: ACTRN: 12616001036404.

Legal entity responsible for the study: University of Sydney.

Funding: New South Wales Department of Health.

Disclosure: A. Tognela: Travel, accommodation, expenses: Merck Serono. P.S. Haber: Stock/Membership: Cleveland Biolab; Honoraria, advisory board, HCV drugs: Gilead; Research funding: Braeburn (opioid product clinical trial). M. Stockler: Research funding: Astellas Pharma, Celgene, Bayer, Bionomics, Medivation, Sanofi, Pfizer, AstraZeneca, Bristol-Myers Squibb, Roche, Amgen, Merck Sharpe & Dohme, Tilray; Travel, accommodation, expenses: Medivation/Pfizer. N. Lintzeris: Consulting/advisory role: Mundipharma International, Indivumed; Research funding: Braeburn Pharmaceuticals (to institution). J. Simes: Research grants to institution: Abbvie, AGITG, Amgen, ANZ Breast Cancer Trials Group, Astellas Pharma, Bayer Pharmaceuticals, BBI, Bristol-Myers Squibb, Cancer Australia, Cancer Institute NSW, Cure Brain Cancer Foundation, Merck-Serono, MSD, NHMRC, Novartis, Pfizer, Roche. I. McGregor: Patents, royalties, other IP: University of Sydney, Kinoxis Therapeutics. I. Olver: Research funding: MSD, Jansen. C. Gedye: Employment: Novotec CRO; Research funding: CPI for co-operative group trials supported by BMS and MSD. R.L. Morton: Honoraria: Amgen, Baxter Healthcare; Research funding: Edwards Life Sciences. P. Grimison: Research funding to institution: Tilray, Pfizer, MSD, Gilead Sciences, Boston Biochemical, Tigermed; Personal research funding: Specialised Therapeutics, Progen, Medimmune. All other authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii641–viii644, 2018
doi:10.1093/annonc/mdy301

THORACIC MALIGNANCIES, OTHER

1806PD Multiple primary cancers (MPC) in a series of lung cancer (LC) patient: Incidence and outcome

S. Cedres Perez[1], M. Sanso[2], A. Hernando-Calvo[1], A. Callejo[1], N. Pardo Aranda[1], A. Navarro Mendivil[1], A. Martinez[1], J. Remon[1], J.M. Miquel[1], G. Rodriguez[1], V. Monton[1], G. Villacampa[3], R. Dienstmann[3], A. Vivancos[4], E. Felip Font[1]

[1]Medical Oncology, Vall d'Hebron University Hospital/Vall d'Hebron Institute Oncology, Barcelona, Spain, [2]Cancer Genomics Group, Vall d'Hebron University Hospital/Vall d'Hebron Institute Oncology, Barcelona, Spain, [3]Oncology Data Science, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Genomic Group, Vall d'Hebron University Hospital, Barcelona, Spain

1807P STELLAR: Final results of a phase II trial of TTFields with chemotherapy for first-line treatment of pleural mesothelioma

F. Grosso[1], J.G. Aerts[2], J. Madrzak[3], R. Dziadziuszko[3], R. Ramlau[4], S. Cedres[5], B. Hiddinga[6], J.P. van Meerbeeck[6], M. Mencoboni[7], D. Planchard[8], A. Chella[9], L. Crino[10], M.J. Krzakowski[11], G.L. Ceresoli[12]

[1]Oncology, SS Antonio e Biagio Hospital, Department of Oncology, Alessandria, Italy, [2]Oncology, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Oncology, Medical University of Gdansk Clinical Hospital, Gdansk, Poland, [4]Oncology, Medical University of Poznan, Poznan, Poland, [5]Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [6]Oncology, Antwerp University Hospital, Antwerp, Belgium, [7]Oncology, Ospedale Villa Scassi, Genoa, Italy, [8]Oncology, Institut Gustave Roussy, Villejuif, France, [9]Oncology, Cisanello University Hospital Pisa, Pisa, Italy, [10]Oncology, Ospedale S. Maria della Misericordia, Perugia, Italy, [11]Department of Lung & Thoracic Tumours, The Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland, [12]Oncology, Humanitas Gavazzeni, Bergamo, Italy

Background: Tumor Treating Fields (TTFields) are an anti-mitotic, regional treatment modality, using low intensity alternating electric fields delivered non-invasively to the tumor using a portable, medical device. In vitro, human mesothelioma cells were highly susceptible to TTFields. TTFields have been shown to extend survival of patients with glioblastoma when added to chemotherapy.

Methods: The trial accrued 80 patients with unresectable, untreated mesothelioma. Patients were treated with continuous 150 kHz TTFields in combination with pemetrexed and platinum. Inclusion criteria included ECOG 0-1 and at least one measurable lesion according to modified RECIST. Patients were followed q3w (CT scan q6w) until disease progression. The primary endpoint was overall survival (OS). This single arm study assumed historical control with a median survival of 12.1 months (Vogelzang et al. 2003). The sample size provided 80% power with a two-sided alpha of 0.05 to detect an increase in median OS of 5.5 months.

Results: All patients had a minimum follow up of 12 months. Median age was 67 (range 27-78), 84% were male and 56% smokers. 16% (13 patients) had metastatic disease and 44% (35 patients) had an ECOG PS of 1. 66% (53 patients) had epithelioid histology. Compliance with TTFields was 68% (16.3 hours/day) during the first 3 months of therapy. Median OS was 18.2 months (95% CI 12.1-25.8) compared to 12.1 months in historical controls. Median PFS was 7.6 months (95% CI 6.7-8.6) compared to 5.7 months in historical controls. Partial responses were seen in 40.3% of patients and clinical benefit (PR+SD) was seen in 97.2% of patients. No device-related serious adverse events (AEs) were reported. Expected TTFields-related dermatitis was reported in 46% (37 patients). Only 4 patients (5%) had grade 3 dermatitis.

Conclusions: The study met its primary endpoint of significant extension of survival for previously untreated mesothelioma patients. Secondary efficacy endpoints were also improved compared to historical control. The study demonstrated no safety concerns for the combination of TTFields to the thorax with chemotherapy. These results support the addition of TTFields to chemotherapy in the first-line treatment of malignant pleural mesothelioma.

Clinical trial identification: NCT02397928.

Legal entity responsible for the study: Novocure.

Funding: Novocure.

Disclosure: J.G. Aerts: Advisory boards: BMS, MSD, Roche, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Amphera; Stock owner: Amphera. R. Ramlau: Consultant: Novocure. All other authors have declared no conflicts of interest.

1808P Role of evaluating tumor infiltrating lymphocytes, programmed death-ligand 1 and mismatch-repair proteins expression in malignant mesothelioma

L. Losi[1], F. Bertolini[2], L. Scurani[1], G. Guaitoli[2], C. Baldessari[2], A. Ambrosini Spaltro[3], L. Botticelli[3], A. Maiorana[3], F. Barbieri[2], S. Cascinu[2]

[1]Department of Life Sciences, Unit of Pathology, University of Modena and Reggio Emilia, Modena, Italy, [2]Department of Oncology and Haematology, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, [3]Department of Diagnostic Medicine, Clinic and Public Health, Unit of Pathology, University of Modena and Reggio Emilia, Modena, Italy

Background: Malignant mesothelioma (MM) is an aggressive and fatal tumor, mainly related to prolonged exposure to asbestos. MM can induce infiltration of immune cells and immunity-mediated death. Tumor microenvironment plays a major role in neoplastic progression, favoring tumor cell evasion from adaptive immunity and T-cell checkpoint pathways. Expression of programmed death-ligand 1 (PD-L1) on tumor cells and tumor-infiltrating lymphocytes (TILs) has been described in literature. Cancer cells expressing PD-L1 increase apoptosis of antigen-specific human T-cell clones and inhibit CD4+ and CD8+ T-cell activation, thus decreasing the immune action on the tumor cells. Some mismatch repair–deficient tumors make them sensitive to immune checkpoint blockade, because of the increased number of neoantigens encoded by cancers, which enhances anti-tumor response.

Methods: The aim of this study is to analyze the expression of PD-L1 on both tumor cells and TILs and to characterize TILs. Furthermore, MisMatchRepair (MMR) protein expression was evaluated. Immunohistochemistry was applied using the automated system BenchMark XT (VENTANA) for PD-L1 (DAKO, clone 22C3), CD4, CD8 and MLH1, MSH2, MSH6, PMS2.

Results: 55 malignant mesotheliomas, 10 from women and 45 from men, were studied. The range of age was 43-88 years old. Tumors consisted of 44 epithelioid, 3 sarcomatoid, 7 biphasic and 1 desmoplastic. 51 were localized to pleura and 4 to peritoneum. 18 tumors were in stage I, 13 in stage II, 15 in stage III and 5 in stage IV. For 4 cases the stage was not evaluable. Our results showed expression of PD-L1 $\geq$50% in tumor cells in 9 cases (5 epithelioid, 2 sarcomatoid, 1 biphasic and 1 desmoplastic). In two of these the positivity was observed both in tumor cells and in TILs. 15 tumors were negative and 31 showed a positive staining $\geq$1. A presence of TILs was observed in 53 cases. A prevalence of CD4+ expression was highlighted in 45 cases. 6 of them showed elevated expression of PD-L1 ($\geq$50%). Alteration in MMR staining was not found.

Conclusions: Our data underline the role of tumor immune microenvironment and its characterization in MM and open the possibility to use combined therapies according to different PD-L1 expression.

Legal entity responsible for the study: Modena University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1809P Development and validation of a deep learning model using biomarkers in pleural effusion for prediction of malignant pleural mesothelioma

S. Ikegaki[1], Y. Kataoka[1], T. Otoshi[2], T. Takemura[1], M. Shimada[1]

[1]Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan, [2]Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Background: Malignant pleural mesothelioma (MPM) is an aggressive asbestos-related disease that is challenging to diagnose. The value of tumour biomarkers in pleural effusion fluid is limited in patients with the disease. We have developed and validated a deep learning model that can predict a diagnosis of MPM using pleural tumour biomarkers and patient characteristics.

Methods: This retrospective cohort study included patients who underwent thoracentesis for undiagnosed pleural effusion at a single tertiary medical centre between September 2014 and August 2016. The diagnosis was established by two independent physicians who were blinded to the pleural effusion data. A deep learning model was constructed to differentiate MPM from other diseases and evaluated using biomarkers in pleural effusion (carcinoembryonic antigen, cytokeratin 19 fragment, soluble mesothelin-related peptides, lactate dehydrogenase), total protein in pleural effusion, and patient age and sex as input parameters. Missing data were handled by single imputation. The model consisted of three hidden layers and was trained for 4000 steps. The data were divided into a training set and a test data set and processed using TensorFlow 1.7.0 and Python 3.6 software. The performance of the model was evaluated by accuracy and the area under the receiver-operating characteristic curve (AUROC).

Results: Twenty-eight of the 188 patients who underwent thoracentesis were diagnosed to have MPM and divided into a training data set (containing first 150 records with 20 MPM patients) and a test data set (38 records with 8 MPM patients). The accuracy values for the training and test data sets were 0.99 and 0.97, respectively, and the respective AUROC were 1.00 and 0.92.

Conclusions: Our deep neural network model had good diagnostic accuracy for MPM and may help in making a definitive diagnosis when there is an indication for invasive pleural biopsy.

Legal entity responsible for the study: Hyogo Prefectural Amagasaki General Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1810P Elective nodal irradiation as adjuvant radiotherapy for advanced thymomas and thymic carcinomas

Y.J. Kim[1], S.S. Kim[2], S.Y. Song[2], E.K. Choi[2]

[1]Radiation Oncology, Kangwon National University Hospital, Chuncheon, Republic of Korea, [2]Radiation Oncology, Asan Medical Center, Seoul, Republic of Korea

Background: Elective nodal irradiation (ENI) targeting the entire mediastinal and supraclavicular regions is not routinely recommended as adjuvant treatment for thymomas due to the low rate of lymphogenous metastasis. Also, it is not widely used for thymic carcinomas since the majority of nodal disease metastasized to anterior mediastinal lymph nodes. However, there are little clinical data directly comparing the local radiation therapy (LRT) targeting the tumor bed and anterior mediastinal areas only and ENI for thymic tumors. We evaluated the clinical outcome of patients with stage III–IV thymomas (Ts) or stage II–IV thymic carcinomas (TCs) treated with complete thymectomy and LRT or ENI.

Methods: Data from 47 patients diagnosed with Ts or TCs and treated with surgery and adjuvant RT from May 2002 to May 2015 were analyzed. The standard RT dose was 50.4 Gy in 25 fractions; patients with a positive resection margin received a further 4–10 Gy. Survival outcomes determined at 5 years included local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), and overall survival (OS).

Results: Five year LRFS was similar in both groups (LRT, 94.7% vs ENI, 96.2%; $p = 0.849$). Significant differences were seen in 5 year RRFS (LRT, 55.1% vs ENI, 83.7%; $p = 0.006$); however, tumor size was seen to be a significant factor (<7 cm, 95.2% vs ≥ 7 cm, 48.9%; $p = 0.000$) and the LRT group contained a greater proportion of patients with ≥ 7 cm tumors (70% vs 33%). Multivariate analysis demonstrated that tumor size was the only significant prognostic factor ($p = 0.000$). No differences in 5 year OS were seen (LRT, 91.7% vs ENI, 100%; $p = 0.106$).

Conclusions: ENI showed no additional benefit in reducing recurrence or improving survival. LRT can, therefore, be considered sufficient to achieve excellent patient outcomes.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1811P Clinicopathological features of thymoma with the expression of programmed death-ligand 1

S. Hakiri[1], T. Fukui[1], S. Mori[1], K. Kawaguchi[1], S. Nakamura[1], N. Ozeki[1], T. Kato[1], M. Goto[1], Y. Yatabe[2], K. Yokoi[1]

[1]Thoracic Surgery, Nagoya University, Graduate School of Medicine, Nagoya, Japan, [2]Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Background: Programmed death-ligand 1 (PD-L1) is reportedly expressed in various malignancies and is considered a prognostic factor. We attempted to characterize the association between the PD-L1 expression and the clinicopathological features of patients with thymoma.

Methods: Eighty-one patients with thymoma who underwent surgical resection between 2004 and 2015 were retrospectively reviewed. The PD-L1 expression was evaluated by immunohistochemistry and stratified by the proportion of positive tumor cells. Strong membranous reactivity of the PD-L1 antibody in $\geq 1\%$ of tumor cells was considered 'positive'. The association between the PD-L1 expression and the clinicopathological features was investigated.

Results: The PD-L1 expression was positive in 22 patients (27%) and negative in 59 patients (73%). PD-L1 positivity was significantly associated with type B2 and B3 thymoma ($p < 0.001$) and stage III and IV disease ($p = 0.048$). In addition, PD-L1-positive tumors showed a significantly higher maximum standardized uptake value (SUVmax) than PD-L1-negative tumors ($p = 0.026$). The 5-year disease-free survival (DFS) rate was 83% in PD-L1-positive patients and 88% in PD-L1-negative patients, showing no significant difference ($p = 0.576$). Furthermore, PD-L1 positivity was not an independent prognostic factor for the DFS on a Cox proportional hazard analysis ($p = 0.590$).

Conclusions: A strong expression of PD-L1 in thymoma was significantly associated with type B2 and B3 and higher pathological stages. In addition, PD-L1 positivity was associated with an increased SUVmax of the tumor. However, patients with PD-L1-positive thymomas did not show a significantly worse prognosis than those with PD-L1-negative tumors.

Legal entity responsible for the study: Department of Thoracic Surgery, Nagoya University Graduate School of Medicine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1812P The impact of PD-L1, TGF-β expression and tumor-infiltrating CD8+ T cells on clinical outcome of patients with advanced thymic epithelial tumors

J. Duan[1], X. Liu[2], H. Chen[3], H. Bai[4], T. Xu[5], S. Cai[6], J. Wang[7]

[1]Department of Medical Oncology, Cancer Hospital of Chinese Academy of Medical Sciences, Beijing, China, [2]Oncology Department, Dong Ying People's Hospital, Dongying, China, [3]Peking University Cancer Hospital, Peking University Health Science Center, Beijing, China, [4]Department of Medical Oncology, Cancer Hospital of Chinese Academy of Medical Sciences, Beijing, China, [5]Medical Department, 3D medicines Inc., Shanghai, China, [6]The Medical Department, 3D medicines Inc., Shanghai, China, [7]Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: Thymoma and thymic carcinoma are indolent and poorly responsive to chemotherapy. PD-1/PD-L1 inhibitors have shown remarkable clinical benefit in several cancers. However, many immunomodulatory molecules have been identified to affect the efficacy of immunotherapy. This study aimed to examine the expression of PD-L1, transforming growth factor-β (TGF-β), and $CD8^+$ tumor-infiltrating lymphocytes ($CD8^+$ TILs) in patients with advanced thymic epithelial tumors (TETs) and evaluated their prognostic roles.

Methods: Retrospective analysis was performed on 20 patients with stage IV thymic carcinoma and 13 patients with stage III/IV invasive thymoma. Tissue biopsies were obtained before the first-line chemotherapy. The expression level of PD-L1, TGF-β and CD8 were assessed using IHC. The high or low expression was seprated by the median value of the IHC score. The outcomes including objective response rate (ORR), overall survival (OS) and progression-free survival (PFS) were then analized.

Results: The proportion of PD-L1 high was relatively higher in patients with advanced thymic carcinoma compared to patients with advanced invasive thymoma (65.0% vs 46.2%, $p = 0.472$). The proportion of TGF-β high in patients with thymic carcinoma was significantly higher than that in patients with invasive thymoma (65.0% vs 15.4%, $p = 0.011$). 5 of 7 patients in advanced thymic carcinoma with low PD-L1/TGF-β expression exhibited high level of CD8 staining. Among all patients, the median OS was 29.5 ms (95%CI: 20.0-39.0) with PD-L1 high versus 42.6 ms (95%CI: 0-98.3) ($p = 0.186$) with PD-L1 low. The median OS was 29.5 ms (95%CI: 18.6-40.4) with TGF-β high versus 62.9 ms (95%CI: 15.6-110.1) ($p = 0.052$) with TGF-β low. Among patients in advanced thymic carcinoma, the ORR was 30.0% with CD8 high versus 14.3% with CD8 low ($p = 0.603$), the median PFS was 13.3 ms with PD-L1 high versus 23.5 months ($p = 0.043$) with PD-L1 low. Furthermore, the ORR was 40.0% with TGF-β low vursus 16.7% with TGF-β high ($p = 0.538$).

Conclusions: Our results showed the prognostic role of PD-L1, TGF-β and $CD8^+$ TILs in patients with advanced TETs, and their potential for development of anti-PD-1/PD-L1 therapies.

Legal entity responsible for the study: Jie Wang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1813P Prevalence and prognostic value of PD-L1 expression in molecular subtypes of metastatic large cell neuroendocrine carcinoma (LCNEC)

B.C.M. Hermans[1], J.L. Derks[1], E. Thunissen[2], R.J. van Suylen[3], M.A. den Bakker[4], H.J.M. Groen[5], E.F. Smit[6], R.A. Damhuis[7], E.C. van den Broek[8], P. PALGA-group[8], C.M. Stallinga[9], G.M. Roemen[9], E.J. Speel[9], A-M.C. Dingemans[1]

[1]Pulmonary Diseases, Maastricht University Medical Center (MUMC), Maastricht, Netherlands, [2]Pathology, VU Medical Centre, Amsterdam, Netherlands, [3]Pathology-DNA, Jeroen Bosch Ziekenhuis, Den Bosch, Netherlands, [4]Pathology, Erasmus University Medical Center, Rotterdam, Netherlands, [5]Pulmonary Disease, University Hospital Groningen (UMCG), Groningen, Netherlands, [6]Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands, [7]Research, Comprehensive Cancer Association, Utrecht, Netherlands, [8]PALGA foundation, Houten, Netherlands, [9]Pathology, Maastricht University Medical Center, Maastricht (MUMC), Netherlands

Background: Pulmonary LCNEC is a rare tumor. Two mutually exclusive subtypes of LCNEC are recognized, the co-mutated TP53 and RB1 and the STK11/KEAP1 (predominantly RB1 wildtype) group. We investigated PD-L1 expression in a well characterized stage IV LCNEC cohort and compared expression in the two subtypes.

Methods: Panel-consensus pathology revision was performed along with targeted next generation sequencing (TNGS) for genes TP53, RB1, STK11 and KEAP1 and immunohistochemical (IHC) analysis of RB1, on pretreatment tumor samples of stage IV LCNEC treated with chemotherapy (Derks et al. CCR 2018). IHC staining for PD-L1 (DAKO 28-8) was performed according to standard protocols on the DAKO autostainer and evaluated by an experienced screener. Tumors were scored positive if > 1% of tumor cells showed any membranous staining. Overall survival (OS) was evaluated by Kaplan Meier analysis and differences estimated with Log-Rank test. Cox-regression analysis included PD-L1, age and gender.

Results: PD-L1 IHC expression data could be generated in 98/147 confirmed LCNEC samples along with RB1 IHC (n = 97) of which 77 passed quality control for TNGS. PD-L1 expression was positive in 16/98 cases (16%); n = 5 (5%) with >50%, n = 11 (11%) having >1-50% and n = 82 (82%) with ≤1% membranous staining, respectively. No significant correlation of PD-L1 expression with molecular subtyping of LCNEC was identified (Table). PD-L1 expression was correlated with a superior OS, hazard ratio (HR) 0.54 ((95% Confidence interval (CI), 0.31-0.96) P = 0.034.

Table: 1813P Expression of PD-L1 in LCNEC, correlated to molecular data

	PD-L1 +	PD-L1 -	P-value
LCNEC (n = 98)	16%	84%	-
1-5%	7 %	-	-
5-20	4%	-	-
>50	5%	-	-
Rb1 IHC (n = 97)			
RB1 (+) (n = 29)	10%	90%	NS
RB1 (-) (n = 68)	19%	81%	
Mutation status (n = 76)			
RB1/TP53 mutated (n = 33)	15%	85%	NS
RB1 wildtype (n = 43)	16%	84%	
OS in months (95% CI)	8.9 (4.2-13.6)	6.6 (5.7-7.6)	HR 0.54 (0.31-0.96) P = 0.034

Conclusions: PD-L1 expression was positive in 16% of stage IV LCNEC tumors. PD-L1 expression is an independent process from LCNEC molecular subgroups. In LCNEC patients with PD-L1 expression superior OS is observed compared to those with negative PD-L1 tumors.

Legal entity responsible for the study: Maastricht University Medical Centre, Department of Pulmonary Disease.

Funding: Bristol-Meyers Squibb.

Disclosure: All authors have declared no conflicts of interest.

1814P Computed tomography features of resected lung adenocarcinomas with spread through air spaces

Y. Yamada[1], G. Toyokawa[2], T. Tagawa[3], T. Kamitani[4], Y. Yamasaki[4], F. Shoji[2], K. Yamazaki[2], S. Takeo[2], Y. Oda[1]

[1]Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [2]Department of Thoracic Surgery, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan, [3]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [4]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Background: Spread through air spaces (STAS) is a recently-recognized invasive pattern of lung cancer defined as 'micropapillary clusters, solid nests or single cells beyond the edge of the tumor into air spaces.' Since STAS has been shown to be a significant prognosticator for the postoperative survival, predicting STAS preoperatively by computed tomography (CT) might help determine the optimum surgical procedures.

Methods: Information on STAS and preoperative CT were availablen 327 patients with resected lung adenocarcinomas. STAS was defined as tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor. The association of STAS with CT characteristics, such as vascular convergence, ground glass opacity (GGO), air bronchogram, notch, pleural indentation, spiculation, and cavitation, was analyzed.

Results: Among the 327 patients with resected adenocarcinoma, 191 (58.4%) were positive for STAS. A univariable analysis demonstrated that STAS-positive adenocarcinomas were significantly associated with a larger radiological tumor diameter (P = 0.02), the presence of vascular convergence (P < 0.01), notch (P < 0.01), pleural indentation (P = 0.03), spiculation (P < 0.01), and the absence of GGO (P < 0.01) compared with STAS-negative ones. In a multivariable analysis, the presence of notch (P = 0.01) and the absence of GGO (P < 0.01) were shown to be significantly associated with the STAS phenomenon. The odds ratio for STAS of notch-positive and GGO-negative adenocarcinomas against notch-negative and GGO-positive ones was 5.01 (P < 0.01).

Conclusions: The presence of notch and the absence of GGO were independently associated with the STAS phenomenon. These results will prove helpful in identifying STAS-positive adenocarcinoma by CT prior to surgical resection.

Legal entity responsible for the study: Gouji Toyokawa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1815P Comparative proteomic analysis of acetylation profiles in esophageal squamous carcinoma cells

Y. Dai[1], J. Li[2]

[1]Radiation Oncology, Fujian Medical University Cancer Hospital, Fujian Medical University, Fuzhou, China, [2]Radiation Oncology, Fujian Cancer Hospital, Fuzhou, China

Background: To explore the different expression of proteins and the acetylations between esophageal squamous carcinoma cells (ESCCs) and cancer stem-like cells (CSCs) by proteomic analysis.

Methods: The Eca109 cells were divided into CSCs group and ESCCs group by using serum-free culture and serum culture. We measured the CD44 expression levels, CCK8 cell proliferations and plate cloning formation to identify the characteristics of cancer stem cells. Furthermore, Tandem Mass Tags (TMT)-based quantitative proteomics and bioinformatic analysis were used to detect proteomics and bioinformatic analysis.

Results: The positive rate of CD44 and CCK8 cell proliferation experience in the CSCs group were higher than ESCCs group (P < 0.05). The plate cloning formation showed that the values of D0, Dq, N and SF2 were significantly higher in the CSCs group, and the radiation sensitization ratio was 1.556. Furthermore, 5,262 proteins were identified in the two groups in total. The up-regulation of 187 proteins and down-regulation of 83 proteins were detected in CSCs group (>1.5 times). Bioinformatic analysis further revealed that those quantifiable proteins were mainly involved in multiple biological functions and metabolic processes, including steroid biosynthesis, protein processing in endoplasmic reticulum, metabolic pathways and oxidative phosphorylation pathways. In addition, 53 acetylated sites were increased and 67 acetylated sites were decreased in CSCs group (>1.5 times). Those acetylated sites were involved in the regulation of DNA metabolic process, the function of cell adhesion, glycolysis and gluconeogenic pathway.

Conclusions: We provides a global survey of proteins and acetylations in ESCCs and CSCs. These proteins and acetylations may be related to the radiosensitivity, recurrence and metastatic of esophageal squamous carcinoma and could be a potential new target for esophageal squamous carcinoma.

Legal entity responsible for the study: Jiancheng Li.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1816P Survival outcomes for patients with lobectomy and wedge resection in lung cancer

S. Alshafie, S. Ahmed

Faculty of Medicine, Suez Canal University, Ismailia, Egypt

Background: Lobectomy is the most performed surgical procedure for lung cancer, however, patients who are eligible to lobectomy undergo wedge resection. The purpose of this study is to compare the survival of patients who underwent wedge resection versus lobectomy.

Methods: Using SEER18 Registries Research Database, we collected the data of 638 patients diagnosed with lung cancer from 2010 to 2012. Out of these patients, 423 underwent wedge resection, while 156 had lobectomy. We assessed the prognostic value of age, sex, stage, laterality and primary site. Kaplan-Meier method was used for survival analysis.

Results: Patients with lung cancer who underwent lobectomy had significantly better 3-year relative survival rates 47.2% than those who underwent wedge resection (47.2% versus 26.7%, respectively, p-value = 0.044). Subgroup analysis revealed better survival rates among female patients and stage III lung cancer. However, no advantage was associated with specific age, laterality, or primary site.

Conclusions: Patients who underwent lobectomy were associated with better 3-year relative survival rate compared to wedge resection.

Editorial acknowledgement: Inas Uthman.

Legal entity responsible for the study: Somia Alshafie.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1817TiP SAKK 17/16 - Lurbinectedin monotherapy in patients with progressive malignant pleural mesothelioma: A multicenter, single-arm phase II trial

Y. Metaxas[1], A. Xyrafas[2], M.T. Mark[1], M. Pless[3], M. Frueh[4], P.R. Froesch[5], M. Schneider[6], C. Biaggi Rudolf[6], F. Grosso[7], R. von Moos[1]

[1]Oncology/Hematology, Kantonsspital Graubünden, Chur, Switzerland, [2]Statistics, SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland, [3]Oncology/Hematology, Kantonsspital Winterthur, Winterthur, Switzerland, [4]Oncology/Hematology, Kantonsspital St. Gallen, St. Gallen, Switzerland, [5]Medical Oncology, IOSI Istituto Oncologico Svizzera Italiana, Locarno, Switzerland, [6]Clinical Trial Management, SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland, [7]Oncology/Hematology, Ospedale di Alessandria, Alessandria, Italy

Background: Unresectable malignant pleural mesothelioma (MPM) is treated with first-line platinum-based chemotherapy. Unfortunately, there is no standard second-line treatment for progressive patients. As widely available options like gemcitabine and vinorelbine provide only modest efficacy, progressive MPM poses an unmet medical need for further treatment strategies. Lurbinectedin (PM01183) is a novel compound, which covalently binds to the DNA minor groove, inducing double-strand breaks, as well as selectively reducing the tumor-associated macrophages. It has already been tested as monotherapy or in combination with chemotherapy in several Phase I-III trials in different tumor entities (including small cell lung cancer and ovarian cancer) with encouraging results. Based on MPM cases treated with lurbinectedin within the respective Phase I trials, where promising activity had been shown, we are currently conducting this proof-of-concept trial of safety and efficacy of lurbinectedin monotherapy in progressive MPM.

Trial design: This is a prospective 2-stage single-arm multicenter phase II trial. MPM patients progressing after platinum-based chemotherapy with good performance status are eligible for the trial. Prior surgery and/or radiotherapy and pretreatment with immunotherapy are allowed. Treatment will be given with 3.2 mg/m^2 lurbinectedin intravenously every 3 weeks (one cycle) until progression, unacceptable toxicity or patient withdrawal. Re-staging using contrast-enhanced computer tomography will be performed every 6 weeks. The primary endpoint of the trial is progression-free survival (PFS) at 12 weeks. Secondary endpoints are PFS, objective response rate, disease control rate at 12 weeks, overall survival, time-to-treatment failure and adverse events. A total of 6 Swiss and 3 Italian sites will participate for a total of 43 patients, as required by Simon's two-stage design. Accrual has already begun in Switzerland, is expected for February 2018 in Italy, and is estimated to be completed by beginning of 2019. Up to now 11 patients have been treated within the trial.

Clinical trial identification: NCT03213301.

Legal entity responsible for the study: Swiss Group for Clinical Cancer Research (SAKK).

Funding: SAKK, PharmaMar.

Disclosure: All authors have declared no conflicts of interest.

1818TiP Multicentre, double-blind, randomised phase II study evaluating gemcitabine with or without ramucirumab as II line treatment for MPM

M. Pagano[1], F. Zanelli[1], R. Gnoni[1], C. Bonelli[1], M. Tiseo[2], L. Boni[3], G.L. Ceresoli[4], P.A. Zucali[5], F. Grosso[6], G. Pasello[7], F. Cappuzzo[8], C. Pinto[1]

[1]Oncology Unit, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy, [2]Medical Oncology, AOU di Parma, Parma, Italy, [3]Istituto Toscano Tumori, Clinical Trial Coordinating Center, AOU Careggi, Florence, Italy, [4]Oncology Unit, Humanitas Gavazzeni, Bergamo, Italy, [5]UO Oncologia Medica e Ematologia, Humanitas Cancer Center Istituto Clinico Humanitas - IRCCS, Rozzano, Italy, [6]Oncology Unit, Ospedale di Alessandria, Alessandria, Italy, [7]Oncology Unit, Istituto Oncologico Veneto IRCCS, Padua, Italy, [8]Oncology Unit, Ospedale Civile di Ravenna - S.ta Maria delle Croci, Ravenna, Italy

Background: Malignant Pleural Mesothelioma (MPM) is still a fatal cancer and median overall survival is still approximately 1 year after diagnosis and new therapies are being awaited. After first line therapy patients inevitably progress and usually they are in good conditions and inquire about a second-line treatment. Even if a second line therapy is frequently considered in common clinical practice, the optimal treatment has not been defined yet. Gemcitabine was largely used in association with platinum compounds before the registration of platinum-pemetrexed doublet in first line setting. Pre-clinical data suggest the importance of angiogenesis in tumour biology of MPM. Considering the documented high VEGFR-2 expression in MPM and the high affinity of ramucirumab for the same receptor, and given the failure of previous anti-angiogenetic drugs as single agent, we hypothesised a significant activity of ramucirumab in MPM in association with gemcitabine.

Trial design: RAMES is a multicentre, double-blind, randomised Phase 2 study,to evaluate the efficacy and the safety of the addition of ramucirumab to gemcitabine as the second-line treatment of patients with MPM.Randomisation will be done via a centralized system and will stratified by performance status (0-1 vs 2) age ($\leq$70 vs $>$ 70) histology (epithlioid vs others) and time to progression after first line therapy ($<$ 6 months vs $\geq$ 6 months).The primary objective is overall survival. Secondary objectives are progression free survival and safety. Patients will be randomly assigned (1:1) to receive intravenous gemcitabine (1000 mg/mq) on days 1 and 8 every 21 days with placebo or combined with intravenous ramucirumab 10 mg/kg (ramucirumab group) on day 1 of a 21-day cycle until progression disease or unacceptable toxicity. The interim analysis was performed 6 weeks after enrolment of the 80th patient. Blood samples were collected for pharmacokinetic and immunogenic analyses. The study duration will be 24 months for the accrual. The great amount of interest and the scarce availability of ongoing trials have made recruitment rapid. This will allow information on the possible benefit of ramucirumab in MPM to be given much earlier than expected.

Clinical trial identification: EudraCT: 2016-001132-36.

Legal entity responsible for the study: AUSL-IRCCS Reggio Emilia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 1816P Comparison of 3-year relative survival rates between patients undergoing wedge resection vs lobectomy

Variables	Wedge resection	Lobectomy	p-value
Sex Male Females	20.2 33.3	33.5 64.4	0.000**
Stage I II III IV	- - 50.6% 26%	- 34.1% 52.2% 47.4%	0011*
Age 20-39 40-59 60-79 >80	30.9% 27.4% 27.1% 22.6%	66.9% 57.5% 42.3% 30.9%	0.416
Primary site Upper Lobe Middle Lobe Upper Lobe Lung, NOS	24.1% 17.5% 29.6% 25.6%	49.9% 46.9% 46.2% 44,9%	0.934
Laterality Right Left	25.4% 28.3%	49.7% 43.4%	0.902

*Statically significant at p-value $\leq$ 0.05.

**Highly significant at p-value $\leq$ 0.001.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii645–viii648, 2018
doi:10.1093/annonc/mdy302

THYROID CANCER

1819O Tumor growth rate and lenvatinib efficacy in radioiodine-refractory differentiated thyroid cancer

S. Leboulleux[1], E.K. Lee[2], L. Bastholt[3], M. Tahara[4], L.J. Wirth[5], S.I. Sherman[6], B.G. Robinson[7], A. Teng[8], P. Joshi[8], S. Misir[8], C.E. Dutcus[8], R.M. Tuttle[9], M.J. Schlumberger[1]

[1]Gustave Roussy, University Paris-Saclay, Villejuif, France, [2]Center for Thyroid Cancer, National Cancer Center, Goyang-Si, Republic of Korea, [3]Oncology, Odense University Hospital, Odense, Denmark, [4]Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [5]Cancer Center, Massachusetts General Hospital, Boston, MA, USA, [6]Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [7]Kolling Institute of Medical Research, The University of Sydney, New South Wales, Australia, [8]Oncology Business Unit, Eisai Inc., Woodcliff Lake, NJ, USA, [9]Endocrinology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

1820PD Synergistic anti-cancer activity of tyrosine kinase inhibitors and paclitaxel with radiation on anaplastic thyroid cancer in vitro and in vivo

Y.S. Lee, H. Chang, S.Y. Kim, H-S. Chang, C.S. Park

Thyroid Cancer Center, Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

1821PD Updated efficacy and safety data of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E–mutated anaplastic thyroid cancer (ATC)

B. Keam[1], R.J. Kreitman[2], Z.A. Wainberg[3], M.E. Cabanillas[4], D.C. Cho[5], A. Italiano[6], A. Stein[7], J.Y. Cho[8], J.H.M. Schellens[9], P.Y. Wen[10], C.C. Zielinski[11], A.D. Boran[12], B. Mookerjee[13], P. Burgess[14], F. Rangwala[13], V. Subbiah[15]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [2]Laboratory of Molecular Biology, National Institutes of Health, Bethesda, MD, USA, [3]Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA, [4]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [5]Department of Medicine, New York University Langone Medical Center, New York, NY, USA, [6]Early Phase Trials and Sarcoma Units, Institute Bergonié, Bordeaux, France, [7]Department of Internal Medicine II (Oncology Center), University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [8]Department of Medical Oncology, Yonsei University College of Medicine Gangnam Severance Hospital, Seoul, Republic of Korea, [9]Department of Clinical Pharmacology, Netherlands Cancer Institute, Amsterdam, Netherlands, [10]Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [11]Department of Medicine I, Comprehensive Cancer Center Medical University Vienna, Vienna, Austria, [12]Oncology Precision Medicine, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [13]Global Clinical Program, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [14]Oncology Global Development Unit, Novartis Pharma AG, Basel, Switzerland, [15]Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, TX, USA

1823P Synergistic anti-cancer effect of histone deacetylase inhibition and blockade of the glycolytic pathway

S.Y. Kim, Y.S. Lee, H. Chang, H-S. Chang, C.S. Park

Thyroid Cancer Center, Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Background: Advanced cancer has been shown to have a higher percentage of epigenetic changes are more often events than genetic mutations. Preclinical models have showed that combination of the HNHA (N-hydroxy-7-(2-naphthylthio) heptanomide) and 2DG (2-Deoxy-D-glucose) is a play crucial role in ATC (cancer stem-like cell, anaplastic thyroid cancer). The aim of this research is to study that caspase cleavage dependent apoptosis by combination therapy of HNHA and 2DG in ATC.

Methods: ATC cell lines were exposed to HNHA and 2DG alone or combined, and cell viability was determined by MTT assay. Synergistic anti-cancer effects of the combination therapy on cell cycle and intracellular signaling pathways were estimated by flow cytometry and immuno blot analysis. The ATC cell lines xenograft model was used to examine the anti-tumor activity in vivo.

Results: Consequently, our results are suggest that combination therapy of HNHA and 2DG is synergistically decreased cell viability in ATC cell, and also significantly induced apoptotic cell death in this cells, as showed by the cleavage of caspase-3. HNHA and 2DG combination was reduced anti-apoptotic factor in these cells. Thus, combination therapy with HNHA and 2DG most significantly reduced tumor volume in ATC cell xenografts.

Conclusions: The current study suggests that HNHA and 2DG combination treatment was more effective than treatment with the HNHA or 2DG alone. These findings may offer a new therapeutic approach to ATC include the cancer stem-like cells.

Legal entity responsible for the study: Sang Yong Lee.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1824P Lenvatinib and pembrolizumab as save and effective combination treatment in 8 patients with metastasized anaplastic (ATC) or poorly differentiated thyroid carcinoma (PDTC)

C. Dierks[1], C. Miething[1], O. Thomusch[2], N. von Bubnoff[1], J. Duyster[1]

[1]Haematology Oncology, University Medical Center Freiburg, Freiburg, Germany, [2]Surgery, University Medical Center Freiburg, Freiburg, Germany

Background: Introduction: Anaplastic thyroid carcinomas (ATC) and metastasized PDTC have a dismal prognosis of only few months despite extensive multimodal therapy. The tumors are high-proliferative and aquire numerous somatic mutations (often over several hundred mutations). These specifics implicate a special sensitivity of the tumors towards anti-angiogenic therapies and immune checkpoint inhibitors.

Methods: In the presented cases, we have combined anti-angiogenic therapy with lenvatinib and the immune checkpoint inhibitor pembrolizumab in 8 patients with metastasized ATC (n = 6) or metastasized PDTC (n = 2). All patient tumors had more than 100 somatic mutations as identified by whole exome sequencing (WES) and PD-L1 > 1%. Lenvatinib was started at 24 mg/kg BW and reduced to minimally 14 mg/kg BW upon appearance of intolerable side effects (uncontrollably high blood pressure, weight loss, loss of appetite). Pembrolizumab was started 3 - 8 weeks later and was given at a fixed dose of 200 mg every 3 weeks. Maximum treatment duration with this combination was 27 months (27, 24, 19, 11, 7, 6, 3, 1 month) and 6 patients are still on therapy.

Results: No continuous °III/IV toxicities were seen with the combination treatment. Weight loss (3 pts) and uncontrollably high blood pressure (3 pts) were normalized after reducing lenvatinib doses. One patient died 5 days after the first dose of pembrolizumab due to disease progression of the cervical tumor. All other patients have reached at least a SD (n = 2), most patients had reached a PR (n = 4) and one patient has reached a complete remission (CR). The majority of patients is still on therapy (27,24,19,7,6 and 3 months), implicating this treatment combination as a safe and effective treatment regimen for this extremely bad prognostic patient cohort.

Conclusions: Our results implicate that a combination of lenvatinib and pembrolizumab is safe and effective in patients with ATC or PDTC. The combination treatment shall now be systematically examined in a phase II clinical trial (ATLEP) in ATC/PDTC patients.

Legal entity responsible for the study: Uniklinik Freiburg.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1825P Both HIF-1α and GAB1 can regulate pim-1 in the papillary thyroid carcinoma

X. Zhu[1], Q. Wen[2], M. Ge[2]

[1]Zhejiang Cancer Institution, Hangzhou, China, [2]Head and Neck Surgery, Zhejiang Cancer Hospital, Hangzhou, China

Background: As a oncogene, Pim-1 has been proved to play key role in proliferation, apoptosis and angiogenesis. Thyroid cancer represents the most common malignancy in the endocrine system, and a marked increase in the incidence has occurred in recent years. Among them, papillary thyroid carcinoma (PTC) is the most common form. So it is worthwhile to discuss the function of Pim-1 in the development and progression of PTC.

Methods: 34 PTC patients were selected to investigate the levels of Pim-1, HIF-1α and GAB1 protein by IHC. After hypoxia treatment for 24h, Westernblot was carried out to detect the Pim-1, HIF-1α and GAB1 in the PTC cell BCPAP and TPC-1. BCPAB was trasfected with GAB1 shRNA and Full-length vector to achieve GAB1 knockdown and overexpression. CCK-8 assay was used to measure the ell proliferation. The migration and invasion capacity were tested by wound-healing and transwell methods respectively.

Results: Both Pim-1 and HIF-1α were overexpressed in the PTC tissues and Pim-1 levels were significant correlated with HIF-1α. Meanwhile, Pim-1 had a significant relationship with the tumor number - patients with multiple tumor have a higher Pim-1 level than that have solitary tumor and HIF-1α showed a significant correlation with patients' age. After bioinformatics screen, we found that there were 4 hypoxia response elements (HRE) in the Pim-1 promoter area, which suggested HIF-1α could transcriptional regulate Pim-1 directly. Moreover, hypoxia could signifcantly drive HIF-1α and Pim-1 elevation in both BCPAP and TPC-1. GAB1 was found to express higher in PTC tissues than that in the adjacent normal tissues and GAB1 level was significant associated with the tumor size. Morover, Pim-1 expression was significantly decrease and increase after GBA1 knockdown and overexpression in BCPAP. Meanwhile, GAB1 did not affect the cell viability but exerted a strong effect on the migration and invasion capacity of BCPAP. However, there was no change in GAB1 expression after hypoxia treatment in both BCPAP and TPC-1.

Conclusions: Taken together, our current data showed the important role of Pim-1 in the PTC. It also can be deduced that both HIF-1α and GAB1 are involved in the upstream regulation of Pim-1, but the detailed mechanism are different, which depended on the different tumor microenvironment.

Legal entity responsible for the study: Zhejiang Cancer Hospital.

Funding: National Natural Science Foundation of China.

Disclosure: All authors have declared no conflicts of interest.

1826P Increase in thyroid cancer (TC) incidence in Cyprus: Overdiagnosis or true increase of clinically relevant TC?

H.C. Charalambous[1], A. Demetriou[2], S. Frangos[3], P. Pavlou[2]

[1]Oncology, Bank of Cyprus Oncology Centre, Nicosia, Cyprus, [2]Cyprus Cancer Registry, Ministry of Health, Nicosia, Cyprus, [3]Nuclear Medicine, Bank of Cyprus Oncology Centre, Nicosia, Cyprus

Background: An increase in Thyroid Cancer (TC) incidence has been seen in most countries worldwide. The same has also been reported for Cyprus[1]. The most fundamental issue is whether this increase is due to increased investigations (opportunistic screening) and overdiagnosis of small incidental TC or due to a true increase in clinically relevant TC.

Methods: Data collection in the Cyprus Cancer Registry (CyCR) is guided by the MECC Manual of Coding and Staging for Cancer Registration. In this study, we considered only invasive cancer (ICD-O-3 behavior code=3). From 1998 until 2015 there were 2490 thyroid cancer diagnoses recorded in the CyCR, from which 2309 (92.7%) had histology and staging information recorded. We undertook analysis of the staging of recorded cases in the CyCR and calculated APC (Annual Percent Change) to ascertain whether the increase seen is due to small localized cancers (suggesting opportunistic screening) or also true for locally advanced / Lymph node positive tumours.

Results: The APC for all patients is 11.1% yearly increase. When analyzing by stage, the APC for regional (i.e. locally advanced) TC was 16.3% higher than for localized disease at 11.9%. There was also a statistically significant increase in metastatic cases, but this needs to be interpreted with caution due to the small number of patients with metastatic disease (data not presented).

Table: 1826P

Subgroup	Joinpoints	APC	Lower CI of APC	Upper CI of APC	Significance probability at $\alpha = 0.05$
Total	0	11.1	9.4	12.8	0.000
Local	1	11.9	10.1	13.7	0.000
Regional	0	16.3	12.5	20.2	0.000

Conclusions: Analysis of the Cyprus Cancer Registry data provide evidence of a large increase in TC in Cyprus, being due to an increase of both localized and also locally advanced tumours. It is therefore likely that the increase in TC is not only due to opportunistic screening, but also due to a true increase of larger, clinically relevant tumours.

Legal entity responsible for the study: Haris Charalambous.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1827P Surgery for lymph node metastases of sporadic medullary thyroid carcinoma

W. Fan, H. Jiang

Medical Oncology, The First Affiliated Hospital, Zhejiang University, Hangzhou, China

Background: Medullary thyroid carcinoma (MTC) arises from malignant proliferation and differentiation of C cells, approximately 2% of all thyroid malignancies. Calcitonin (CT) and carcinoembryonic antigen (CEA) secreted by C cells are the main secretory product and serves as a marker for the diagnosis of this disease. It is also used in the follow-up of MTC patients after thyroidectomy for the identification of relapse or progression of disease. Compared with other thyroid cancers, MTC has unique biological characteristics and is insensitive to radiotherapy, chemotherapy and iodine therapy. Surgical intervention is currently the only effective, curative treatment for medullary thyroid cancer. The 2015 American Thyroid Association recommended total thyroidectomy and different range of lymph node dissection, but controversy remains surrounding the indication for prophylactic lateral lymph node dissection. This study was performed to analyze the risk factors for cervical lymph node metastases and predict the indication for prophylactic lateral neck dissection in patients with sporadic medullary thyroid carcinoma (SMTC).

Methods: The aims of this study were to analyze the risk factors of cervical lymph node metastases, and also to predict the indication of prophylactic lateral neck dissection in SMTC patients.

Results: Metastases rates in central and lateral compartment were 46.2% (30/65) and 40.0% (26/65), respectively. Univariate analyses showed the incidence of cervical lymph node metastases was significantly higher in patients with tumor size >1cm, tumor multifocality and thyroid capsule invasion. Multivariate analyses revealed that only thyroid capsule invasion was an independent predictive factor for central compartment metastases ($p < 0.001$, OR = 11.080) and lateral neck metastases ($p < 0.001$, OR = 9.067). Moreover, the possibility of central compartment metastases was higher when preoperative value of serum carcinoembryonic antigen (CEA) was above 30 ng/mL (60% vs 34.3%, χ^2=4.298, P = 0.038).

Conclusions: The medullary thyroid carcinoma has a high incidence of cervical lymph node metastases. Prophylactic lateral node dissection is necessary in patients with thyroid capsule invasion or with high value of serum carcinoembryonic antigen (CEA).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1828P Role of SPECT-CT somatostatin-receptor scintigraphy in the management of medullary thyroid cancer (MTC)

S. Sergieva[1], M. Atanasova[2], A. Fakirova[3], S. Velchova[4]

[1]Nuclear Medicine, Specialized Hospital for Active Treatment in Oncological Diseases-Sofia City, Sofia, Bulgaria, [2]Medical Oncology, UH "City Clinic", Sofia, Bulgaria, [3]Pathology, Military Medical Academy, Sofia, Bulgaria, [4]Medical Oncology, Sofia Cancer Center, Sofia, Bulgaria

Background: The MTC arises from the parafollicular, calcitonin-secreting malignant transformed thyroid C-cells who express on the surface somatostatin SSTR receptors. The most of aggressive locally advanced/metastatic MTC tumors, found to be positive for RET proto-oncogene mutation, are treated with Vandetanib. SPECT-CT somatostatin-receptor scintigraphy with 99mTc-Tektrotyd should be considered for MTC imaging before and after therapy for exact staging and follow-up of the disease due to its highly sensitivity and specificity for detection of neuroendocrine tumors, expressed SSTR. The aim of this study was to evaluate clinical role of SPECT-CT scintigraphy with ^{99m}Tc-Tektrotyd in the management of patients with MTC.

Methods: 25pts (7M;18F) with MTC were studied; whole body somatostatin scintigraphy followed by target SPECT-CT studies were performed 2-4 hrs post i.v.inj. of 740 MBq ^{99m}Tc-Tektrotyd (Polatom). SPECT-CT camera Symbia T2, Siemens was used. Three of them were studied for initial pre-operative N/M-staging, 17 were follow-up after surgery. In 5 patients with metastatic disease SPECT-CT with ^{99m}Tc-Tektrotyd were performed before and after target therapy with Caprelsa (Vandetanib), 300mg/d orally.

Results: Initial pre-operative staging showed 3 positive results for the primary tumor and metastatic lymph nodes and 2 false negative imaging of small 1-4 mm lung metastases. True negative results were obtained in 5 cases after thyroidectomy. True positive results were obtained in 17 cases with local recurrence in the thyroid bed, lymphadenopathy, osteolytic bone metastases, lung and subcutaneous lesions. False positive result was in 1 case with benign ovary cyst. Plasma levels of calcitonin vary from 94 to 5496 pg/ml in all 17 patients with local recurrence and/or metastatic lesions. In 5/17 cases SPECT-CT studies were used to evaluate effect of target therapy, respectively: partial response – in 2 cases, stable disease – in 2 cases and progressive disease – in 1 cases.

Conclusions: SPECT-CT somatostatin-receptor scintigraphy with ^{99m}Tc-Tektrotyd is very useful functional imaging modality in patients with MTC in order to determinate personalized therapeutic disease approach.

Legal entity responsible for the study: Sonya Sergieva.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1829TiP A noninferiority trial of cabozantinib (C) comparing 60 mg vs 140 mg orally per day to evaluate the efficacy and safety in patients (pts) with progressive, metastatic medullary thyroid cancer (MTC)

J. Krajewska[1], B.G. Robinson[2], B. Keam[3], J. Capdevila[4], A. Klochikhin[5], H. Gan[6], E. Kapiteijn[7], R. Elisei[8], J. Partyka[9], A.E. Borgman[9], M. Schlumberger[10]

[1]Oncology Center, M. Sklodowska-Curie Institute, Gliwice, Poland, [2]Sydney Medical School, The University of Sydney, Sydney, Australia, [3]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [4]Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Oncology, Yaroslavl Regional Clinical Oncology Hospital, Yaroslavl, Russian Federation, [6]Clinical Trials Austin Health, Olivia Newton-John Cancer Wellness & Research Centre, Heidelberg, Australia, [7]Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [8]Endocrine Unit, University Hospital of Pisa, Pisa, Italy, [9]Clinical Research & Development, Exelixis, Inc, San Francisco, CA, USA, [10]Department of Nuclear Medicine and Endocrine Oncology, Gustave Roussy, Villejuif, France

Background: C inhibits receptor tyrosine kinases including MET, VEGF receptors, AXL, and RET. C has been approved in the US for the treatment of progressive, metastatic MTC and in the EU for progressive, unresectable locally advanced or metastatic MTC. In the phase 3 registrational study EXAM, pts were randomized 2:1 to receive 140 mg C or placebo (P) once daily (qd). The primary analysis for EXAM demonstrated a statistically significant improvement in progression-free survival (PFS) with a median PFS of 11.2 mo for C vs 4.0 mo for P (hazard ratio [HR] 0.28, 95% CI, 0.19–0.40; $p < 0.001$) (Elisei, JCO 2013). Dose reductions occurred commonly in the C arm with 82% of pts experiencing at least one dose reduction. While overall survival (OS) was

not significantly improved in the overall population (median OS of 26.6 mo for C vs 21.1 mo for P; HR 0.85, 95% CI 0.64–1.12; p = 0.24), median OS was 44.3 mo for C vs 18.9 mo for P (HR 0.60, 95% CI 0.38–0.94) in the RET M918T-positive subgroup (Schlumberger, Ann Oncol 2017).

Trial design: EXAMINER (NCT01896479) is a global, randomized, double-blind study comparing the safety and efficacy of C at 60 vs 140 mg qd in pts with progressive, metastatic MTC using a noninferiority study design. Approximately 188 pts will be randomized 1:1 to receive C at 140 mg qd as capsules or 60 mg qd as tablets in Europe, Asia, Canada, and other regions. Eligible pts must have measurable disease and documented progressive disease within 14 mo prior to enrollment. A recent tumor tissue sample to test for RET and RAS mutations or documentation of a RET or RAS mutation is required. Pts will be stratified based on RET M918T status. After randomization, pts will be treated until disease progression per RECIST 1.1 or intolerable toxicity. Tumor assessments will be performed every 12 weeks. PFS and objective response rate evaluated by independent review are the primary and secondary efficacy endpoints, respectively; safety and correlation of tumor mutation status with clinical response are additional endpoints. The EXAMINER study continues to enroll pts.

Clinical trial identification: NCT0189647.

Legal entity responsible for the study: Exelixis, Inc.

Funding: The study was supported by Exelixis, Inc.

Disclosure: J. Krajewska: Honoraria and subinvestigator in clinical trials: Eisai, Exelixis, Sanofi-Genzyme, Bayer Health Care; Travel, accommodations, expenses: Sanofi-Genzyme, Ipsen, Novartis. B.G. Robinson: Stock or other ownership: Cochlear Ltd.; Honoraria, consulting or advisory role, speakers' bureau: Eisai; Travel, accommodations, expenses: Loxo. H. Gan: Consulting or advisory role: MSD, AbbVie; Speakers' bureau, travel, accommodations, expenses: Ignyta; Research funding: BMS, Ignyta. R. Elisei: Consulting or advisory role: Sanofi-Genzyme, Eisai, Loxo, Exelixis; Speakers' bureau: Sanofi-Genzyme, Eisai; Travel, accommodations, expenses: Sanofi-Genzyme. J. Partyka: Employment, research funding, travel, accommodations and expenses, stock or other ownership: Exelixis. A.E. Borgman: Employee, stock or other ownership: Exelixis. M. Schlumberger: Honoraria, research funding: Bayer, Eisai, Exelixis-Ipsen, Sanofi-Genzyme; Consulting or advisory role: Bayer, Eisai, Exelixis-Ipsen, Sanofi-Genzyme; Travel, accommodations, expenses: Bayer, Eisai, Sanofi-Genzyme. All other authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii649–viii669, 2018
doi:10.1093/annonc/mdy303

TRANSLATIONAL RESEARCH

1830O Liquid biopsy as tool to monitor and predict clinical benefit from chemotherapy (CT) and immunotherapy (IT) in advanced non-small cell lung cancer (aNSCLC): A prospective study

L. Bonanno[1], E. Zulato[2], I. Attili[3], A. Pavan[3], P. Del Bianco[4], G. Nardo[2], M. Verza[2], L. Pasqualini[2], G. Pasello[1], G. Zago[1], S. Frega[3], M. Fassan[5], F. Calabrese[6], A. Amadori[2], V. Guarneri[3], P.F. Conte[7], S. Indraccolo[2]

[1]Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padua, Italy, [2]Immunology and Molecular Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy, [3]Department of Surgery, Oncology and Gastroenterology, University of Padua, Istituto Oncologico Veneto IRCCS, Padua, Italy, [4]Clinical Trial and Biostatistics Unit, Istituto Oncologico Veneto IRCCS, Padua, Italy, [5]Surgical Pathology Unit, Department of Medicine (DIMED), University-Hospital of Padua, Padua, Italy, [6]Department of Cardiothoracic and Vascular Sciences, University of Padova, Padua, Italy, [7]Surgery, Oncology and Gastroenterology, University of Padova, Istituto Oncologico Veneto IRCCS, Padua, Italy

1831PD Molecular differences between colorectal cancers with mutations in histone modifiers genes vs wild-type (WT) tumors

A. Puccini[1], K. Poorman[2], R. Goldberg[3], A.F. Shields[4], M. Winerip[2], W.M. Korn[5], M.D. Berger[6], R. Tokunaga[6], M. Naseem[6], F. Battaglin[6], W. Zhang[6], S. Soni[6], J.J. Hwang[7], P. Philip[4], J.L. Marshall[8], H-J. Lenz[6]

[1]Medical Oncology 1, IRCCS AOU San Martino - IST - Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [2]Molecular Biology, Caris Life Sciences, Phoenix, AZ, USA, [3]Medical Oncology, West Virginia University Cancer Institute, Morgantown, WV, USA, [4]Medical Oncology, Karmanos Cancer Institute, Detroit, MI, USA, [5]Molecular Biology, Caris Life Sciences, Phoenix, AZ, USA, [6]Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [7]Hematology/ Medical Oncology, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA, [8]Lombardi Cancer Center, Georgetown University Hospital, Washington DC, USA

1832PD Phase I study of CC-90011 in patients with advanced solid tumors and relapsed/refractory non-Hodgkin lymphoma (R/R NHL)

A. Hollebecque[1], J. de Bono[2], R. Plummer[3], N. Isambert[4], P. Martin-Romano[1], E. Baudin[1], S. Mora[5], A. Harding[6], A. Nguyen[7], E. Filvaroff[7], M. Lamba[8], K. Liu[9], J. De Alvaro[10], J. DiMartino[7], M. Zuraek[11], Z. Nikolova[5]

[1]Drug Development Department (DITEP), Institut Gustave Roussy, Villejuif, France, [2]Division of Clinical Studies, The Institute of Cancer Research and Royal Marsden, London, UK, [3]Newcastle University, Northern Institute for Cancer Research, Newcastle, UK, [4]Unité de Phases Précoces U2P – CLIP[2] BFC, Centre Georges-François Leclerc (Dijon), Dijon, France, [5]Translational Development, Celgene Institute Translational Research Europe-CITRE, Seville, Spain, [6]Translational Development, Celgene Ltd, London, UK, [7]Epigenetics, Celgene Corporation, South San Francisco, CA, USA, [8]Translational Development, Celgene Corporation, Summit, NJ, USA, [9]Biostatistics, Celgene Corporation, Berkeley Heights, USA, [10]Hematology, Celgene Institute Translational Research Europe-CITRE, Seville, Spain, [11]Translational Medicine, Celgene Corporation, South San Francisco, CA, USA

1834PD **Genomic profile and T cell receptor repertoire of lung adenosquamous carcinomas**

G. Lin[1], C. Li[2], W-Z. Fang[3], W. Chen[4], C. Huang[1]

[1]Department of Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China, [2]Department of Pathology, Fujian Cancer Hospital, Fuzhou, China, [3]Department of Medical Oncology, Fuzhou General Hospital, Fuzhou, China, [4]Clinical Genetics, Geneplus-Beijing Institute, Fuzhou, China

1833PD **Lack of efficiency of precision oncology with target-based investigational treatments for patients in early phase clinical trials based on pre-screened molecular alterations**

B. Doger de Spéville[1], V. Moreno[2], T. Hernandez[2], V. Boni[3], M.J. de Miguel[4], F. Rojo[5], F. Lopez-Rios[6], E. Calvo[4]

[1]Start-Madrid Phase 1 Unit, Fundación Jiménez Díaz, Madrid, Spain, [2]Medical Oncology-Start Madrid-FJD, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [3]Oncology, Hospital Madrid Norte San Chinarro Centro Integral Oncologico Clara Campal, Madrid, Spain, [4]Start-Madrid Phase 1 Unit, Hospital Madrid Norte San Chinarro Centro Integral Oncologico Clara Campal, Madrid, Spain, [5]Pathology Service, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain, [6]Pathology Service, Hospital Madrid Norte San Chinarro Centro Integral Oncologico Clara Campal, Madrid, Spain

1835PD **Comparative molecular analysis between microsatellite instability-high (MSI-H) tumors with high tumor mutational burden (TMB-H) versus MSI-H tumors with TMB-intermediate/low**

M.E. Salem[1], A. Puccini[2], A. Grothey[3], J. Xiu[4], R. Goldberg[5], E.S. Kim[1], W.M. Korn[4], H-J. Lenz[6], D. Raghavan[7], J.L. Marshall[8], M.J. Hall[9]

[1]Medical Oncology, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA, [2]Medical Oncology 1, IRCCS AOU San Martino – IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [3]Medical Oncology, Mayo Clinic, Rochester, MN, USA, [4]Molecular Biology, Caris Life Sciences, Phoenix, AZ, USA, [5]Division of Medical Oncology, West Virginia University Cancer Institute, Morgantown, WV, USA, [6]Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [7]Medical Oncology, Carolinas HealthCare System, Charlotte, NC, USA, [8]Lombardi Cancer Center, Georgetown University Hospital, Washington DC, USA, [9]Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA, USA

1836PD Representative sequencing: Profiling extreme tumor diversity

K. Litchfield[1], L. Au[2], C. Swanton[2], S. Turajlic[2]

[1]Swanton Lab, The Francis Crick Institute, London, UK, [2]Translational Cancer Therapeutics, The Francis Crick Institute, London, UK

1837PD Characterization through whole exome sequencing of individuals presenting extreme phenotypes of high and low risk to develop tobacco-induced non-small lung cancer (NSCLC)

J.L. Perez Gracia[1], M.J. Pajares[2], J.P. Fusco[1], M. Andueza[1], V. Segura[3], M.I. Mora[4], E. Guruceaga[5], R. Sanchez Bayona[1], A. Gurpide[1], J.M. Lopez-Picazo[1], I. Gil-Bazo[1], J.P. de Torres[6], J. Zulueta[6], R. Pio[2], I. Melero[7], M.F. Sanmamed[1], M. Rodriguez-Ruiz[1], A. Gonzalez Neira[8], L. Montuenga[2], A. Patiño-Garcia[4]

[1]Oncology, Clinica Universidad de Navarra, Pamplona, Spain, [2]Program in Solid Tumors and Biomarkers, CIMA, Universidad de Navarra, Pamplona, Spain, [3]IDISNA and Bioinformatics Unit, CIMA, Universidad de Navarra, Pamplona, Spain, [4]Pediatrics and CIMA LAB Diagnostics, Clinica Universidad de Navarra, Pamplona, Spain, [5]Proteomic, Bioinformatic and Biostatistics, Universidad de Navarra, Pamplona, Spain, [6]Pneumology, Clinica Universidad de Navarra, Pamplona, Spain, [7]Laboratory of Immunology, Clinica Universidad de Navarra, Pamplona, Spain, [8]Human Genetics, CNIO, Madrid, Spain

(cancer-cohort, n = 50) or that did not present NSCLC or any other tumors at an advanced age (cancer-free cohort, n = 50). We sequenced their germline DNA using the Agilent Human Exome Capture v5, which includes 21,522 genes (357,999 exons). We selected genetic variants located in the exonic regions and splice sites of the genes evaluated; that codified for non-synonymous codons; and that showed allelic differences >15% between both cohorts.

Results: The mean age for the cancer and cancer-free cohorts was 50 (range 34-55) and 78 years (72-90). Mean tobacco consumption was 44 (range 6-72) and 55 pack-years (20-124). Median exome sequencing coverage was 96% at > 10X and median depth was 97X. We identified 229 differential variants between both cohorts, located in 189 genes. The most significant variants ($p < 10^{-4}$) are shown in the table. Twenty genes or family genes included >3 differential genetic variants (range 3-25): ADAMTS, ALPK2/3, ankyrins, APOL4, CCDC, CRIPAK, FYCO1, HLA-A, keratins, mucins, olfactory receptors, PDPR, PRAME family, RFPL2, RP1L1, SAMD9, SLC transporters, anoctamins, TTN, and ZNF family.

Conclusions: We identified genetic variants associated with individuals presenting extreme phenotypes of high and low risk to develop tobacco-induced NSCLC. These variants warrant further study to characterize their impact in the development of these extreme phenotypes.

Legal entity responsible for the study: Universidad de Navarra.

Funding: Spanish Society of Medical Oncology, Fundación SEOM and Fundación Salud 2000, Government of Navarra.

Disclosure: All authors have declared no conflicts of interest.

1838P CANscript™ as a patient-derived predictive platform for individualizing treatment in lung cancer

G. Babu[1], K. Deepak[2], B. Balakrishnan[3], M. Biswas[4], A. Prasath[3], P. Radhakrishnan[5], A. Chatterjee[3], S. Thiyagarajan[3], P. Chaudhuri[3], P.K. Majumder[5]

[1]Kidwai Memorial Institute of Oncology, HCG Curie Centre of Oncology, Bangalore, India, [2]Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore, India, [3]Cancer Biology, Mitra Biotech, Bangalore, India, [4]Molecular Pathology, Mitra Biotech, Bangalore, India, [5]Cancer Biology, Mitra Biotech, Woburn, MA, USA

Background: Lung cancer causes nearly 1.69 million deaths globally and 5-year survival rate is less than 20%. Several biomarkers have improved treatment selection and overall prognosis in lung cancer to some extent (JNCCN; 2017;15:504). However, clinical relevance of these biomarkers is limited to only a small percentage of patients. Hence, there is a need for an individulized tool that can accurately predict an individual's response to a therapy, especially in scenarios where there is a choice of equivalent treatment regimens and no specific biomarkers.

Methods: CANscript™ effectively recreates a patient's tumor microenvironment ex vivo by preserving the native contexture. The platform provides phenotypic assessment of response to the drug(s) tested for a given tumor and generates clinically relevant predictions for real-time treatment selection (Nat. Commun. 2014, 6:6169). We used this platform to assese phenotypic response of lung tumors.

Results: Twenty-one lung cancer patient tumors were treated with one or more FDA approved regimens including targeted therapy and chemotherapy in CANscript platform. We did not observe any advantage of targeted therapy (EGFR, PD1 inhibitors) over chemotherapy. Six tumors, which were non-responders to gefitinib, were predicted responders to carboplatin/pemetrexed and/or carboplatin/docetaxel. Further, out of 4 gefitinib responders, 3 were predicted to respond to chemotherapies carboplatin/pemetrexed or carboplatin/docetaxel. Highest efficacy was observed in carboplatin/pemetrexed and carboplatin/docetaxel (47% and 46% respectively). 25% tumors treated with anti-PD1 responded to the therapy, matching the reported clinical response rate of anti-PD-1 therapy.

Conclusions: CANscript™ is used as an ex-vivo, personalized platform that can predict an individual's response to various classes of anticancer drugs. The platform has been validated over a large number of clinical samples and the current study indicates that CANscript is a preferred platform for selecting individualized drug responses for treatment of lung cancer.udy indicates that CANscript is a preferred platform for selecting individualized drug responses for treatment of lung cancer.

Legal entity responsible for the study: Mitra Biotech and Kidwai Memorial Institute of Oncology.

Funding: Has not received any funding.

Disclosure: G. Babu: Consultant: HCG Hospital, Mitra Biotech. All other authors have declared no conflicts of interest.

1839P Whole-exome cfDNA profiling captures the mutational signatures of metastatic breast cancer for monitoring disease evolution

R.K. Hastings[1], M.R. Openshaw[1], M. Vazquez[2], D. Fernandez-Garcia[1], D. Guttery[1], K. Page[1], B. Toghill[1], A. Thomas[1], S. Ahmed[3], R.A. Toledo[4], J.A. Shaw[1]

[1]Leicester Cancer Research Centre, University of Leicester, Leicester, UK, [2]Genome Informatics, Barcelona Supercomputing Center, Barcelona, Spain, [3]Leicester Cancer Research Centre, University Hospitals of Leicester NHS Trust Leicester Royal Infirmary, Leicester, UK, [4]CIBERONC, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Whole-exome sequencing of plasma cell-free DNA (WES-cfDNA) is an emerging liquid biopsy approach for identification of somatic mutations and yields high-concordance when compared to WES of the tumours of patients with advanced disease. Here we show that sequential WES-cfDNA provides insight regarding the evolution of metastatic breast cancer and that global mutation profiles relate to clinical response and progression to different lines of treatment.

Methods: A patient with inherited BRCA2 breast cancer was recruited at disease relapse and blood samples were then taken over a 2 year period on treatment until death. Whole-exome sequencing was performed on 12 DNA samples: primary tumor, 2 biopsies at relapse and 8 sequential cfDNA samples. Results were validated by targeted amplicon sequencing and ddPCR. Somatic Single Nucleotide Variants (SNVs) were called with Mutect2. Mutational signatures (MS) and their contributions to each sample were detected using the R package deconstructSigs.

Results: WES profiling showed that MS-3 (associated with germline BRCA2 status) was the predominant signature in the primary tumour, whereas the signature of the two relapse biopsies were MS-3, MS-4 and MS-5, and MS-3, MS-4 and MS-6. The first blood sample taken at relapse with bone disease also had a mixed MS profile. The MS-3 signature was detected in cfDNA with progression to lung and initially resolved in response to carboplatin treatment. MS-3 also predominated in cfDNA on subsequent disease progression and was the dominant MS at the time of death. SNV analysis identified a Tier-1 PIK3CA mutation in the primary and relapse tissue, whereas three other Tier-2 mutations in DNM2, DCC and ATP1A1 were specific to relapse, indicative of cancer evolution. All four variants were detected at high levels by WES-cfDNA. Lastly, an ESR1 emergent mutation was identified by targeted sequencing in cfDNA and predicted failure of letrazole therapy.

Conclusions: Our study demonstrates the capacity of sequential WES-cfDNA to capture the genomic profiles of advanced cancer. The MS in cfDNA can be used track tumour evolution, and give insight into the characteristic of the dominant and lethal clone.

Legal entity responsible for the study: University of Leicester.

Funding: Hope Against Cancer, Cancer Research UK, Leicester ECMC.

Disclosure: A. Thomas: Honoraria: Amgen, Servier, BMS. S. Ahmed: Consulting: Novartis, Eisai, AstraZeneca, MSD, BMS. J.A. Shaw: Scientific advisory board: Qiagen; Board member: International Journal of Experimental Pathology. All other authors have declared no conflicts of interest.

1840P Preclinical evaluation of a non-depleting, first-in-class humanized IgG4 agonist anti-ICOS antibody

S. Brett[1], S. Yadavilli[2], L. Seestaller-Wehr[2], S. Bhattacharya[3], H. Jackson[3], M. Bi[3], J. Willoughby[4], T. Zhang[2], Y-B. Liu[2], Y.K. Katlinskaya[2], H. Shi[3], J. Jing[3], A. Hahn[3], S. Speller[5], D. David Figueroa[2], J. Yu[2], D. Olive[6], M. Cragg[4], P. Mayes[2], A. Hoos[3]

[1]Immuno-Oncology and Combinations, GlaxoSmithKline, Stevenage, UK, [2]Oncology, GlaxoSmithKline, Collegeville, PA, USA, [3]Immuno-Oncology Combinations DPU, GlaxoSmithKline, Collegeville, PA, USA, [4]Antibody and Vaccine Group, University of Southampton, Southampton, UK, [5]Biopharm Discovery, GlaxoSmithKline, Stevenage, UK, [6]Inserm U1068, Centre de Recherche en Cancérologie de Marseille (CRCM), Marseilles, France

Background: Inducible T cell Co-Stimulator (ICOS) is a co-stimulatory receptor, induced on activated T cells (TC) upon TC receptor engagement. Emerging clinical and preclinical data for checkpoint inhibitors demonstrate increased ICOS expression on effector TC, which has been linked to improved clinical outcomes. We have therefore developed an ICOS antibody optimized for agonist activity.

Methods: Syngeneic mouse tumor models and human ex-vivo PBMC and tumor infiltrating lymphocyte culture assays were utilized to evaluate the activity of a murine (7E.17G9) or human (H2L5) specific ICOS agonist antibody alone and in combination with PD-1 blockade. A selection of flow cytometry, IHC, multiplex IF, nanostring, and in silico analysis was performed to characterize and develop H2L5 for subsequent clinical evaluation.

Results: ICOS induction either with 7E.17G9 or H2L5 agonist antibody induced significant activation and clonal expansion of both CD4+ and CD8+ effector TC. These TC had increased effector function (higher IFN-γ and Granzyme B) and increased homing to tumors resulting in antitumor responses when administered alone and in combination with PD-1 blockade. The level of expression of ICOS on effector and regulatory TC was found to overlap, suggesting that Fc-mediated depletion associated with IgG1 may result in depletion of effector TC. Preclinical data using different Fc isotypes supported the selection of the stabilized IgG4PE isotype for optimal agonism in the absence of NK-mediated depletion of effector TC. Drug concentrations associated with ICOS receptor occupancy, increases in TC activation and tumor reduction, support selected

doses and biomarker strategy in the clinic. Select solid tumors types were identified for clinical studies based on expression of ICOS, ICOS-L, PD-L1 and PD-1.

Conclusions: IgG4PE provides the optimal isotype for delivering ICOS agonism whilst reducing the risk of depletion of ICOS positive effector TC. The comprehensive preclinical data package generated, supports clinical testing of the H2L5 IgG4PE ICOS agonist antibody (GSK3359609), currently being investigated alone and in combination with pembrolizumab, in a first in human clinical study (INDUCE-1).

Legal entity responsible for the study: GlaxosmithKline.

Funding: GlaxoSmithKline.

Disclosure: S. Brett, S. Yadavilli, L. Seestaller-Wehr, S. Bhattacharya, H. Jackson, M. Bi, T. Zhang, Y.K. Katlinskaya, H. Shi, J. Jing, A. Hahn, S. Speller, D. David Figueroa, J. Yu, A. Hoos: Employee and stockholder: Glaxosmithkline Pharmaceuticals. D. Olive: Cofounder and shareholder: Imcheck Therapeutics. M. Cragg: Consultant: Bioinvent; Educational and advisory roles: Baxalta; Research funding: Roche, Bioinvent, Gilead, GSK. P. Mayes: Stockholder and employee: Incyte. All other authors have declared no conflicts of interest.

1841P Refining criteria of hyperprogression (HPD) with immune checkpoint inhibitors (ICIs) to improve clinical applicability

I. Matos Garcia[1], A. García Ruiz[2], J. Martin-Liberal[1], C. Hierro[1], M. Ochoa De Olza Amat[3], C. Viaplana[4], G. Mur[1], M. Vieito Villar[1], I. Brana[3], A. Azaro[3], C. Perez[1], V. Rodriguez Freixinos[3], G. Argiles[5], M. Oliveira[3], E. Felip Font[6], E. Muñoz-Couselo[3], J. Tabernero[3], R. Dienstmann[4], E. Garralda[7]

[1]Medical Oncology, Vall dHebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [2]Radiomics Group, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain, [3]Department of Medical Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [4]Oncology Data Science (ODysSey) Group, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Gastrointestinal and Endocrine Tumors Group, Vall d'Hebron Institute of Oncology, VHIO, Barcelona, Spain,[6]Medical Oncology Service (Lung Cancer Unit), Vall d'Hebron University Hospital, Barcelona, Spain, [7]Early Drug Development Unit, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain

Background: Rapid progression while on ICIs has been clinically described as HPD, however there is still not a consensus definition for this phenomenon. Institute Gustave Roussy (IGR) firstly described HPD as $\geq$ two-fold increase in tumor growth rate (TGR) during experimental period (EXP) vs. Reference period (REF). We recently described VHIO HPD using EXP only, as the following: PD at first restaging with $\geq$40% increase in sum of target lesions or $\geq$ 20% with appearance of multiple new lesions, with minimum absolute increase in measurable lesions of 10 mm (Matos I. et al. ASCO 2018).

Methods: Patients (pts) treated with ICIs in Ph1 trials at VHIO were analysed (n = 214). Our aim was to assess overall survival (OS) in pts who achieved PD as best response, evaluate HPD according to IGR or VHIO criteria and investigate discordances between both definitions.

Results: From Jan'12 to Oct'17, 214 pts were treated with ICIs (53% in combinations). Best response was PD in 47% pts (n = 101). Only 50 pts were evaluable for the primary endpoint (20 had PD before the first evaluation and 31 had no REF CT-scan). Using IGR criteria, median OS was 4.5 m (95% CI: 3.6-5.3) in HPD group (n = 15) versus 6.3 m (95% CI 1.7-10.9) in non-HPD group (HR = 1.85; 0.86-3.9; p = 0.11). Using VHIO criteria, median OS was 3.6 m (0.8-6.3) in HPD group (n = 21) versus 8.7 m (4.2-13.2) in non-HPD group (HR = 2.33; 1.10-4.95; p = 0.02). Overall concordance rate between the two criteria was 56% (p = 0.45). Most discordances were HPD by VHIO and non-HPD by IGR (28%). Baseline target lesion summatory in EXP was not different in pts with HPD by IGR or VHIO (p > 0.1). Importantly, pts with HPD by IGR had significantly lower TGR-REF (p < 0.001). Using VHIO criteria, we found no difference in TGR-REF between HPD vs non-HPD (p = 0.15). However, higher TGR-EXP was found in pts with HPD using VHIO criteria (p < 0.001).

Conclusions: We were able to validate IGR HPD criteria in our cohort, despite substantial loss in evaluable pts due to missing REF CT scans. No concordance was observed between IGR and VHIO HPD definitions. VHIO HPD criteria is strongly prognostic, easy-to-use in the clinic (EXP only) and biologically sound (not affected by small TGR during previous therapy and linked to high TGR during ICI exposure).

Legal entity responsible for the study: Vall d'Hebron Institute Oncology.

Funding: Has not received any funding.

Disclosure: J. Tabernero: Advisory role: Bayer, Boehringer Ingelheim, Genentech/Roche, Lilly, MSD, Merck Serono, Merrimack, Novartis, Peptomyc, Roche Sanofi, Symphogen, Taiho. E. Garralda: Advisory boards: Roche, NeoMed Therapeutics, Ellypses Pharma. All other authors have declared no conflicts of interest.

1842P Foretinib circumvents the NTRK1 G667C mutation-associated entrectinib-resistance in the brain and liver metastases produced by NTRK1 fusion-positive tumor cells

S. Yano, A. Nishiyama, K. Kita, S. Takeuchi

Division of Medical Oncology, Kanazawa University, Kanazawa, Japan

Background: Rearrangement of the neurotrophic tropomyosin receptor kinase 1 (NTRK1) gene, which encodes tyrosine receptor kinase A (TRK-A), occurs in various cancers, including colon cancer. Although entrectinib is effective in the treatment of central nervous system (CNS) metastases that express NTRK1 fusion proteins, acquired resistance inevitably results in recurrence. CNS is a sanctuary for targeted drugs; however, the mechanism by which CNS metastases become entrectinib-resistant remains elusive and must be clarified to develop better therapeutics.

Methods: The entrectinib-resistant cell line KM12SM-ER was developed by continuous treatment with entrectinib in the brain metastasis-mimicking model inoculated with the entrectinib-sensitive human colon cancer cell line KM12SM, which harbors the TPM3-NTRK1 gene fusion. The mechanism of entrectinib resistance in KM12SM-ER cells was examined by next-generation sequencing. Compounds that overcame entrectinib resistance were screened from a library of 122 kinase inhibitors.

Results: KM12SM-ER cells, which showed moderate resistance to entrectinib in vitro, had acquired the G667C mutation in NTRK1. The kinase inhibitor foretinib inhibited TRK-A phosphorylation and the viability of KM12SM-ER cells bearing the NTRK1-G667C mutation in vitro. Docking-simulated models based on the crystal structures of the foretinib/EphA2 and entrectinib/Alk complexes support the inhibitory effects of foretinib and entrectinib on the wild-type and G667C mutant of TRK-A. Moreover, foretinib markedly inhibited the progression of entrectinib-refractory KM12SM-ER-derived liver metastases and brain tumors in animal models, predominantly through inhibition of TRK-A phosphorylation.

Conclusions: These results suggest that foretinib may be effective in overcoming entrectinib resistance associated with the NTRK1-G667C mutation in NTRK1 fusion-positive tumors in various organs, including the brain, and provide a rationale for clinical trials of foretinib in cancer patients with entrectinib-resistant tumors harboring the NTRK1-G667C mutation, including patients with brain metastases.

Legal entity responsible for the study: The authors.

Funding: Japan Agency for Medical Research and Development (AMED) and JSPS KAKENHI.

Disclosure: All authors have declared no conflicts of interest.

1843P Molecular alterations and matched treatment in older patients: Results from the MOSCATO 01 trial

P. Vuagnat[1], C. Baldini[1], L. Verlingue[1], P. Martin Romano[1], A. Varga[1], A. Hollebecque[1], S. Postel-Vinay[1], A. Gazzah[1], R. Bahleda[1], A. Marabelle[1], V. Ribrag[1], S. Champiat[1], J-M. Michot[1], J-C. Soria[2], C. Massard[1]

[1]Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, [2]Drug Development Department (DITEP), Medimmune, Gaithersburg, MD, USA

Background: Previous works in molecular portraits of cancer have shown differences by ages with the accumulation of somatic mutations, suggesting that older patients may have aged specific genomic profiles. However, there is a lack of data concerning genomic alterations in metastatic older patients. We aimed at analyzing the clinical and pathological characteristics and outcomes by genomic alterations of older patients enrolled in MOSCATO-01 trial.

Methods: We retrospectively collected data from MOSCATO-01 trial from all patients over > 70 years old enrolled from November 2011 to March 2016 and performed a descriptive analysis of this sub group of patients with advanced solid tumor.

Results: Among the 1035 patients enrolled in the MOSCATO trial, 85 patients (8,2%) over 70 years old were included, with a median age of 74 (range 71-86). Urologic cancers were the most frequent cancer. All tumor biopsies were performed and a molecular portrait was obtained in 66 patients (77.6%). Almost 40 different molecular alterations were identified. An actionable molecular alteration was identified in 46 patients (54%). Among them, 13 patients had $\geq$ 2 (range 1-5) actionable targets. The most frequent alteration pathways were: Pi3K (21%), NOTCH (11,3%), FGF and FGFR mutation (both 9.7%), PTEN (6,5%), FBXW7, MDM2 and EGFR (4,8% each). A total of 23 (27%) patients were treated with a targeted therapy matched to a genomic alteration, and 15 of them were enrolled in phase 1 or 2. The PFS2/PFS1 ratio was >1.3 in 31.8 % of the patients (7/22, one missing data). Among the 46 patients with actionable molecular alteration, median overall survival was better in the group of patient with matched therapy (18.4 vs 5.4 months, p = 0,07 NS).

Conclusions: The genomic profile > 70 years old is feasible in advanced geriatric malignancies and can lead to a better understanding in the biology of cancer among the elderly and could improve outcomes with molecular target agents.

Clinical trial identification: MOSCATO 01 (NCT01566019).

Legal entity responsible for the study: Christophe Massard.

Funding: Gustave Roussy.

Disclosure: L. Verlingue: Consultant: Adaptherapy. A. Hollebecque: Honoraria: Merck Serono; Consulting: Amgen; Expenses: Amgen, Servier. J-C. Soria: Employement and

ownership: AstraZeneca; Honoraria and consulting: AstraZeneca, BMS, Pfizer, Roche, Sanofi, Pierre Fabre. C. Massard: Other relationship: Amgen, Astellas Pharma, AstraZeneca, Bayer, Celgene, Genentech, Ipsen, Novartis, Pfizer, Roche, Sanofi, Orion Corporation, Lilly Pharma, Janssen Inc. Pharmaceutical. All other authors have declared no conflicts of interest.

1844P Prognostic implications of mismatch repair deficiency in patients with early-stage colorectal and endometrial cancer

E. Fountzila, V. Kotoula, G. Pentherdoudakis, K. Manousou, E. Vrettou, C. Poulios, C. Papadimitriou, G. Raptou, E. Pectasides, G. Polychronidou, G. Karayannopoulou, S. Chrisafi, P. Papakostas, T. Makatsoris, A. Psyrri, E. Samantas, M. Bobos, C. Christodoulou, D.G. Pectasides, G. Fountzilas

Data Office, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece

Background: The clinical relevance of mismatch repair deficiency (MMRd) in patients with early-stage cancer remains unclear. Our goal was to investigate the prognostic role of MMRd in patients with colorectal and endometrial cancer.

Methods: From 05/1990 to 03/2013, formalin-fixed paraffin-embedded primary tumors were prospectively collected from patients with early-stage colorectal (991) and endometrial (167) cancer, referred to the Departments of Medical Oncology affiliated with the Hellenic Cooperative Oncology Group. Protein expression of MMR proteins was evaluated by immunohistochemistry. The primary outcome measure was overall survival (OS).

Results: Overall, 1158 patients were included (median age, 64 years). Stage III disease was diagnosed in 58% and 19% of patients with colorectal and endometrial cancer, respectively. All patients with colorectal cancer but only 13% of those with endometrial cancer received adjuvant treatment. MMRd was observed in 114 (11.5%) of colorectal and 80 (48%) of endometrial tumors. MMRd was associated with younger age at diagnosis (62 vs. 60y, Mann-Whitney, $p = 0.003$), higher tumor grade (26.3% vs 16.5%, chi-square, $p < 0.001$) and lower tumor stage (72% vs. 42.6%, $p < 0.001$). Colorectal MMRd tumors were more likely right-sided (64.6% vs. 27.2%, $p < 0.001$), and with a mucinous component (63.7% vs. 41.4%, $p < 0.001$). Endometrial MMRd tumors were more often endometrioid (74/144, 51.4%) than serous/clear cell (3/15, 20%) carcinomas ($p = 0.020$). Compared to MMR proficiency, MMRd was associated with improved OS in the entire cohort (HR = 0.66, 95% CI 0.47-0.92, Wald's $p = 0.013$) and in patients with endometrial cancer, (HR = 0.39, 95% CI 0.20-0.77, $p = 0.006$) but not in patients with colorectal cancer (HR = 0.73, 95% CI 0.49-1.09, $p = 0.120$). In multivariate analysis adjusting for tumor type, stage and grade, MMRd maintained its favorable prognostic significance in the entire cohort (Wald's $p = 0.014$) and in patients with endometrial cancer ($p = 0.017$).

Conclusions: MMRd is associated with improved outcomes in patients with early-stage endometrial cancer, but not in patients with early-stage colorectal cancer.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group.

Funding: Hellenic Cooperative Oncology Group Internal Research Grant.

Disclosure: All authors have declared no conflicts of interest.

1845P Safety, clinical activity and pharmacological biomarker evaluation of the DNA-dependent protein kinase (DNA-PK) inhibitor M3814: Results from two phase I trials

M. Mau-Sorensen[1], M. van Bussel[2], M. Kuipers[3], D.L. Nielsen[4], H.M. Verheul[5], P. Aftimos[6], M.J.A. de Jonge[7], B. van Triest[2], J. Falkenius[8], J. Debus[9], E. Troost[10], M. Samuels[11], B. Sarholz[12], V. Budach[13], S. Goel[14], G. Locatelli[15], P.F. Geertsen[16]

[1]Department of Oncology, SKACCD - Rigshospitalet, Copenhagen, Denmark, [2]Department of Clinical Pharmacology, Netherlands Cancer Institute, Amsterdam, Netherlands, [3]Early Oncology, Merck KGaA, Darmstadt, Germany, [4]Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark, [5]Medical Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands, [6]Medical Oncology Clinic, Institut Jules Bordet, Leuven, Belgium, [7]Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands, [8]Department of Oncology, Karolinska University Hospital, Stockholm, Sweden, [9]Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany, [10]Department of Radiotherapy and Radiation Oncology, University Hospital Carl Gustav Carus and Faculty of Medicine of Technische Universität Dresden, Dresden, Germany, [11]Department of Radiation Oncology, University of Miami, Miami, FL, USA, [12]R&D Global Biostatistics & Epidemiology, Merck KGaA, Darmstadt, Germany, [13]Klinik fuer Radioonkologie, Klinik fuer Radioonkologie und Strahlentherapie Charite, Berlin, Germany, [14]Medical Oncology, Montefiore Medical Center (East campus) , Medical Park at Eastchester Albert Einstein Cancer Center, Bronx, NY, USA, [15]Global Clinical Development Unit - Oncology, Merck KGaA, Darmstadt, Germany, [16]Medical Oncology, Herlev Hospital, University of Copenhagen, Herlev, Denmark

Background: Agents that generate breaks in DNA are frequently used in the treatment of cancer. These agents induce different forms of DNA damage including double-strand breaks (DSBs), which are the most lethal if left unrepaired. M3814 targets tumor cell growth and survival by inhibiting DNA-PK, which is part of a critical DSB DNA damage repair mechanism. M3814 has been explored as a single agent (A; NCT02316197) and in combination with radiotherapy (RT) (B; NCT02516813).

Methods: In both trials patients (pts) were treated with ascending doses of M3814 to establish the safety and maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) (primary endpoint) and efficacy (secondary endpoint). Dose-limiting toxicity (DLT) was evaluated after 3 (A) or 5 weeks (B). Rich pharmaco-kinetic and -dynamic (PK and Pd) sampling was performed (exploratory endpoint). In A, M3814 was continued until progression, unacceptable toxicity, pt wish, or physician decision. In B, M3814 was given during RT to tumor or metastasis in the head and neck or thoracic region, 10 x 3 Gy.

Results: Up to Apr 1, 2018, 31 pts in A and 16 pts in B have been enrolled. In A one DLT was seen (prolonged low-grade AEs), the RP2D selected was 400 mg BID. In B, dose escalation is ongoing with DLTs of grade 3 mucositis ($n = 3$) and grade 3 odynophagia tox ($n = 1$). Most frequent adverse events (AE) were in A, nausea, vomiting, decreased appetite, constipation, diarrhea, pyrexia, fatigue, and rash, in B, dysphagia, prolonged mucosal inflammation/ stomatitis and radiation skin injury. One case of radiation pneumonitis has been reported. No pts discontinued due to AE. PK analysis demonstrated high variability of exposure. Pd in surrogate tissue showed robust inhibition of the induction of phosphoDNA-PKi (pDNA-PKi) for up to 6 hours. No objective responses were reported in A, while in B durable in field responses were seen ($n = 7$).

Conclusions: M3814 was found to be well tolerated as monotherapy and dose escalation combination with palliative RT is ongoing. PK of the current formulation showed a high inter-pt variability, Pd suppression of pDNA-PKi was observed as predicted by modelling and simulation.

Clinical trial identification: NCT02316197 and NCT02516813.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: M. Kuipers, B. Sarholz, G. Locatelli: Employee: Merck KGaA. P. Aftimos: Honoraria: Synthon, Boehringer Ingelheim, Macrogenics, Amgen, Novartis; Travel grants: Amgen, Merck, Roche. J. Debus: Advisory role and funding for the conduct of a clinical trial: Merck. All other authors have declared no conflicts of interest.

1846P Role of TP53 mutations in relation to response to anti-ALK agents in EML4-ALK-translocated NSCLC patients

M. Canale[1], A. Delmonte[2], C. Dazzi[3], A. Gamboni[4], C. Casanova[3], M. Papi[5], M. Mariotti[2], N. De Luigi[2], M.A. Burgio[2], G. Minuti[6], D. Calistri[1], M. Bonafè[1], L. Crinò[2], P. Ulivi[1]

[1]Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [2]Medical Oncology, Istituto Scientifico Romagnolo per Lo Studio e La Cura Dei Tumori (IRST)- IRCCS, Meldola, Italy, [3]Medical Oncology, Umberto I Hospital, Lugo, Italy, [4]Medical Oncology, Degli Infermi Hospital, Faenza, Italy, [5]Medical Oncology, Ospedale Infermi, Rimini, Italy, [6]Medical Oncology, Santa Maria delle Croci, Ravenna, Italy

Background: EML4-ALK translocation is a predictive mutation for responsiveness to anti-ALK drugs, and it is present in 3-7% cases of NSCLC patients. Though patients are usually responsive to targeted therapy against EML4-ALK translocation, about 30-40% show drug resistance. We analyzed the impact of TP53 mutations on response to anti-ALK treatment in EML4-ALK-translocated NSCLC patients.

Methods: 83 EML4-ALK-translocated NSCLC patients were enrolled, and TP53 status was evaluated in 61 patients, on the basis of DNA availability. Of these patients, 28 patients received an anti-ALK agent in second-or-more line treatment and follow up data were available. TP53 status was considered in relation to disease control rate (DCR: complete response [CR], partial response [PR] or stable disease [SD]).

Results: In the overall case series, TP53 mutations were observed in 14 (23%) patients, 6 (43%), 1 (7%), 3 (21%) and 4 (28%) in exon 5, 6, 7 and 8, respectively. We found 1 insertion (7%), 1 deletion (7%) and 12 point mutations (86%). In the subgroup of 25 patients treated with an anti-ALK agent and evaluable clinical response, TP53 mutations were observed in 5 (20%) patients, 2 (40%), 1 (20%) and 2 (40%) in exon 5, 6 and 8, respectively. The DCR was 60% in TP53-mutated patients with respect to 92% in TP53 wild type (wt) patients. Three patients had a non evaluable clinical response, as they early stopped anti-ALK agent treatment due to rapid PD/deterioration of general conditions and they succumbed to their disease in a few weeks. Two of these where found with a stop mutation in exon 5.

Conclusions: TP53 mutations are associated with a worse DCR in EML4-ALK-translocated NSCLC patients treated with an anti-ALK agent. These results highlight the importance of tumor-suppressor genes in determining response to TKIs. Data analysis for PFS and OS of patients are ongoing.

Legal entity responsible for the study: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.) – IRCCS.

Funding: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.) – IRCCS.

Disclosure: All authors have declared no conflicts of interest.

1847P Meta-enrichment analysis to identify a higher response patient population to S-1/cisplatin for advanced gastric cancer

M. Takeuchi[1], M. Takeuchi[2], H.W.M. van Laarhoven[3], X. Fang[1], P. Pfeiffer[4], J.A. Ajani[5]
[1]Clinical Medicine (Biostatistics), Kitasato University, Tokyo, Japan, [2]Faculty of Environment and Information Studies, Keio University, Fujisawa, Japan, [3]Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]Experimental Research in Medical Cancer Therapy, Odense University Hospital, Odense, Denmark, [5]GI Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

Background: Previous publications of the FLAGS and the DIGEST trials have shown that S-1/Cisplatin (CS) had a similar overall survival (OS) compared to 5-fluorouracil/cisplatin (CF) in patients with advanced gastric cancer (AGC) (Ajani JA et al, Eur J Cancer 2013. Ajani JA et al, Ann Oncol 2017). Although a co-enrichable population (Eastern Cooperative Oncology Group performance status (ECOG PS) 1) that respond favorably to CS compared to CF was identified with predictive enrichment strategy analysis by the FLAGS and the DIGEST trials respectively (Takeuchi et al, ESMO 2017), a more enrichable population may exist. Here we report the result of a meta-enrichment analysis assessing whether such a population exists.

Methods: To overcome differences in baseline characteristics of the FLAGS and the DIGEST a meta-enrichment analysis was performed after combining the data from the two trials. Since the treatment effect is consistent in the FLAGS and the DIGEST trial, meta-enrichment analysis allows for the combination of the two datasets and identify a robust subgroup of high response patients. Eleven clinicopathological factors were selected and a high response enrichable population was determined. It must be noted that although peritoneal metastases was included in the previous analysis as a clinicopathological factor, it was removed from this analysis due to inconsistent date readings between the individual and the central review committee.

Results: The efficacy of the combined data set of 1365 patients (n = 1019 from FLAGS and n = 346 from DIGEST) were analyzed. A total of 683 patients (n = 374 from CS, n = 309 from CF) were identified as the high response enrichable population. High response patients were classified as patients with ECOG PS1, more than two metastatic sites and low Neutrophil-Lymphocyte ratio (log(NL ratio)) In the high response enrichable population, the median OS in the CS group was 241 days compared to 210 days in the CF group (Hazard ratio 0.776 ; 95% Confidence interval 0.658 to 0.915 ; P value 0.004).

Conclusions: Through meta-enrichment analysis, a higher response enrichable population to CS was identified. This statistically robust analysis indicated that for selected patients with AGC, CS is more beneficial compared to CF.

Clinical trial identification: FLAGS trial: NCT00400179. First received: June 30, 2005. Last updated: April 23, 2012. Last verified: March 2012. DIGEST trial: NCT01285557. First received: January 28, 2011. Last updated: October 21, 2016. Last verified: October 2016.

Legal entity responsible for the study: Taiho Pharmaceutical Co., Ltd.

Funding: Taiho Pharmaceutical Co., Ltd.

Disclosure: M. Takeuchi: Honoraria: Shionogi & Co., Ltd.; Consulting or advisory role: Taiho pharmeceutical Co., Ltd., Hisamitsu Pharmaceutical Co. Inc., AstraZeneca K.K., AbbVie Inc. M. Takeuchi: Consulting: Taiho Pharmaceutical Co., Ltd.; Travel, accommodations, expenses: AnGes MG, Inc. H.W.M. van Laarhoven: Consultant: Celgene, Lilly, Nordic; Unrestricted research funding: Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Roche. P. Pfeiffer: Research Funding: Taiho pharmeceutical Co., Ltd. J.A. Ajani: Honoraria: Bristol-Myers Squibb, Five Prime Therapeutics, Inc., Medscape, LLC., Celgene, Taiho Pharmaceutical Co., Ltd., Eli Lilly and Company, Merck KGaA; Research funding: Bristol-Myers Squibb, Merck, Taiho Pharmaceutical Co., Ltd., Delta-Fly Pharma, Inc., Gilead Sciences Inc. All other authors have declared no conflicts of interest.

1848P Predictive significance of tumour angiogenic and anti-angiogenic VEGF-A splice variants in patients with metastatic colorectal cancer

G. Pentheroudakis, V. Kotoula, G-A. Koliou, K. Papadopoulou, E. Samantas, T. Makatsoris, V. Karavasilis, D. Mauri, I. Efstratiou, D. Bafaloukos, P. Papakostas, A. Psyrri, G. Papatsibas, G. Zarkavelis, A. Goussia, I. Bompolaki, G. Oikonomopoulos, A.N. Christopoulou, D.G. Pectasides, G. Fountzilas
Data Office, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece

Background: Alternate (distal) splicing of VEGF-A isoforms results in production of VEGF-Axxxb anti-angiogenic proteins that fail to activate the angiogenic cascade. Bevacizumab, widely used in patients with metastatic colorectal cancer (mCRC), binds both VEGFA and VEGFAxxxb isoforms.

Methods: Formalin-fixed paraffin-embedded primary tumours from mCRC patients treated in 1st line with FOLFIRI+Bevacizumab (Nbev=285) or FOLFIRI only (Nchem=75) were collected, mRNA was extracted, amplified and quantified with qRT-PCR (Taqman-MGB-assays) for the relative expression of VEGF-A 121a, 121b, 145a, 145b, 165a, 165b mRNA transcripts.

Results: At a median follow-up of 101.5 months, patients with left-sided (L-CRC) compared to those with right-sided primaries (R-CRC) had longer overall survival (OS) [median OS: 29.2 vs. 18.2 months, p = 0.015]. High VEGFA 145b mRNA expression was an unfavourable factor for PFS (HR = 1.66,95% CI 1.13-2.44, p = 0.009) in Nbev patients, with no prognostic significance in Nchem patients (HR = 0.70, 95% CI 0.34-1.44, p = 0.33). The adverse PFS prognostic effect of 145b was more pronounced in R-CRC patients (HR = 2.62, 95% CI 1.35-5.12, p = 0.005), especially when bevacizumab-treated (HR = 2.85, 95% CI 1.31-6.21, p = 0.008). High VEGFA 121b was adversely prognostic for PFS (HR = 2.48, 95% CI 1.23-5.04, p = 0.012) , OS (HR = 2.00, 95% CI 1.08-3.72, p = 0.028) in right, but not left colon, while high 165b was a favourable prognosticator in left sided disease (PFS HR = 0.76, 95% CI 0.59-0.99, p = 0.044, OS HR 0.68, 95% CI 0.52-0.90, p = 0.006). At multivariate analysis, right-sided primary was associated with inferior PFS (HR = 1.28, 95% CI 1.00-1.64, p = 0.051) and OS (HR = 1.33, 95% CI 1.02-1.73, p = 0.037), while high 145b mRNA expression consistently retained predictive significance for lack of PFS benefit from bevacizumab therapy (HR = 1.71, 95% CI 1.16-2.53, p = 0.007).

Conclusions: In a cohort of mCRC patients treated with bevacizumab, RQ of VEGF-A 145b mRNA, an anti-angiogenic isoform, may predict for resistance to bevacizumab, without prognostic utility in patients not exposed to the antibody. Differences in biological relevance of various VEGF-A isoforms were shown for right versus left-sided primaries.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group (HeCOG).

Funding: Roche Hellas.

Disclosure: E. Samantas, G. Fountzilas: Advisory board: Roche. T. Makatsoris: Honoraria, advisory role: Roche. P. Papakostas: Advisory role: Roche. A. Psyrri: Consultation, honoraria: Roche. All other authors have declared no conflicts of interest.

1849P ATR inhibition with radiation creates an inflammatory tumour microenvironment

M.T. Dillon[1], K. Bergerhoff[1], M. Pedersen[1], H. Whittock[1], E. Patin[1], H. Smith[1], J. Paget[1], R. Patel[1], G. Bozhanova[1], S. Foo[1], J. Campbell[1], C. Ragulan[2], E. Fontana[3], A. Wilkins[1], A. Sadanandam[3], A. Melcher[4], M. McLaughlin[1], K.J. Harrington[1]
[1]Targeted Therapy Team, The Institute of Cancer Research, London, UK, [2]Systems and Precision Cancer Medicine, The Institute of Cancer Research, London, UK, [3]Division of Molecular Pathology, The Institute of Cancer Research, London, UK, [4]Translational Immunotherapy, Institute of Cancer Research, London, UK

Background: ATR inhibitors (ATRi) are in early phase clinical trials and have been shown to sensitise to chemotherapy and radiotherapy (RT) in preclinical data. No data have been published about the effect of these drugs on the tumour microenvironment. We demonstrate significant modulation of the immune microenvironment by ATRi + RT.

Methods: We used an immunocompetent mouse model of HPV-driven malignancies (TC1) to investigate the effect of the ATRi, AZD6738, in combination with RT 8 Gy in 4 fractions. Gene expression analysis, flow cytometry and cytokine quantification were used.

Results: There was sensitisation to RT by ATRi in this model. ATRi + RT caused a marked increase in a number of adaptive immune cells infiltrating the tumour at 5 days after treatment. There were significantly more dendritic cells, macrophages, and myeloid-derived suppressor cells after ATRi + RT. We also identified increased numbers of CD3+ and NK cells after the combination treatment. Transcriptional analysis found evidence of increased T-cell activation with the combination therapy. We found evidence of an interferon (IFN) response, with transcriptional upregulation of IFN-stimulated genes including those playing a role in nucleic acid sensing: Ddx58/RIG-I, and Ifih1/MDA5, Zbp1/DAI and Ddx60. We identified significant modulation of cytokine gene expression (CCL2, CCL5, CXCL10), and found that cultured tumour cells secreted CCL3, CCL5 and CXCL10 after ATRi + RT. We hypothesise that DNA damage and micronucleus formation caused by ATR + RT (as previously reported by us, Dillon et al. MCT 2016;16:25-34) leads to an IFN response through activation of nucleic acid sensing pathways, leading to influx of innate immune cells.

Conclusions: To our knowledge this is the first comprehensive analysis of the immune tumour microenvironment after radiation with a radiosensitising targeted drug. Further understanding of the effect of this combination on immune response may allow modulation to maximise tumour control through activation of anti-tumour immunity. MTD is a CRUK clinical research fellow. AZD6738 provided by AstraZeneca. MM, KJH joint senior authors.

Legal entity responsible for the study: The Institute of Cancer Research.

Funding: Cancer Research UK.

Disclosure: M.T. Dillon: Co-investigator on clinical study of AZD6738 which is partially funded by AstraZeneca. A. Melcher: Compensated consultant/advisor and received honoraria: Amgen, BMS, Merck Serono; Research funding: Oncolytics Biotech Inc. K.J. Harrington: Payment for consulting fees: Amgen, AstraZeneca/Medimmune, BMS, Lytix Biopharma, MSD, Merck, Oncos Therapeutics, Pfizer, Viralytics Inc.; Research grant funding: MSD, Oncolytics Biotech., Viralytics Inc. All other authors have declared no conflicts of interest.

1850P RNA-based analysis of anaplastic lymphoma kinase (ALK) fusions in non-small cell lung cancer (NSCLC) cases showing immunohistochemistry/fluorescence in-situ hybridisation (IHC/FISH) discordance

C. Vollbrecht[1], D. Lenze[1], M. Hummel[1], A. Lehmann[1], M. Moebs[1], N. Frost[2], P. Jurmeister[3], L. Schweizer[1], U. Kellner[4], M. Dietel[1], M. von Laffert[1]

[1]Institute of Pathology, Charité – Universitätsmedizin Berlin Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), Berlin, Germany, [2]Department of Infectious Diseases and Pneumonology, Charité – Universitätsmedizin Berlin Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Medical Department, Berlin, Germany, [3]Charité Comprehensive Cancer Center, Charité – Universitätsmedizin Berlin Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany, [4]Institute for Pathology, Johannes Wesling Klinikum Minden, Minden, Germany

Background: Rearrangements of ALK are established targets in the current therapy of advanced NSCLC and are predominantly detected by IHC and/or FISH. However, both methods occasionally produce discordant results. This may occur especially in so-called borderline (BL) cases, showing ALK FISH-positive signals in 10–20% of tumour nuclei around the cutoff (15%) for ALK FISH-positivity. This leads to a diagnostic, and thus therapeutic, dilemma.

Methods: We selected 18 unequivocal samples (12 ALK IHC- and FISH-negative; 6 ALK IHC- and FISH-positive) and 15 equivocal samples with discordance between FISH (Vysis LSI ALK Dual Color) and IHC (D5F3), including cases with FISH-BL results, for further RNA based-analysis. To detect ALK rearrangement at the transcriptional level, RNA was analysed using a targeted multiplex-PCR panel followed by S5 sequencing and direct transcript counting using a digital probe-based assay (Nanostring). Sensitivity of both methods was defined using RNA obtained from an ALK-positive NSCLC cell-line dilution series.

Results: Cases with unequivocal IHC/FISH results showed concordant data with both RNA-based methods. Three IHC-negative/FISH-positive samples were negative with both RNA-based methods. The four IHC-negative/FISH-BL-negative cases, as well as the five IHC-negative/FISH-BL-positive samples, showed negative results by sequencing and digital probe-based assay. The two IHC-positive/FISH-BL-positive cases were both positive on the RNA level; whereas a tumour with questionable IHC and FISH-BL-positive status displayed no ALK fusion transcript.

Conclusions: The comparison of methods for the confirmation of ALK rearrangements revealed that the detection of ALK protein by IHC and ALK fusion transcripts on transcriptional level by sequencing and probe-based assay leads to concordant results. Only a small proportion of clearly ALK FISH-positive cases are unable to express the ALK protein and ALK fusion transcript, which might explain non-response to ALK inhibitors. Therefore, our findings led us to conclude that ALK testing should be based on IHC- or RNA-based methods, especially for ALK FISH BL cases.

Editorial acknowledgement: Support for third-party editorial assistance for this abstract, furnished by John Carron, PhD, of Health Interactions, was provided by Roche Pharma AG, Germany.

Legal entity responsible for the study: Roche Pharma AG, Germany.

Funding: Part of the study was sponsored by Roche Pharma AG, Germany (ALK-IHC-FISH-NGS Head to Head Study ML39478)

Disclosure: M. Hummel: Expert testimony, travel, accommodation, expenses: ThermoFisher. M. Moebs: Consulting or advisory roles, expert testimony, travel, accommodation, expenses: Thermofisher Scientific. All other authors have declared no conflicts of interest.

1851P The combination of MEK inhibitor and anti PD-L1: Effects on organoid models from NSCLC biopsies

C.M. Della Corte[1], G. Barra[2], V. Ciaramella[3], R. Di Liello[3], M. Fasano[3], F. Ciardiello[3], F. Morgillo[3]

[1]Thoracic Head and Neck, MD Anderson Cancer Center, Houston, TX, USA, [2]Immunologia, AOU Seconda Università degli Studi di Napoli (AOU-SUN), Naples, Italy, [3]Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: The combination of immune-checkpoint (IC) inhibitors with targeted therapies represent a new goal of immunotherapy, aimed at personalizing and potentiating the self-response against cancer. Organoids as novel 3D cancer models, allow the study in vitro of the tumor microenvironment (TME), including tumor-infiltrating lymphocytes (TILs) and their interaction with tumor cells. In this study we analyzed whether the combination of anti-PD-L1 drugs with MEK inhibitor (MEKi) affect the growth of organoids and TILs obtained from tumor biopsy of NSCLC patients.

Methods: Lung biopsies from 3 NSCLC patients were enzymatically digested. Cells were cultured in matrigel for 6 days and treated with atezolizumab or avelumab, alone or in combination with MEKi. Immunofluorescence (IF) staining for CD3, CD8 and CD45 was conducted; cells were also stained for FACS analysis with anti- CD45, CD3, CD4, CD8, CD14, CD56, CD19, CD11c, PD-1; a staining for EPCAM and PD-L1 allowed a better characterization of tumor cells. After 6 days of treatment, MTT assay verified cell viability; the expression levels of IFNg, IL-10, PD-1, PD-L1, TIM-3, LAG-3 and IDO-1 were analysed through real-time PCR.

Results: IF staining revealed that in organoids the interactions between tumor cells and TILs are preserved. FACS analysis confirmed that TILs were mainly TCD8+ and tumor cells analysed were EPCAM+ for almost 40%. The combination of anti PD-L1 and MEKi is associated with a reduction in organoid's dimensions and viability, especially in PD-L1+ tumors and with a higher percentage of TCD8+/PD-1+ lymphocytes. The combination of MEKi with anti PD-L1 is also associated to a higher expression of the pro-inflammatory cytokine IFNg and a reduction of the anti-inflammatory IL10. The expression of IC molecules was also modified by this combination; in particular LAG-3 and IDO-1 expression were dramatically reduced.

Conclusions: Organoid models allow to study tumors more realistically, because they show some typical features of the organ they derive. This model become particularly useful for the analysis of TME of each patient and for the testing of combination drugs and the development of precision and personalized immunotherapies.

Legal entity responsible for the study: Università degli Studi della Campania.

Funding: AIRC.

Disclosure: All authors have declared no conflicts of interest.

1852P Intraoperative fluorescent image-guided detection of esophageal cancer in rabbit and patient specimens

J. Rho[1], Y.H. Quan[2], B.H. Choi[2], B-M. Kim[3], K.N. Han[4], Y.H. Choi[4], H.K. Kim[4]

[1]Biomedical Science, Korea University College of Medicine, Seoul, Republic of Korea, [2]Department of Biomedical Sciences, Korea University College of Medicine, Seoul, Republic of Korea, [3]Department of Bio-Convergence, Korea University, Seoul, Republic of Korea, [4]Department of Thoracic and Cardiovascular Surgery, Korea University Guro Hospital, College of Medicine, Seoul, Republic of Korea

Background: This is the first study, to our knowledge, aimed at assessing the feasibility of intraoperative detection of esophageal cancer (EC) after intravenous indocyanine green (ICG) injections in rabbit and patient specimens using near-infrared (NIR) fluorescence imaging.

Methods: VX2 tumors were surgically implanted in the esophageal muscular layer of 45 rabbits 2 weeks before esophagectomy. They received 1, 2, or 5 mg/kg of intravenous ICG injections 3, 6, 12, 24, or 48 hours before surgery. Twenty-five consecutive patients (21 men; age, 63.9±8.59 years) who were scheduled to undergo esophagectomy for squamous cell EC were enrolled. Five patients received neoadjuvant concurrent chemoradiotherapy (CCRT) before surgery. All patients received 1 or 2 mg/kg of ICG intravenously 6, 12, or 24 hours before surgery. The fluorescence intensity was measured in all resected rabbit and patient specimens using an NIR fluorescence imaging system on a back table after surgery.

Results: EC was successfully detected in all rabbits; the mean tumor size was 0.86±0.21 (range, 0.5–1.3) cm. Fluorescence signals were detected in all animals. The tumor-to-normal fluorescence signal ratio (TNR) in rabbits was higher between 6 (6.89±0.35) and 12 (7.53±0.26) hours at 1 mg/kg ($p < 0.01$), between 12 (10.59±0.41) and 24 (12.06±0.57) hours at 2 mg/kg ($p < 0.01$), and between 24 (14.88±0.63) and 48 (13.73±0.19) hours at 5 mg/kg ($p < 0.01$) of ICG than at other times. Fluorescence signals were detected in all except 4 patients without residual tumors after preoperative CCRT. One false-positive case involved no residual tumor with inflammation (TNR, 13.64). The mean tumor size in 20 patients was 3.9±2.1 (1.1–10) cm. The TNR in the patients was higher between 6 (15.22±0.59) and 12 (17.01±0.18) hours at 1 mg/kg ($p < 0.01$) and between 12 (18.92±0.01) and 24 (19.81±0.73) hours at 2 mg/kg ($p < 0.01$) of ICG than at other times.

Conclusions: NIR fluorescence imaging revealed EC 6 to 24 hours after systemic ICG injections per their doses. However, passive ICG accumulation could not help discriminate tumors with inflammation; thus, tumor-targeted fluorescence should be developed to solve this problem in the future.

Clinical trial identification: This study was approved by the Institutional Review Board, Korea University Guro Hospital (2017GR0075).

Legal entity responsible for the study: Korea University.

Funding: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C0654).

Disclosure: All authors have declared no conflicts of interest.

1853P Interaction between cancer associated fibroblasts and cancer cells influence immune infiltrate and is modulated by therapeutic agents

A.J. Rullan Iriarte[1], E. Arwert[1], E. Milford[1], P. Chakravarty[1], A. Melcher[2], K. Harrington[3], E. Sahai[1]

[1]Tumour Cell Biology Laboratory, The Francis Crick Institute, London, UK, [2]Translational Immunotherapy, Institute of Cancer Research, London, UK, [3]Head and Neck/Skin Units, The Institute of Cancer Research, London, UK

Background: Cancer associated fibroblasts (CAFs) can help tumours evade immune-surveillance by affecting the immune cell infiltrate, mainly via secretion of cytokines and chemokines. CAFs phenotype and spatial relationship to cancer cells alter the kind of cytokines and chemokines they secrete. In Squamous cell carcinoma (SCC), cancer-associated fibroblasts can trigger a Type I Interferon when in direct cell-cell contact with cancer cells.

Methods: Bioinformatics: we used publicly available RNAseq data from The Cancer Genome Atlas (TCGA) for Head and Neck Squamous Cell Carcinoma (HNSCC 518 tumours. [http://firebrowse.org/]) . Using the RSEM normalized gene expression, we divided tumours according to the expression of CAF markers not expressed in cancer cells (FAP, Thy-1, s100a4and PDGFRb). We used CIBERSORT to estimate the abundance of immune cells in the tumours. In vitro assays: we used A431 (human SCC cell line) and CAFs extracted from a human tumour in our lab. We cultured them in either direct cell-to-cell contact or using a transwell. We treated the A431 with AZD6738 (ATR inhibitor), 5-aza-2′-deoxycytidine and cisplatin. We analysed mRNA expression of different interferon response genes by qRT-PCR.

Results: To explore the relevance of CAF influence in the immune infiltrate we analysed RNA seq data from HNSCC in TCGA. Tumours with higher expression of FAP and PDGFRb showed a higher proportion of infiltrating M0 and M2 macrophages. Tumours with lower expression of FAP and PDGFRb had higher proportions of activated dendritic cells and CD8 positive lymphocytes. In an "in vitro" human SCC model, heterotypic cancer cell-CAF contact leads to transfer of double stranded DNA from the cancer cell to the fibroblasts. This interaction triggers cGAS-STING mediated production of Interferon b (IFNb) in the CAFs. We treated cancer cells with drugs that generate genomic damage i.e. AZD6738, 5-aza and cisplatin. Treatment with these drugs increased the signal initiated by IFNb.

Conclusions: CAF subtypes abundance correlates with an immunosuppressive tumour microenvironment in HNSCC. Drugs currently used for routine treatment or in clinical trials for HNSCC modulate cytokine and chemokine production by CAFs in an "in vitro" model.

Legal entity responsible for the study: The Francis Crick Institute.

Funding: Cancer Research UK.

Disclosure: K. Harrington: Consultancy (Includes expert testimony): Amgen, AstraZeneca, BMS, Merck, MSD, Pfizer; Research funding: AstraZeneca, MSD; Honoraria: Amgen, AstraZeneca, BMS, Merck, MSD, Pfizer, Replimune; Speakers' bureau: Amgen, AstraZeneca, BMS, Merck, MSD, Pfizer; Membership on any entity's Board of Directors or advisory committees: Amgen, AstraZeneca, BMS, Merck, MSD, Pfizer, Replimune (Scientific advisory board memberships). All other authors have declared no conflicts of interest.

1854P Dynamic change of immune-related gene expression status during chemoradiotherapy in locally advanced esophageal cancer

T. Mizukami[1], Y. Sunakawa[1], H. Arai[1], M. Chosokabe[2], A. Doi[1], Y. Horie[1], M. Hirakawa[1], O. Saji[3], S. Naruki[2], N. Izawa[1], T. Ogura[1], T. Tsuda[1], T. Enomoto[3], S. Mikami[3], T. Fujino[2], T. Otsubo[3], T.E. Nakajima[1]

[1]Clinical Oncology, St. Marianna University School of Medicine, Kanagawa, Japan, [2]Pathology, St.Marianna University School of Medicine, Kanagawa, Japan, [3]Gastroenterological and General Surgery, St. Marianna University School of Medicine, Kanagawa, Japan

Background: Either chemotherapy or radiotherapy is standard of care for esophageal cancer (EC), and they are known to offer enhancement of both tumor and host immune system [B Park, et al. Int J Mol Sci 2014; Emens LA, et al. Cancer Immunol Res 2015]. However, there are few reports regarding the impact of chemoradiotherapy (CRT) on the tumor immunity.

Methods: We retrospectively examined patients (pts) with available tumor samples at 2 points (pre- and post-treatment) among EC pts who received chemotherapy with platinum and/or radiation in our institute between 2010 and 2015. Immunohistochemistry (IHC) staining for the samples was performed and the positivity of PD-L1 was determined as score >1 of the Allred methods. In addition, expression levels of immune-related genes were analyzed using HTG EdgeSeq Immuno-Oncology Assay (HTG Molecular Diagnostics, Inc., Tucson, United States).

Results: Eighty-four pts were evaluable (median age of 68yrs, 88% male, 7%/9%/34%/48%/1% for primary tumor of Ce/Ut/Mt/Lt/Ae, 12%/19%/52%/17% for Stage I/II/III/IV, 95% squamous cell carcinoma, 48%/52% pts treated with chemotherapy/CRT). Frequency of PD-L1 IHC expression was higher in the samples after chemotherapy compared in those before chemotherapy (14% to 36%), while it was lower in the samples after CRT compared in those after CRT (13% to 7%). There was a significant difference in the positive rate at post-treatment between chemotherapy and CRT ($P = 0.01$). Comprehensive analysis to compare gene expression levels of immune-related genes between pre- and post-treatment found 17 up-regulated and 34 down-regulated genes in pts treated with CRT. Specially, IL18, GZMA, and SPINK5 genes were identified for elevated genes, while PDGFRB, TNFRSF12A, and ITGB1 genes for degraded genes.

Conclusions: Positivity of PD-L1 was different after the treatment between in EC pts receiving chemotherapy and in those receiving CRT. Genes related to inflammatory response and angiogenesis may contribute to the change of tumor immune status by CRT in EC.

Legal entity responsible for the study: Takako Eguchi Nakajima.

Funding: Has not received any funding.

Disclosure: T.E. Nakajima: Personal financial interests: Eli Lilly, Sanofi, Chugai, Sawai, Bayer, BMS, Taiho, Merck, Ono, Takeda, Mochida, MSD; Institutional financial interests: Ono, Taiho, A2 Health Care, JCRO, Daiichi-Sankyo, Mediscience Planning. All other authors have declared no conflicts of interest.

1855P CD5 and CD6: Evaluation of their role as prognostic biomarkers in resectable non-small cell lung cancer

A. Moreno[1], S. Calabuig Fariñas[1], S. Gallach Garcia[1], A. Fernando[2], I. Simoes[2], E. Carreras[2], M. Consuegra-Fernández[2], A. Blasco Cordellat[3], A.J. Cunquero Tomas[3], M. Martorell[4], C. Camps[5], F. Lozano[6], R. Sirera Perez[7], E. Jantus-Lewintre[8]

[1]Molecular Oncology Laboratory, Fundación de Investigación Hospital General Universitario de Valencia - CIBERONC, Valencia, Spain, [2]Immunoreceptors of the Innate and Adaptative System, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain, [3]Medical Oncology Service, Hospital General Universitario Valencia - CIBERONC, Valencia, Spain, [4]Pathology Service, Hospital General Universitario de Valencia, Valencia, Spain, Pathology Department, Universitat de València, Valencia, Spain, [5]Molecular Oncology Laboratory, Fundación para la Investigación, Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain, Medical Oncology Service, Hospital General Universitario de Valencia - CIBERONC Valencia, Spain, Medicine Department, Universitat de València, Valencia, Spain, [6]Immunoreceptors of the Innate and Adaptative System, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain, Servei d'Immunologia, Centre de Diagnòstic Biomèdic, Hospital Clínic de Barcelona, Barcelona, Spain, Departament de Biomedicina, Facultat de Medicina, Universitat de Barcelona, Barcelona, Spain, [7]Biotechnology Department, Universidad Politécnica de Valencia, Valencia, Spain, [8]Laboratorio de Oncología Molecular, Fundación para la Investigación, Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain, Biotechnology Department, Universitat Politécnica de València, Valencia, Spain

Background: Non-Small Cell Lung Cancer (NSCLC) represents almost 80% of lung cancer cases. Despite the advances achieved in the last years, there is still a lack of knowledge concerning tumour microenvironment. This research is focused on two immunoregulatory genes, CD5 and CD6 as potential prognostic biomarkers in resectable NSCLC.

Methods: CD5 and CD6 gene expression was analysed by RTqPCR in 201 paired fresh-frozen tumour and normal tissue samples of resected NSCLC (training cohort). The Cancer Genome Atlas (TCGA) database was used to obtain an independent validation cohort with available gene expression data for normal and tumour tissue. Relative gene expression was calculated by Pfaffl formula. Prognostic value was assessed by Cox regression and Kaplan-Meier curves (log rank-test), considering significant $p < 0.05$.

Results: Training cohort consisted mainly of men, current or former smokers, with good performance status ($PS = 0$). Survival analyses showed that patients with higher CD5 expression had significantly increased overall survival (OS, 53.3 vs. NR months, $p = 0.011$). A multivariate analysis reported that CD5 expression could be established as an independent prognostic biomarker for OS in early-stage NSCLC [HR = 0.539; 95% CI, 0.329-0.883; $p = 0.014$]. Survival analyses performed on 97 patients from TCGA database confirmed that higher expression levels of both CD5 and CD6 had a significant prognostic value for relapse-free survival (34.98 vs. 75.57 months, $p = 0.033$; 25.31 vs. 75.57 months, $p = 0.020$, respectively) and OS (40.49 vs. 77.97 months, $p = 0.038$; 39.02 vs. 77.97 months, $p = 0.034$, respectively). Therefore, these analyses support that NSCLC patients with higher expression levels of CD5 are associated with better outcomes. Besides, CD6 could potentially be a prognostic biomarker.

Conclusions: Our results support a role of the inmmunodulatory receptor CD5 as an independent prognostic biomarker in resectable NSCLC. Supported from Fundació La Marató TV3 (201319-30), ISCIII (PI12-02838 and PI15-00753), and MECD (SAF2016-80535-R) -co-financed by European Development Regional Fund. FA and IS are recipients of fellowships from ISCIII (Sara Borrell Program; CD15/00016) and Portuguese FCT (SFRH/BD/75738/2011), respectively.

Legal entity responsible for the study: Fundación para la Investigación del Hospital General Universitario de Valencia.

Funding: Supported from Fundació La Marató TV3 (201319-30), Instituto de Salud Carlos III (PI12-02838 and PI15-00753), and MECD (SAF2016-80535-R) -co-financed by European Development Regional Fund. FA and IS are recipients of fellowships from ISCIII (Sara Borrell Program; CD15/00016) and Portuguese Fundação para a Ciência e a Tecnologia (SFRH/BD/75738/2011), respectively.

Disclosure: All authors have declared no conflicts of interest.

1856P Identification of the rational combination of two epigenetic inhibitors therapy in refractory AML using patient tumor derived ex vivo platform

P.K. Majumder[1], G. Babu[2], C. Rajagowda[2], S. Thiyagarajan[3], M. Biswas[4], P. Radhakrishnan[1], P. Chaudhuri[3], A. Chatterjee[3]

[1]Cancer Biology, Mitra Biotech, Woburn, MA, USA, [2]Kidwai Memorial Institute of Oncology, HCG Curie Centre of Oncology, Bangalore, India, [3]Cancer Biology, Mitra Biotech, Bangalore, India, [4]Molecular Pathology, Mitra Biotech, Bangalore, India

Background: Acute myeloid leukemia (AML) is a highly heterogenous hematological malignancy. Though there has been substantial progress in understanding of AML biology and identification of new therapeutic targets, treatment of AML has largely remained unchanged over the last couple of decades, with ∼40% patients not achieving remission with standard chemotherapies.

Methods: In this study, we employed an ex-vivo tumor explant model (CANscript™) to select a treatment course for AML patients. CANscript™ offers a comprehensive system that mimics patient tumor microenvironment. 31 AML patients tumors were analyzed to predict response to cytarabine. We next evaluated azacitidine and panobinostat alone and in combination, as alternate treatment regimens for cytarabine refractory tumors.

Results: More than 50% of the treated samples showed response to the combination therapy. In AML, frequent upregulation of DNA-methyltransferase enzymes (DNMTs) have been reported with poor survival. We assessed the level of DNMTs using RNAseq and methylation data (n = 100) from the TCGA database. Data indicated increased expression of DNMT and hyperacetylation of HDACs indicating mechanism of high responsiveness to treatment by epigenetic modulators in these tumors. We further noted hypomethylation of IFNGR1 and IFNGR2 genes in TCGA data suggesting activation of JAK/STAT pathway. Hypomethylation of several gene components of JAK-STAT pathway was correlated with an increased expression of these genes in RNAseq data. 8 out of 12 cytarabine refractory tumors were showed response of which 5 were non-responders to epigenetic modulators.

Conclusions: Taken together our data indicates that CANscript™ is capable in guiding optimal treatment selection for various classes of agents including novel targeted therapies.

Legal entity responsible for the study: Mitra Biotech and Kidwai Memorial of Institute of Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1857P Tyrosine kinase inhibitors and acid-inhibitory drugs: Strong concomitant dispensing and drug-drug interaction risk

F. Grude[1], C. Vigneau-Victorri[2], D. Deniel Lagadec[3], E. Michaud[4], H. Bourgeois[5], B. Forestier[4], F. Marhuenda[1]

[1]Cancer Observatory, ICO Paul Papin, Angers, France, [2]Service de Pharmacologie Clinique, Faculté de Médicine, Nantes, France, [3]Cancer Observatory, CHRU Brest, Brest, France, [4]Medical Department, Regional Health Insurance, Nantes, France, [5]Oncology Department, Clinique Victor Hugo Le Mans, Le Mans, France

Background: Tyrosine Kinase Inhibitors (TKIs) have rapidly become an established therapy in oncology and have been shown to be effective in a wide variety of solid and hematologic malignancies. Acid-inhibitory drugs (AID) (such as antacids, anti-ulcerous drugs and proton pump inhibitors - PPIs) increase the intragastric pH, which may subsequently decrease TKI solubility, bioavailability, and treatment efficacy. The Observatory of Drugs Bretagne/ Pays de la Loire (B-PL) and the Medical Department of the French Regional Health Insurance (FRHI PL) has made an observational study about TKIs and AIDs concomitant dispensing.

Methods: FRHI has made an extract in its database for patients treated with TKIs and AIDs in 2016. Concomitant dispensing is defined as the dispensing of a TKI and AIDs during the same calendar month. To complete the study, a survey about PPIs prescription has been proposed to cancer specialists from B and PL areas during 15 days last December.

Results: 2309 patients, mean age of 62.9 y (2-93) have been treated with TKIs in 2016 in the PL area. 6.6 dispensings have been done per patient. 795 pts (34%) had no AID dispensing. 274 pts (12%) had no concomitant dispensing of AID and TKI. 1240 pts (54%) had at least one concomitant dispensing. 67% of these patients had a concomitant dispensing of PPIs and 25% a concomitant prescription throughout the TKI treatment. Among these concomitant takes, 34% showed no interaction, 23% showed interactions (34% unknown cases, 9% diverging data). Data from the Bretagne area will be shown at the meeting. 43 clinicians have answered the survey about PPI prescription: 98% have prescribed them. The major reasons were: treatment of gastroesophageal reflux disease (88%), prevention/treatment of NSAID-associated ulcers (67%) or of esophageal duodenal and stomach ulcers (55%), for unknown reasons (31%), and for Zollinger-Ellison syndrome (31%). Duration of treatment was between 7 days and 2 months.

Conclusions: Drug-Drug Interaction (DDI) analyses would be performed to underline for which TKIs, TKIs-PPIs interaction was the most harmful. Clear practice tools should be created to help clinicians to evaluate this DDI and what to do for their patients. Guidelines will be presented at the meeting.

Legal entity responsible for the study: Cancer Observatory, OMEDIT B and PL.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1858P Intraoperative detection of resection margin by inhalation of ICG in lung cancer preclinical study

Y.H. Quan[1], C.H. Oh[2], D. Jung[2], J-Y. Lim[2], B.H. Choi[1], J. Rho[3], Y. Choi[4], K.N. Han[5], J-H. Park[2], H.K. Kim[5], Y.H. Choi[5]

[1]Department of Biomedical Sciences, Korea University College of Medicine, Seoul, Republic of Korea, [2]Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea, [3]Biomedical Science, Korea University College of Medicine, Seoul, Republic of Korea, [4]Department of Bio-Convergence, Korea University, Seoul, Republic of Korea, [5]Department of Thoracic and Cardiovascular Surgery, Korea University Guro Hospital, College of Medicine, Seoul, Republic of Korea

Background: Identification of tumor margin during surgery is necessary for limited resection of non-small cell lung cancer (NSCLC). In this study, we developed a novel technique of lung cancer margin visualization by intraoperative inhalation of indocyanine green (ICG) and verified its clinical applicability using mouse and rabbit lung cancer model.

Methods: By observing the distribution of the inhaled ICG in each organ (lung, liver, brain, spleen, and kidneys) of mice at five different time intervals, we demonstrated that the inhaled ICG was delivered rapidly and was mainly distributed in the lung tissue. In the mouse model of lung cancer, we confirmed that the inhaled ICG entered the normal lung through phagocytosis by alveolar macrophages of normal lung tissue and rarely spread in lung cancer tissue because of mechanical airway obstruction by the tumor.

Results: Therefore, the fluorescent signal of inhaled ICG was mainly visualized in normal lung tissue but not in lung cancer tissue, which could assist in identifying the tumor margin. For clinical applicability, the inhaled dose of ICG was optimized in a rabbit lung cancer model. Compared to intravenous administration, this method accurately defined the tumor margin with 5.3-fold higher detection efficiency when 20 times lower dose of ICG was used. The ICG inhalation technique provided more clear visualization of tumor margin with lower dose and in shorter time during surgery compared to the conventional intravenous injection method.

Conclusions: The ICG inhalation technique provided more clear visualization of tumor margin with lower dose and in shorter time during surgery compared to the conventional intravenous injection method. Lung-specific delivery of the clinically approved ICG could be used effectively and safely in real clinical practice in the near future.

Legal entity responsible for the study: Korea University.

Funding: This work was supported by a grant from the Korean Health Technology R & D Project, Ministry of Health & Welfare, Republic of Korea (No: HI17C0654), and a National Research Foundation of Korea (NRF) grant funded by the Ministry of Education, Science, and Technology (NRF-2015R1A2A2A04005760).

Disclosure: All authors have declared no conflicts of interest.

1859P Proteomic-based machine learning computational analysis discovered biomarkers of aberrant vesicle-exosomal trafficking to determine chemotherapeutic responses in breast cancer

H. Ryu[1], D.H. Han[2], K-M. Lee[3], K. Kim[3]

[1]Pathology and Proteomics Core Facility, Seoul National University Hospital (SNUH)-Yongon Campus, Seoul, Republic of Korea, [2]Proteomics Core Facility, Seoul National University Hospital, Seoul, Republic of Korea, [3]Biomedical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea

Background: The chemotherapeutic response is still low, and the need for a biomarker to overcome chemo-resistance is necessary.

Methods: We performed quantitative proteomics mass spectrometry in paired 20 FFPE biopsy breast cancer samples consist of non-responsive and responsive groups to chemotherapy. For verification of enriched biomarkers and biological pathways, ten human breast cancer cell lines enrolled and verified biological functions through molecular biology-driven assays, including RNAi, celltiter-glo luminescent assay, mitochondrial membrane potential assay (MMPA), IF, exosome uptake assay, time-lapse live cell imaging system, and the 3D tumor spheroid-based function assays. Machine learning analysis using r-caret recursive feature elimination to select and apply them to an independent cohort with 50 FFPE biopsy samples to discover the most optimal combination of immunohistochemical biomarkers to predict chemo-responsiveness.

Results: A total of 6,424 proteins were identified and 254 were confirmed to be significantly altered proteins related to chemotherapeutic response. From the patient group with chemo-resistance, we featured 56 upregulated proteins considerably in six closely related subcellular organelles concerning transcellular transportation system based on domain knowledge for text-mining and public network databases for network analysis.

14 intracellular exosomal transportation markers were identified to control chemosensitivity through siRNA array panel assay. Live cell images showed changed exosomal trafficking in cell lines manipulated by candidate markers. Through the verification step by machine learning analysis, we selected five markers and applied them to an independent cohort with FFPE biopsy samples to discover the most optimal combination of immunohistochemical biomarkers to predict chemo-responsiveness.

Conclusions: The present study provides the first evidence to identify a predictive biomarker for chemotherapeutic response based on in-depth proteomics. The newly discovered biomarkers and biological evidence can provide the novel insight to overcome chemoresistance in breast cancer.

Legal entity responsible for the study: Han Suk Ryu.

Funding: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea.

Disclosure: All authors have declared no conflicts of interest.

1860P Carcinoma of unknown origin: Deep genomic profile helps to achieve an accurate diagnosis

A.B. Fernandez Díaz[1], V. Iranzo Gonzalez-Cruz[2], A.J. Cunquero Tomas[1], C. Avila Andrade[1], E. Jantus-Lewintre[3], S. Calabuig Fariñas[4], J.E. Ales[5], M. Valero[6], G. D'Errico[7], R.A. Pazo Cid[8], A. Gallego Martínez[9], A. Viana[10], S. Ponce Aix[11], J.A. Pérez-Fidalgo[12], A. Terradez[13], A. Rodrigo[13], L. Alvarez[13], G. Beniuga[14], M. Martorell[15], C. Camps[16]

[1]Medical Oncology Service, Hospital General Universitario de Valencia, Valencia, Spain, [2]Medical Oncology Service, Hospital General Universitario de Valencia, Valencia, Spain, Centro Investigación Biomédica en Red de Cáncer (CIBEROnc), Valencia, Spain, [3]Laboratorio de Oncología Molecular, Fundación para la Investigación, Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain, Centro Investigación Biomédica en Red de Cáncer (CIBEROnc), Madrid, Spain, Dept. of Biotechnology, Universitat Politècnica València, Valencia, Spain, [4]Medical Oncology Service, Molecular Oncology Lab., Fundación Investigación Hospital General Universitario Valencia, Valencia, Spain, Centro Investigación Biomédica en Red de Cáncer (CIBEROnc), Madrid, Spain, Dept. of Pathology, Universitat de València, Valencia, Spain, [5]Medical Oncology, Hospital Nuestra Señora de Sonsoles, Avila, Spain, [6]Medical Oncology, ONCOAVANZE, Seville, Spain, [7]Medical Oncology, Hospital Universitario Quirónsalud Madrid, Madrid, Spain, [8]Medical Oncology, Hospital Miguel Servet, Zaragoza, Spain, [9]Medical Oncology, Hospital Universitario La Paz, Madrid, Spain, [10]Medical Oncology, Hospital Nuestra Señora del Prado, Toledo, Spain, [11]Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain, [12]Medical Oncology, Hospital Clínico Universitario de Valencia, Valencia, Spain, [13]Scientific Department, OncoDNA S.A., Gosselies, Belgium, [14]Pathology Department, Institute Pathology and Génétique, Charleroi, Belgium, [15]Dept. of Pathology, Hospital General Universitario de Valencia, Valencia, Spain, [16]Medical Oncology, Hospital General Universitario de Valencia, Valencia, Spain, Centro Investigación Biomédica en Red de Cáncer (CIBEROnc), Madrid, Spain, Dept. of Medicine, Universitat de València, Valencia, Spain

Background: Diagnosis and treatment of Cancer of Unknown Origin (CUP) continues to be a challenge. In the era of personalized medicine, genomic profile by Next-Generation-Sequencing (NGS) in addition to immunohistochemistry (IHC) tests may complement clinical features improving diagnosis and detecting targetable mutations. In the present study we have analysed the clinical utility of theOncoDEEP® CUP platformfor tissue of origin assessment and genotyping in a cohort of CUP patients.

Methods: We conducted this multicentric prospective exploratory study across 22 institutions (September 2017- March 2018). The cohort included 60 patients with histologically diagnosed metastatic CUP and available FFPE tumor samples. The molecular analysis was performed using the OncoDEEP® CUP platform, which includes a deep genomic tumor characterization as well as a panel of IHC tests.

Results: Patient's median age was 60 years [24-80], 61.7% were females. At time of diagnosis,48% presented a single metastatic site whereas 52% has multimetastaticlocations. Predominant histology was adenocarcinoma (36.7%) followed by carcinoma NOS (25%), squamous cell carcinoma (13.3%) and others (25%). In 10% of the cases, the analysis could not be completed due to insufficient tumor samples. In the remaining 54 samples, a probable primary origin was assessed in 43 patients (80%). Potentially actionable mutations were found in 36 cases (61%). As expected, the most frequently mutated gene was TP53 (12/36), followed by KRAS, TPMT, ARID1A,BRAF, CDKN2A, PI3KCA, PTEN and STK11. During follow up 11 deaths have been recorded, whereas the rest of the patients remain in the study.

Conclusions: OncoDEEP® CUP may provide an opportunity for CUP patients to benefit from site-specific treatments and personalized therapies if druggable mutations are identified. Acknowledgments to the rest collaborating centers: H. U. de Ceuta, H. U. Virgen Macarena, H. Ramón y Cajal, H. U. Santa Lucía, HC Marbella International Hospital, H. Parc Taulí, H. U. La Ribera, H. Marina Baixa, H. Morales Meseger, H. U. Lucus Augusti and Instituto Valenciano de Oncología (IVO).

Legal entity responsible for the study: Hospital General Universitario de Valencia, Valencia, Spain, Valencia.

Funding: The Spanish Institute for Foreign Trade (ICEX).

Disclosure: A. Terradez, A. Rodrigo, L. Alvarez, G. Beniuga: Employee: OncoDNA. All other authors have declared no conflicts of interest.

1861P Pre-treatment circulating cytokines predict toxicity with combination anti-PD1 and anti-CTLA4 immunotherapy

J.H. Lee[1], S.Y. Lim[2], A.M. Menzies[3], M.S. Carlino[4], A. Guminski[3], K. Nahar[5], D. Palmieri[6], E. Breen[2], R. Kefford[7], R. Scolyer[8], G.V. Long[3], H. Rizos[1]

[1]Biomedical Science, Macquarie University, Melanoma Institute Australia, Sydney, Australia, [2]Biomedical Science, Macquarie University, Sydney, Australia, [3]Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, North Sydney, Australia, [4]Medical Oncology, The Crown Princess Mary Cancer Centre, Melanoma Institute Australia, Sydney University, Westmead, Australia, [5]Medical Oncology, Melanoma Institute Australia, University of Sydney, North Sydney, Australia, [6]Medical Oncology, The Crown Princess Mary Cancer Centre, Westmead, Australia, [7]Clinical Medicine, Macquarie University, Melanoma Institute Australia, Westmead Hospital, The University of Sydney, Sydney, Australia, [8]Pathology, Royal Prince Alfred Hospital, Melanoma Institute Australia, Sydney University, Camperdown, Australia

Background: Immune checkpoint inhibitors improve survival of patients with advanced melanoma. Combination anti-PD1 and anti-CTLA4 therapy improves the response rate compared to single agent anti-PD1, at the expense of far greater toxicity. While efforts have been made to identify biomarkers to predict treatment response, there are no biomarkers to predict for immunotherapy toxicity.

Methods: 198 plasma samples from 99 patients (discovery cohort – 50 patients, validation cohort – 49 patients) receiving combination anti-PD1 (nivolumab or pembrolizumab) and anti-CTLA4 (ipilimumab) were studied. The expression of 65 cytokines, measured at baseline (PRE) and early during treatment (EDT: week 1-3), was correlated with immune-related toxicity, defined as toxicity that warranted discontinuation of treatment and administration of high dose steroids ($\geq$ 50mg PO prednisolone equivalent), within 6 months of starting treatment (hypophysitis requiring steroid replacement was excluded).

Results: Toxicity rates were comparable between the discovery and validation cohorts, 21/50 (42%) and 22/49 (45%) respectively. The median expression of all 65 cytokines was significantly higher in patients with immune-related toxicity, compared to patients without toxicity in both the discovery cohort (PRE; $p = 0.01$, EDT; $p < 0.01$) and validation cohort (PRE; $p = 0.03$, EDT; $p = 0.02$). In addition, the median expression of six pro-inflammatory cytokines associated with autoimmune disease (IFN, IL-2, IL-17A, IL-1α, IL-1β, IL12) was significantly higher at baseline and EDT in patients with toxicity; discovery (PRE and EDT, $p < 0.01$) and validation (PRE, $p < 0.01$; EDT, $p = 0.01$). Expression of FGF-2, IL-12P70, IL13, IL-1 β, IL-2, MIL-1β and VEGF-A was also significantly higher in patients with toxicity at PRE and EDT, in both the discovery and validation cohorts, compared to patients without toxicity.

Conclusions: Elevated levels of circulating cytokines at baseline and EDT predict development of immune-related toxicity. Pre-treatment measurement of circulating inflammatory cytokines may have an important role in treatment selection for metastatic melanoma patients.

Legal entity responsible for the study: Macquarie University.

Funding: National Health and Medical Research Council.

Disclosure: A.M. Menzies: Consultant or advisory role: BMS, MSD, Novartis, Roche, Pierre-Fabre; Honoraria: BMS, MSD, Novartis, Roche. M.S. Carlino: Consultant or advisory role: MSD, BMS, Amgen, Novartis; Honoraria: BMS, Novartis, MSD A. Guminski: Consultant or advisory role: BMS, Roche, Sun Pharma, Merck KgA Travel support: BMS, Sun Pharma. R. Kefford: Consultant or advisory role: BMS, Merck; Honoraria: BMS Conference attendance: BMS, Amgen. G.V. Long: Consultant or advisory role: BMS, Novartis, Roche, Amgen, Pierre Fabre, MSD, Array; Honoraria: BMS, MSD, Roche, Novartis, Incycte. All other authors have declared no conflicts of interest.

1862P A phase I trial of vorolanib (X-82t vascular endothelial growth factor receptor (VEGFR) inhibitor, in patients (pts) with advanced solid tumors

J. Bendell[1], K.N. Moore[2], M.R. Patel[3], C. Chua[4], H-T. Arkenau[5], G. Dukart[6], K. Harrow[7], C. Liang[8]

[1]GI Oncology Research, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA, [2]Medical Oncology, Stephenson Cancer Center/University of Oklahoma, Oklahoma City, OK, USA, [3]Oncology, U Minnesota Medical School, Minneapolis, MN, USA, [4]Medical Oncology, Oncology Hematology Care, Inc., Blue Ash, OH, USA, [5]SCRI, Sarah Cannon Research Institute SCRI UK, London, UK, [6]Xcovery Holdings, Inc., Palm Beach Gardens, FL, USA, [7]Clinical Operations, Xcovery Holding Company, LLC, Palm Beach Gardens, FL, USA, [8]Xcovery Holdings, Inc., Palm Beach Gardens, FL, USA

Background: Vorolanib is an orally available, potent, small molecule VEGFR inhibitor. It was designed based on the sunitinib scaffold with the goals of a shorter half-life to meet the pharmacokinetic (PK)/ pharmacodynamic (PD) requirement of intermittent inhibition and no accumulation in tissues. This first-in-human study (NCT01296581) was designed to determine the maximum tolerated dose (MTD) or the recommended dose, dose-limiting toxicity (DLT), safety, PK, and preliminary antitumor activity of vorolanib.

Methods: Patients aged ≥ 18 years with advanced solid tumors were enrolled at the starting dose of 20 mg and escalating doses in an accelerated design. Safety was evaluated in every 4-week cycles, and tumor assessment was performed every 8 weeks using RECIST 1.1. Plasma PK samples and time-matched ECG data were collected.

Results: 52 patients received vorolanib in 17 cohorts, with doses ranging from 20mg QD to 800 QD and 140-200 mg BID. During the study, the formulation was changed from capsule to tablet. The most common tumor type was ovarian (19%). No DLT occurred and the MTD was not officially reached. Due to apparent saturation of absorption in the 400 – 800 mg QD range, dose escalation was stopped at 800 mg, and 400 mg QD was chosen as the dose for the expansion cohort. The most common treatment-related adverse events (TRAE) were fatigue, nausea, diarrhea, hair color change, vomiting, rash, peripheral edema and asthenia, mostly grade 1-2. Five patients had a grade 3TRAE, with proteinuria (4%) being the most common. The plasma half-life of vorolanib was approximately 6.5 hours, and no accumulation was observed after 21-days of daily dosing. 1 pt with pancreatic adenocarcinoma receiving vorolanib had a complete response, 1 pt with Hurthle cell carcinoma had a partial response, and 11 pts (20%) had stable disease for ≥ 6 cycles.

Conclusions: Vorolanib was generally well tolerated up to 800 mg QD in patients with advanced solid tumors. Based on the safety profile, PK/PD model and patient responses, 400 mg QD was selected as the single agent dose for advanced cancer patients.

Clinical trial identification: NCT01296581.

Legal entity responsible for the study: Xcovery Holdings, Inc.

Funding: Has not received any funding.

Disclosure: K.N. Moore: Advisory boards: AstraZeneca, Advaxis, Clovis, Tesaro, Immunogen, Genentech/Roche, VBL Therapeutics, Janssen. G. Dukart, K. Harrow, C. Liang: Full time employee and stock options: Xcovery Holdings, Inc. All other authors have declared no conflicts of interest.

1863P Longitudinal analysis of circulating biomarkers to monitor advanced EGFR mutated (EGFR+) non-small cell lung cancer (NSCLC)

P.N. Ding[1], T. Becker[1], V.J. Bray[2], W. Chua[2], Y.F. Ma[1], A. Luk[1], J. Po[1], D. Lynch[1], N. Caixeiro[1], P. de Souza[1], T.L. Roberts[1]

[1]Translational Medical Oncology Group, Ingham Institute for Applied Medical Research, Liverpool, Australia, [2]Medical Oncology Department, Liverpool Hospital, Liverpool, Australia

Background: Circulating tumour DNA (ctDNA) and circulating tumour cells (CTC) can be used as a 'liquid biopsy' to detect gene mutations. Serial blood collection for ctDNA and CTC analyses allows monitoring for treatment response and to understand the mechanisms of acquired resistance. We hypothesised that longitudinal ctDNA and CTC analyses may be used for disease monitoring and could have prognostic significance in patients with advanced EGFR+ NSCLC.

Methods: In this prospective study, patients with advanced EGFR+ NSCLC were recruited, with blood and plasma samples collected prior to starting treatment, 4 weeks into treatment and at disease progression. CTCs were enumerated and ddPCR for EGFR activating mutations and the T790M resistance mutation performed on ctDNA. We evaluated the relationship between baseline and decrease in CTC and ctDNA at 4 weeks with clinical outcomes.

Results: A total of 56 plasma specimens from 28 patients were studied. ctDNA was detectable at baseline in 19/28 (68%) patients starting first line EGFR inhibitors. Detectable baseline ctDNA was associated with higher disease burden ($p < 0.01$). Early disappearance of ctDNA at 4 weeks was associated with radiological response 12 weeks into treatment ($p = 0.04$) and improved PFS (Median PFS 136 vs 511 days, HR 4.49, $p < 0.01$) and OS (Median OS 311 days vs NR, HR 5.32, $p = 0.01$), which remained significant after adjustment for burden of disease. Drop in CTC count at 4 weeks was associated with improved PFS (HR 3.11 $p = 0.02$) but not OS. Drop in CTC counts at 4 weeks was associated with radiological response, just reaching significance ($p = 0.05$).

Conclusions: Longitudinal assessment of ctDNA and CTC is an accurate predictor of tumour response and survival outcomes for patients with advanced EGFR+ NSCLC. This offers a potentially cheaper, highly informative and minimally invasive way of monitoring malignancies.

Clinical trial identification: ACTRN12617000985381.

Legal entity responsible for the study: The authors.

Funding: Australian Postgraduate Scholarship, CONCERT top-up scholarship, Lung Foundation Australia.

Disclosure: All authors have declared no conflicts of interest.

1864P Genotyping of circulating tumor DNA in biliary tract cancer reveals diagnostic and prognostic information

T.J. Ettrich[1], D. Schwerdel[1], A. Dolnik[2], F. Beuter[1], T. Blätte[2], S.A. Schmidt[3], N. Stanescu-Siegmund[3], J. Steinacker[3], R. Marienfeld[4], A. Kleger[1], L. Bullinger[2], T. Seufferlein[1], A.W. Berger[1]

[1]Internal Medicine I, Ulm Medical University, Ulm, Germany, [2]Internal Medicine III, Ulm Medical University, Ulm, Germany, [3]Diagnostic and Interventional Radiology, Ulm Medical University, Ulm, Germany, [4]Pathology, Ulm Medical University, Ulm, Germany,

Background: Biliary tract cancer (BTC) shows increasing incidence and is associated with a high mortality. Diagnosis is difficult due to the frequently occurring inaccessibility of the tumor for biopsy. Noninvasive approaches for assessing and monitoring the tumor-specific molecular setup are desirable to improve diagnosis and tailor treatment.

Methods: Blood and tumor tissue samples from patients with locally advanced or metastatic BTC were collected prior to and during palliative treatment. Tumor tissue and corresponding ctDNA samples were subjected to targeted resequencing of 15 genes frequently mutated in BTC (TP53, KRAS, ARID1A, BAP1, PBRM1, PIK3CA, SMAD4, FBXW7, IDH1, BCL2, BRAF, CDKN2A, ERBB2, IDH2, NRAS). Findings were correlated with clinical and imaging data.

Results: 24 therapy naive patients with histologically confirmed BTC were included into the analyses. The mutational concordance (blood/tissue) was 74% overall and 92% for intrahepatic tumors only. Mean variant allele frequency (VAF) detected in tumor tissue was significantly higher compared to ctDNA ($p = 0.0291$). In turn, the sequencing depth for ctDNA was about double of that for tissue samples (1010x vs. 465x), enabling the detection of variants in ctDNA. ctDNA VAF at baseline significantly correlated with tumor load (Spearman, $r = 0.4073$, $p = 0.0433$). Interestingly, for intrahepatic BTC baseline ctDNA VAF also significantly correlated with progression-free survival (Spearman, $r = -0.5878$, $p = 0.0288$). 36% of therapy naive patients had a change in their mutational profile during chemotherapy.

Conclusions: The molecular landscape of BTC is represented in ctDNA and most tumor specific variants are detectable in ctDNA, especially in intrahepatic BTC. In this subgroup the baseline VAF in ctDNA was also of prognostic significance. Additionally, we detected hints for tumor evolution in a relevant portion of the analyzed BTC patients during chemotherapy, which have to be further investigated. Altogether, ctDNA analysis in BTC may support diagnosis, prognosis and the adaption of therapeutic strategies according to the specific molecular setup of the tumor detected at any time point during chemotherapy.

Legal entity responsible for the study: Ulm University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1865P Interactions of cancer stem cell and immune microenvironment in non-small cell lung cancer (NSCLC)

F. Zhang[1], N. Dong[1], S. Torres[1], S. Calabuig Fariñas[2], R. Sirera Perez[3], M. Mosqueda[1], E. Escorihuela[4], E. Jantus-Lewintre[5], C. Camps[6]

[1]Molecular Oncology, Fundación de Investigación Hospital General Universitario de Valencia, Valencia, Spain, [2]Molecular Oncology, Molecular Oncology Lab. Fundación Investigación Hospital General Universitario Valencia, Valencia, Spain; Centro Investigación Biomédica en Red de Cáncer (CIBEROnc), Madrid, Spain; Dept. of Pathology, Universitat de València, Valencia, Spain,[3]Biotechnology Department, Universidad Politécnica de Valencia-CIBERONC, Valencia, Spain, [4]Molecular Oncology, Fundación de Investigación Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain, [5]Molecular Oncology Lab, Fundación Investigación Hospital General Universitario Valencia, Valencia, Spain, Centro Investigación Biomédica en Red de Cáncer (CIBEROnc), Madrid, Spain, Dept. of Biotechnology, Universitat Politècnica València, Valencia, Spain, [6]Medical Oncology, Dept. of Medical Oncology, Hospital General Universitario de Valencia, Valencia, Spain, Centro Investigación Biomédica en Red de Cáncer (CIBEROnc), Madrid, Spain, Dept. of Medicine, Universitat de València, Valencia, Spain

Background: Lung cancer stem cells (CSCs) are a small subpopulation of cells with self-renewal, tumorigenic properties and the ability to grow to form tumorspheres in non-adherent conditions. Recently, the study on soluble molecules has been a new focus to understand the interaction between CSCs and tumor microenvironment. The aim of this work is to compare the release of cytokines between monolayer cells and tumorspheres of NSCLC cultures.

Methods: The study was performed on medium supernatant of cells from 8 NSCLC tumour patients samples and 10 cell lines (A549, H1650, H460, H23, H358, H2228, HCC827, PC9, H1993, SW900) grown in monolayer and tumorspheres at 2 different densities (10^4 and 10^5 cells/ml); supernatant was recollected at 12h and 24h. We analyzed 8 soluble factors with immunosuppressive (IL-4, IL-10, IL-13), and immunoregulatory (IL-6, IL-8, IL-17A, TNFa, IFN) capacity through sensitivity bead-based multiplex assay using the Millipore kit from the Luminex 100/200.

Results: IL-4, IL-6, IL-8, TNFa levels were detected in all samples while IFNγ, IL-10, IL-13, IL-17A were beyond the detectable range in adherents for most of cultures (Detection range [pg/ml] of IL-4: 1.83-7497.38, IL-6: 0.18-813.66, IL-8: 0.31-1042.75, TNFa: 0.43-1758.47, IFNγ: 0.61-2468.39, IL-10: 1.46-6056.85, IL-13: 0.24-1002.76,

IL-17A: 0.73-3074.88). We observed significant differences in levels of IL-6, IL-13, IL-17A, TNFa, IFNγ between adherent cells and tumorspheres. Moreover, IL-4, IL-10, IL-13, IL-17A, IFNγ levels in tumorspheres were higher than monolayer. Otherwise, IL-6 and TNFa were secreted more in monolayer. IL-8 is the most secreted molecule in both adherents and tumorspheres by all cultures.

Conclusions: Our preliminary results suggest that high levels of IL-6 and IL-8 were detected in all samples. IL-8, IL-13, IL-17A and IFNγ secreted by lung CSCs could be involved in the modulation of the immune microenvironment. Additionally, adherent cells show increased levels of IL-6 and TNFa compared to tumorspheres, and IL-8, IL-4, IFNγ, IL-10, IL-13, IL-17A show the opposite. The next is to extend the cohort to validate our results and to study others immunoregulatory factors.

Supported by grants from FEDER and PI12-02838 and PI15-00753 from ISCIII.

Legal entity responsible for the study: Fundación de Investigación del Hospital General Universitario de Valencia.

Funding: Supported by grants from FEDER and PI12-02838 and PI15-00753 from ISCIII.

Disclosure: All authors have declared no conflicts of interest.

1866P Association of the rs1883832 variant of CD40 with NSCLC risk and overall survival

F-I.D. Dimitrakopoulos[1], A. Antonacopoulou[2], A. Kottorou[2], S. Marousi[2], I. Koukourikou[1], C. Scopa[3], D. Dougenis[4], V. Tzelepi[3], H. Kalofonos[5]

[1]Medical Oncology, University Hospital of Patras, Patras, Greece, [2]Molecular and Clinical Laboratory, University of Patras, Patras, Greece, [3]Pathology, University Hospital of Patras, Patras, Greece, [4]Thoracic Surgery, University Hospital of Patras, Patras, Greece, [5]Medical Oncology, University of Patras, Patras, Greece

Background: During the last few years a growing number of studies has attempted to shed light on the role of CD40 (Tumor Necrosis Factor Receptor Superfamily Member 5) in non-small-cell lung cancer (NSCLC), which remains the leading cause of cancer-related deaths worldwide. The aim of the current study was to investigate the clinical relevance of CD40 functional single nucleotide polymorphism (SNP) rs1883832 (-1C/T) with susceptibility to NSCLC, the clinicopathological parameters, relapse and survival rates of NSCLC patients, as well as with the protein expression of CD40.

Methods: CD40 SNP rs1883832 was genotyped in 268 randomly selected NSCLC patients and 279 age- and gender-matched healthy donors. Patients were under observation during a five-year period. Immunohistochemical analysis for CD40 was performed on 106 NSCLC tumor tissue samples. All the participants were Greeks with Caucasian origin.

Results: Genotype frequencies of rs1883832 (CC, CT, and TT) were significantly different between healthy controls and patients. CC homozygotes had higher risk for NSCLC compared to T allele carriers in univariate ($P < 0.001$), as well as in multivariate analysis ($P = 0.006$). In addition, rs1883832 was related to overall survival. More specifically, CT heterozygotes had worse clinical outcome after two-, three- and five-year observation compared to TT and CC homozygotes ($P = 0.015$, $P = 0.005$ and $P = 0.017$, respectively). Stratifying according to histological subtype, this association was observed only in patients with adenocarcinomas ($P = 0.028$) and not in patients with squamous- and large-cell carcinomas. Furthermore, taking into consideration disease stage, worse survival for CT heterozygotes was observed in stage II patients and not in patients of other stages ($P = 0.016$). Moreover, the variant had also strong association with brain metastases, with T allele carriers developing more often metastatic disease in CNS ($P = 0.018$). Interestingly, rs1883832 was related to CD40 protein expression in malignant cells ($P < 0.001$) as well as in stromal cells ($P = 0.004$).

Conclusions: The present findings suggest that investigated SNP rs1883832 may be a useful and independent biomarker in NSCLC. However, more studies are needed in order to further demonstrate their role in NSCLC.

Legal entity responsible for the study: University of Patras.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1867P Circulating tumour DNA (ctDNA) as a tool to assess response and guide therapy adaptation in rectal cancer

S. Khakoo[1], P. Carter[2], N. Valeri[3], R. Shaikh[2], T. Jones[2], R. Begum[1], I. Rana[1], S. Picchia[4], M. Bali[4], G. Brown[4], A. Wotherspoon[5], M. Terlizzo[5], K. von Loga[6], I. Ahmed[5], D. Watkins[1], I. Chau[1], N. Starling[1], D. Tait[1], M. Hubank[2], D. Cunningham[1]

[1]Medicine, Royal Marsden Hospital NHS Foundation Trust, Sutton, UK, [2]Clinical Genomics, Royal Marsden Hospital NHS Foundation Trust, Sutton, UK, [3]Molecular Pathology, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, UK, [4]Radiology, Royal Marsden Hospital NHS Foundation Trust, Sutton, UK, [5]Histopathology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [6]Histopathology, Royal Marsden Hospital NHS Foundation Trust, Sutton, UK

Background: Neo-adjuvant chemoradiation (CRT) is associated with varied response in patients (pts) with localised rectal cancer. Early identification of poor responders and pts at risk of developing systemic disease using ctDNA would allow tailoring of treatment.

Methods: Tissue and serial plasma was collected from 47 pts with localised rectal cancer scheduled to undergo long course CRT. Cell-free DNA (cfDNA) was purified from a mean of 3.6 ml plasma per time-point. Somatic variants were identified in tissue by sequencing using a targeted capture panel. Up to 3 variants per patient in genes of interest were tracked in plasma using custom TaqMan assays on a droplet digital PCR platform. Tumour response assessments were conducted according to RECIST. Statistical analysis included Fisher's exact test and Spearman's correlation.

Results: 62% of pts were male, median age 59, range 30-83. On baseline MRI, circumferential resection margin was involved or threatened in 75% and EMVI positive in 81%. Plasma was collected at a median of: 6 days (d) prior to CRT (baseline), 21 d from the start of CRT (mid) and 37 d after completion of CRT (end). The frequency (%) of mutation detection in tissue was: TP53 (85), APC (74), KRAS (36), PIK3CA (15), NRAS (4) and BRAF (2). ctDNA was detectable in 74% of pts at baseline and in 21% at mid and end of CRT. ctDNA detection increased with stage at baseline: stage 1 ($n = 0/1$), stage 2 ($n = 3/5$, 60%) and stage 3 ($n = 32/41$, 78%). Stage had no impact on detection at mid or end of CRT. At baseline, ctDNA was detectable in all 15 CEA secretors ($\geq$5 ug/l) compared to 63% in 30 non-secretors ($P = 0.008$). Baseline ctDNA levels were not associated with ki67 tumour assessment. MRI response assessment of the primary tumour was not associated with ctDNA detection at any timepoint. 11 patients developed metastases of which 3 occurred after surgery. End of CRT ctDNA detection was higher in pts that developed metastases (64%) compared to those that did not (8.3% $P = 0.0005$). Detection of ctDNA at baseline that persisted at mid CRT was also higher in pts that developed metastases (36% vs 11%, $p = 0.07$).

Conclusions: ctDNA detection can help identify rectal cancer pts with localised disease at risk of developing metastases. These pts could benefit from earlier intervention with systemic therapy.

Clinical trial identification: CCR 3085, NCT00825110.

Legal entity responsible for the study: Royal Marsden Hospital NHS Foundation Trust.

Funding: Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research.

Disclosure: All authors have declared no conflicts of interest.

1868P A genetic analysis of gemcitabine-induced high-grade neutropenia in pancreatic cancer patients

F. Innocenti[1], C. Jiang[2], A.B. Sibley[3], S. Denning[1], A.S. Etheridge[1], D. Watson[3], D. Niedzwiecki[4], A.J. Hatch[3], H. Hurwitz[5], A. Nixon[3], Y. Furukawa[6], M. Kubo[7], D.J. Crona[1], H. Kindler[8], H.L. McLeod[9], M.J. Ratain[8], K. Owzar[2]

[1]Division of Pharmacotherapy and Experimental Therapeutics, UNC-Institute for Pharmacogenomics and Individualized Therapy, Chapel Hill, NC, USA, [2]Alliance Statistics and Data Center, Duke Cancer Institute, Durham, NC, USA, [3]Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA, [4]Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC, USA, [5]Medical Oncology, Duke University Medical Center, Durham, NC, USA, [6]Center for Genomic Medicine, RIKEN, Yokohama, Japan, [7]Center for Integrative Medicine, Riken, Kanagawa, Japan, [8]Oncology, The University of Chicago Medical Centre, Chicago, IL, USA, [9]Department of Cancer Epidemiology, Moffit Cancer Center, Tampa, FL, USA

Background: One of the standard of care regimens for advanced pancreatic cancer is gemcitabine-based chemotherapy. The efficacy of gemcitabine is reduced by dose-limiting hematologic toxicities, especially neutropenia. Uncovering the variability of these toxicities attributed to germline DNA variation is of great importance.

Methods: CALGB 80303 was a randomized study in advanced pancreatic cancer patients treated with gemcitabine with or without bevacizumab. The study protocol included genotyping of genes of gemcitabine disposition (CDA, DCTD, SLC29A1, SLC28A1, SLC29A2), as well as a genome-wide analysis. The clinical phenotype was time to high-grade early neutropenia event accounting for progression or death, with other treatment-terminating adverse events as competing informative events. The inference was conducted on the basis of the association between genotype and cause-specific hazard of a neutropenic event.

Results: The primary analyses were conducted on the basis of 294 genetically estimated Europeans. For CDA rs2072671 (A>C), AC and CC patients had a lower risk of neutropenia than AA patients (unadjusted P-value 0.01, HR 0.61, 95% CI 0.41-0.89). For SLC28A1 rs3825876 (G>A), AA patients have a higher risk of neutropenia than GA and GG patients (unadjusted P-value 0.02, HR 1.51, 95% CI 1.06-2.16). The C allele of CDA rs2072671 was associated with increased mRNA expression in whole blood in three studies (unadjusted P-values 2.7e-14, 6.61e-62, 9.70e-65). In the genome-wide analysis, variants in TGFB2 were among the top hits (unadjusted lowest P-value 1.62e-06) but had no effect in luciferase assays.

Conclusions: The first genetic analysis of gemcitabine-induced neutropenia using a competing risk model in a prospective randomized clinical study has proposed a potentially novel mechanism of the protective effect of the CDA rs2072671 variant. We hypothesize that the rs2072671 (A>C) variant acts through a local effect in either the bone marrow or in circulating neutrophils (or both), by protecting neutrophils from the anti-proliferative effects of gemcitabine. Further confirmation is needed.

Clinical trial identification: NCI-2012-02960; NCT00088894.

Legal entity responsible for the study: Alliance for Clinical Trials in Oncology.

Funding: NIH.

Disclosure: All authors have declared no conflicts of interest.

1869P Effect of a combined treatment with iPS cells derived dendritic cells and proton beam irradiation in a murine subcutaneous melanoma model

Y. Wang[1], L. Sun[1], X. Li[2], K. Tsuboi[1]

[1]Proton Medical Research Center, University of Tsukuba, Tsukuba, Ibaraki, Japan, [2]Division of the Transplantation Immunology, National Research Institute for Child Health and Development, Tokyo, Japan

Background: In situ dying and just died tumor cells after irradiation give danger signals and release tumor-specific antigens which are sequentially incorporated into dendritic cells (DCs). Our previous studies on a murine subcutaneous tumor model showed that injection of bone marrow derived DCs (BM-DCs) after X-ray therapy significantly delayed tumor growth. As compared to X-rays, the unique biological and physical benefits of proton beam therapy may prove superior in the systemic immune effect. In addition, usage of DCs induced from iPS cells (iPS-DCs) may overcome practical problems of BM-DCs such as a limited number of applicable cells and an induction period of 7 days. The purpose of this study is to investigate: 1) whether proton beam therapy are superior in induction of anti-tumor immune response compared to X-ray therapy. 2) whether the function of induced iPS-DCs is superior to that of BM-DCs.

Methods: DCs were induced by using GM-CSF and IL-4 from autologous bone marrow cells or iPS cells of C57BL/6 mice. Syngeneic B16 melanoma cells subcutaneously implanted at the thighs of C57BL/6 mice were treated with X-ray or proton beam 5 days after inoculation. After 1, 3, 5, 7 days from irradiation, induced BM-DCs or iPS-DCs were injected directly into the tumor site. Tumor growth was monitored, and survival analyses were performed.

Results: Proton beam therapy induced superior immunogenicity of cancer cell comparing to X-ray therapy. Also, iPS-DCs showed an excellent ability to incorporate antigens in vitro comparing to BM-DCs. The combination treatment of proton beam and iPS-DCs significantly delayed tumor growth in vivo.

Conclusions: iPS-DCs should overcome the practical problems of BM-DCs in cancer treatment. The combination therapy of proton beam and iPS-DCs administration can offer a promising novel cancer therapy.

Legal entity responsible for the study: Koji Tsuboi.

Funding: Japan Society for the Promotion of Science.

Disclosure: All authors have declared no conflicts of interest.

1870P Developing the liquid biopsy in gastroesophageal adenocarcinoma: Disease monitoring and detection of minimal residual disease

M.R. Openshaw, B. Ottolini, C.J. Richards, D. Guttery, J.A. Shaw, A. Thomas

Leicester Cancer Research Centre, University Hospitals of Leicester NHS Trust Leicester Royal Infirmary, Leicester, UK

Background: Gastroesophageal adenocarcinoma (GOA) is a molecularly defined group of cancers with shared genetic alterations, poor overall survival and no routine blood based biomarker. The liquid biopsy, including circulating tumour DNA (ctDNA) is a promising technology that may improve our ability to monitor disease and enhance survival. This study aimed to determine the utility of ctDNA in GOA.

Methods: A pilot study of 37 patients with GOA were recruited. These comprised 24 patients treated with curative intent and 13 palliative patients. Tumour DNA was sequenced using a custom ampliseq six gene targeted next generation sequencing (NGS) panel. Tumours from patients treated with curative intent with no detectable somatic mutation were also analysed for gene amplification via Nanostring™ nCounter. Plasma from blood samples taken at multiple time points were analysed by NGS and digital droplet PCR to detect ctDNA.

Results: Somatic mutations at $>5\%$ allele frequency were identified in 30 of 37 (81%) tumours, most commonly in TP53. Gene amplification was detected in a further three. In 11 of 13 (85%) palliative patients that had a detectable somatic mutation ctDNA was detected in 9 (82%). These ctDNA levels were dynamic, falling with treatment response and rising with disease progression, often prior to clinical relapse. 22 of 24 (92%) patients treated with curative intent had a detectable somatic mutation or gene amplification. 9 of these 22 (41%) relapsed during follow-up. CtDNA was detected prior to relapse in 7 of 22 (31%) patients and predicted poor survival (median PFS 298 vs $>$ 1000 days, HR = 11.8, $p < 0.001$). In 4 patients, ctDNA was detected in the postsurgical blood test, of these 3 have relapsed and one remains disease free at 5 months (median PFS 203 vs $>$ 1000 days, HR = 9.6, $p = 0.004$). This patient will be followed up for evidence of relapse as these ctDNA positive post surgical bloods suggest detection of minimal residual disease.

Conclusions: Tracking of ctDNA in patients with GOA provides valuable clinical information regarding disease progression and response, and presence of ctDNA is generally a poor prognostic sign. In addition, ctDNA may define patients with minimal residual disease who are at high risk of relapse after surgery.

Legal entity responsible for the study: University of Leicester.

Funding: HOPE against Cancer Experimental Cancer Medicine Centres Network.

Disclosure: B. Ottolini: Previous employee: DiaDx; Holding patents: DiaDx. C.J. Richards: Honoraria: MSD. J.A. Shaw: Travel, accommodation, expenses reimbursements: Thermofisher. A. Thomas: Honoraria: Amgen, Servier, BMS. All other authors have declared no conflicts of interest.

1871P Survival from breast cancer in patients with BRCA1/2, CHEK2, NOD2 mutations and TP53 (c.[215G>C]) polymorphisms

J. Huszno[1], Z. Kolosza[2]

[1]Outpatient Clinic, Maria Sklodowska Curie MSC Memorial Cancer Institute in Gliwice, Gliwice, Poland, [2]Biostatistics Unit, Maria Sklodowska Curie MSC Memorial Cancer Institute in Gliwice, Gliwice, Poland

Background: The purpose of this study is to estimate 5-year survival rates for patients with early onset breast cancer, with and without a BRCA1/2, CHEK2, NOD2 mutation or TP53 polymorphisms and to identify prognostic factors among mutation carriers in breast cancer patients.

Methods: In a study conducted in the years 2007-2016 in the Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch (COI) were analyzed prognostic factors and survival in 622 breast cancer including 60 BRCA mutation carriers, 46 CHEK2 mutation carriers, 29 NOD2 mutation carriers and 87 patients with TP53 polymorphisms. Control group was selected from breast cancer patients without mutation and polymorphisms ($n = 400$).

Results: The five–year rate of OS was 75.9% for pts with BRCA mutation, 94.4% for CHEK2 mutation carriers, 96.6% for NOD2 mutation carriers and 100% for patients with TP53 polymorphisms. BRCA mutation carriers had insignificantly worse survival as compared to control group ($p = 0.180$). Patients with CHEK2 mutation had significantly better OS than control group ($p = 0.032$). Similarly NOD2 mutation carriers had also significantly better OS than control group ($p = 0.043$). Patients with TP53 polymorphisms carriers had higher OS in comparison to control group ($p = 0.002$). In subgroup of pts with N0 (Without lymph node metastases) BRCA mutation carriers was characterized by the worst OS (81.1%) among carriers of other mutations: CHEK2 (94.7%, $P = 0.021$), NOD2 (95.3%, $p = 0.092$) and TP53 polymorphisms (100%, $p = 0.007$) or control group (94.4%, $p = 0.022$). Similar tendency was observed according to N+ subgroup and subgroup with tumor size T1-T2. Higher tumor size (HR = 2.85), lymph node metastases (HR = 2.93) and HER2 overexpression (HR = 1.49) were significant factors for worse OS. Positive ER status was associated with a better OS (HR = 0.52, $p = 0.001$). Age <40 years (HR = 0.71, $p = 0.255$) was insignificantly favorable factor.

Conclusions: CHEK2, NOD2 mutation carriers and patients with TP53 polymorphisms had better 5-year survival in comparison to patients with BRCA mutation and control group. Higher tumor size (T) and lymph node metastases (N+) were negative prognostic factors independently from the presence of mutations and polymorphisms.

Legal entity responsible for the study: Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1872P Phase I pharmacological study of continuous chronomodulated capecitabine treatment

J. Roosendaal[1], B.A.W. Jacobs[2], D. Pluim[2], H. Rosing[1], B. Nuijen[1], J.H. Beijnen[1], A.D.R. Huitema[1], J.H.M. Schellens[2], S. Marchetti[2]

[1]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute and MC Slotervaart, Amsterdam, Netherlands, [2]Division of Clinical Pharmacology, Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Capecitabine is an oral prodrug of the anti-cancer drug 5-fluorouracil (5-FU). The 5-FU degrading enzyme, dihydropyrimidine dehydrogenase, and the target enzyme thymidylate synthase, are subject to circadian rhythmicity. The primary aims of this study were to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), recommended dose (RD) and safety of capecitabine therapy adapted to this circadian rhythm (chronomodulated therapy).

Methods: Patients aged $\geq$ 18 years, with WHO performance status of ≤ 2, and advanced solid tumors potentially benefitting from capecitabine therapy were enrolled. DPYD*2A or 2846A>T mutation carriers were excluded. A classical dose escalation 3 + 3 design was applied. Capecitabine was administered twice daily without interruptions. The daily dose was divided in morning and evening doses that were administered at 09:00h and 24:00h, respectively. The ratio of the morning to the evening dose was 3:5 (morning:evening). Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 4.03. DLT was evaluated during the first three weeks of treatment.

Results: A total of 21 patients was enrolled. The daily capecitabine dose was escalated from 1000 mg/m^2 up to 2550 mg/m^2 over five dose-levels. Three DLTs were observed in two patients at the highest dose-level (grade III hand-foot syndrome (2x) and grade III diarrhea (1x)). The MTD was established at 2000 mg/m^2 per day (750 mg/m^2 at 9:00 h and 1250 mg/m^2 at 24:00 h). Continuous chronomodulated capecitabine therapy was

generally well tolerated at the MTD level with main adverse events being grade 1-2 hand-foot syndrome and fatigue.

Conclusions: The cumulative dose of capecitabine at the MTD/RD (i.e., 750 mg/m^2 at 9:00h and 1250 mg/m^2 at 24:00h, continuous chronomodulated regimen) is 20% higher than the cumulative dose of the approved regimen (1250 mg/m^2 bi-daily on day 1-14 of every 21-day cycle). Chronomodulation therefore represents a promising strategy as it could lead to improved tolerability and efficacy of capecitabine. Further investigation is warranted.

Clinical trial identification: EudraCT: 2014-000889-22.

Legal entity responsible for the study: The Netherlands Cancer Institute.

Funding: The Netherlands Cancer Institute.

Disclosure: All authors have declared no conflicts of interest.

1873P Head and neck (HN) primary sarcomatoid carcinoma (PSC) profile by high-throughput somatic mutation profiling

V. Fallet[1], R. Taouachi[2], R. Saffroy[3], A. Ben Lakhdar[4], N. Rabbe[5], F. André[6], S. Temam[7], A. Lemoine[3], M. Wislez[1]

[1]Thoracic Oncology, APHP, CancerEst, Tenon University Hospital/GRC-04 Theranoscan, Sorbonne Universités, UPMC Université Paris 06, Paris, France, [2]Department of Surgery, Institut Curie, PSL Research University, Saint Cloud, France, [3]Department of Biochiemistry and Oncogenetics, AP-HP, GH Paris-Sud, Hôpital Paul Brousse/Platform Oncomolpath/INCA, Villejuif, France, [4]Pathology, Gustave Roussy Institute, Villejuif, France, [5]GRC n°04, Theranoscan, APHP, CancerEst, Tenon University Hospital, Paris, France, [6]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [7]Department of Head and Neck Surgery, Institut Gustave Roussy, Villejuif, France

Background: The Head & Neck Primary Sarcomatoid Carcinoma (HN PSC) is a rare sub-type of squamous cell carcinoma with poor prognosis. This study sought to describe the mutational profile of HN PSC using high-throughput genotyping technology Massarray, (Agena, Hamburg).

Methods: We included 45 patients with HN PSC. We used PCR mass spectrometry detection to establish the DNA mutation profiles of 72 samples from these patients (45 primary tumors, 5 metastatic cervical nodes and 22 non tumoral tissues) studying 214 mutations affecting 26 oncogenes and tumor suppressor genes.

Results: In total, 33/45 (77.3%) patients were male and 31/45 (69%) were smokers. Median age was 60 years (range 13 – 93 years) and 28/45 (62.2%) were metastatic. The main tumor sites were oral cavities (31.1%) and larynx (28.1%). The predominant histological subtype was the pleomorphic form (66,7%). In the 72 tumors, 18 distinct somatic alterations were identified, 15 tumors (33%) harboring at least one mutation. The most frequent mutations were TP53 (11.1%), PIK3CA (8.9%), EPHA5 (4.4%), MET (4.4%), NOTCH1 (4.9%), NTRK2 (2.2%), BRAF (2.2%), JAK2 (2,2%), KRAS (2,2%) and NRF2 (2,2%). The presence of a mutation was not correlated with any clinical characteristic (age, sex, primary located site, cancer stage, tobacco and alcohol status). Only 1/45 (2.2%) tumor presented a targetable mutation with tyrosine kinase inhibitor (mutation BRAF). The mutational profile was identical between the local tumor site and the cervical node in 4/5 patients.

Conclusions: Our results demonstrated that HN PSC had a similar mutational profile of other HN carcinoma such as TP53, PIK3CA and NOTCH1 mutations. It reinforced the hypothesis of a single cell clone, which is acquired with different histological phenotypes by different, still unknown mechanisms involving epithelial to mesenchymal transition.

Legal entity responsible for the study: Marie Wislez.

Funding: Has not received any funding.

Disclosure: V. Fallet: Travel, accommodations, expenses: GSK, BMS, Novartis, Boeringher Ingelheim. M. Wislez: Research funding: BMS, Boehringer Ingelheim; Consulting or advisory role: AstraZeneca, Roche, BMS, MSD, Novartis, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1874P A composite liquid biomarker for non-invasive diagnosis of resectable pancreatic ductal adenocarcinoma

A.W. Berger[1], T.J. Ettrich[1], D. Schwerdel[1], A. Reinacher-Schick[2], H. Algül[3], A-O. König[4], E. Gallmeier[5], K. Wille[6], S. Daum[7], M. Geissler[8], A. Tannapfel[9], W. Uhl[10], T. Seufferlein[11]

[1]Internal Medicine I, University Medical Center Ulm, Ulm, Germany, [2]Hematology, Oncology and Palliative Care, Ruhr University Bochum, Bochum, Germany, [3]II. Medizinische Klinik und Poliklinik, München, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, [4]Gastroenterology and Gastrointestinal Oncology, Universitätsmedizin Göttingen, Göttingen, Germany, [5]Gastroenterology and Endocrinology, University of Marburg, Marburg, Germany, [6]Hämatology, Oncology, University Hospital Ruhr-University-Bochum, Minden, Germany, [7]Gastroenterology, Infectious Diseases and Rheumatologyh, Charité University Medicine Berlin, Berlin, Germany, [8]Internal Medicine, Oncology/Hematology, Klinikum Esslingen, Esslingen, Germany, [9]Pathology, Ruhr-Universität Bochum, Bochum, Germany, [10]Surgical Clinic, Katholisches Klinikum Bochum - St. Josef-Hospital, Bochum, Germany, [11]Department of Internal Medicine I, Ulm Medical University, Ulm, Germany

Background: Due to the dismal prognosis of the pancreatic ductal adenocarcinoma (PDAC) biomarkers are needed to facilitate the early and preferably noninvasive diagnosis. The use of circulating tumor DNA (ctDNA) was already examined in the metastatic situation but not at all in a resectable stage with lower tumor load. Currently, CA19-9 is the only validated biomarker for PDAC but inherits poor performance. Recently, it has been reported that elevated levels of thrombospondin-2 (THBS2) protein are detectable in PDAC. Here we aimed at improving sensitivity and specificity of THBS2 based detection of early PDAC by combining THBS2 analysis with further markers.

Methods: 39 patients with proven PDAC, enrolled to the NEONAX trial (identifier: NCT02047513), were selected for this study-independent retrospective translational analysis. 15 patients with benign pancreatic disease (IPMN) served as controls. cfDNA concentration was measured fluorometrically. KRAS genotyping of ctDNA was done by digital droplet PCR targeting the 7 most frequently occurring KRAS mutations in PDAC. CA 19-9 (Roche, cut-off 55 U/ml) and THSB2 levels (Quantikine, R&D Systems, cut-off 42 ng/ml) were determined by ELISA.

Results: PDAC patients had significantly more cfDNA (12.6 ng/ml) than IPMN patients (5.5 ng/ml, $p = 0.0006$). Only 5 % of PDAC patients and 7 % of IPMN patients had detectable KRAS mutations in ctDNA. CA19-9 was elevated in 56 % and THBS2 in 44 % of PDAC patients. Both markers were not elevated in any of the IPMN patients. Therefore, the assessment of THBS2 and CA19-9 levels was most suitable to discriminate the PDAC cohort from the IPMN cohort, with a sensitivity of 77 % and a specificity of 100 %.

Conclusions: THBS2 and CA19-9 panel assessed in human blood using a conventional ELISA assay may improve the diagnosis of pancreatic lesions as PDAC at an early stage. While total cfDNA amount differs between patients with benign and malignant pancreatic lesions, ctDNA genotyping for KRAS mutations failed to improve non-invasive diagnostic strategies in resectable PDAC most likely due to a low tumor load.

Clinical trial identification: NCT02047513.

Legal entity responsible for the study: Ulm University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1875P Acquired chemoresistance of colorectal cancer (CRC) cells is accompanied by pro-invasive VEGF-signaling that can be attenuated by aflibercept

A.K. Larsen[1], P. van Dreden[2], B. Chibaudel[3], A. de Gramont[4], G. Gerotziafas[5], S. Thouroude[6]

[1]Cancer Biology and Therapeutics, Centre de Recherche Saint-Antoine, Hôpital Saint-Antoine, INSERM U938 & Sorbonne University, Paris, France, [2]Laboratoire RD, Diagnostica Stago (SAS), Gennevilliers, France, [3]Medical Oncology, Institut Hospitalier Franco-Britannique/Franco-British Institute, Levallois-Perret, France, [4]Medical Oncology, Institut Hospitalier Franco-Britannique, Levallois-Perret, France, [5]Cancer Biology & Therapeutics, APHP, CancerEst, Tenon University Hospital, Paris, France, [6]Cancer Biology and Therapeutics, Centre de Recherche Saint-Antoine, INSERM U938 and Université Pierre et Marie Curie (UPMC), Sorbonne Universités Paris, France

Background: Cancer mortality is principally associated with the presence of drug-resistant, invasive subpopulations of tumor cells. However, the functional and mechanistic interactions between the two phenotypes are incompletely understood. Colorectal cancer (CRC) cells produce the vast majority of VEGF in the cancer environment and display endogenous VEGFR1/VEGF signaling which is believed to promoted survival under stress.

Methods: Migration and invasion was determined by the transwell assay (Boyden Chamber). For the tube formation assay, CRC cells were seeded onto 3D matrigels and incubated at 37° for 24 hr monitored by videomicroscopy. Determination of VEGF ligands was carried out by ELISA.

Results: We here characterize a panel of 4 isogenic CRC cell lines comprised of the parental HCT-116 cells and three independently derived sublines resistant to 5-fluorouracil, oxaliplatin and SN-38. Resistant cells secreted 3-7 fold more VEGF, while the

HCT-116/5-FU cells also secreted 2 times more PlGF, compared to the parental cells. VEGF signaling is known to promote CRC cell migration and invasion. In agreement, resistant cells showed 6-11 fold increased migration, whereas the invasive capacity had increased 6-15 fold. Aflibercept inhibits all three VEGFR1 ligands (VEGF-A, VEGF-B and PlGF) on CRC cells. Accordingly, addition of aflibercept resulted in a significant decrease in both migration and invasion. Two of the three resistant cell lines were able to do vascular/vasculogenic mimicry by forming capillary-like cellular networks which could be significantly attenuated by aflibercept.

Conclusions: Taken together, our results indicate that acquired resistance to genotoxic agents may be accompanied by an increased invasive potential mediated, in part, by VEGF signaling that can be attenuated by aflibercept.

Legal entity responsible for the study: INSERM and Sorbonne University.

Funding: Financed in Part by Sandofi-Aventis Europe.

Disclosure: A.K. Larsen: Research grant: Sanofi-Aventis Europe. All other authors have declared no conflicts of interest.

1876P Actionable mutations and overall survival in 3,211 patients with cancer: The Hellenic cooperative oncology group precision medicine initiative

E. Fountzila[1], V. Kotoula[2], G-A. Koliou[2], E. Giannoulatou[3], H. Gogas[2], C. Papadimitriou[2], I.S. Tikas[2], K. Papadopoulou[2], F. Zagouri[2], C. Christodoulou[2], A. Koutras[2], E. Razis[2], P. Papakostas[2], E. Samantas[2], G. Aravantinos[2], A. Psyrri[2], D.G. Pectasides[2], A. Futreal[4], A-M. Tsimberidou[1], G. Fountzilas[2]

[1]Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, The Univesity of Texas, Houston, TX, USA, [2]Data Office, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece, [3]Department of Bioinformatics, Victor Chang Cardiac Research Institute, Darlinghurst, Australia, [4]Genomic Medicine, MD Anderson Cancer Center, Houston, TX, USA

Background: We evaluated the impact of tumor type and molecular profiling on overall survival of patients (pts) with cancer referred to Medical Oncology Departments affiliated with the Hellenic Cooperative Oncology Group (HeCOG).

Methods: Pts referred from 1989 to 2017 had molecular testing (for research) of archival tumor tissue collected at the time of diagnosis (stage I-III, 82%; stage IV, 18%). Tumor-specific (e.g. breast, colon) gene panels (45-101 genes) were used to identify pathogenic mutations in clinically relevant genes. Deep sequencing was performed at the Laboratory of Molecular Oncology, Aristotle University of Thessaloniki and HeCOG. Mutation annotation was performed at MD Anderson Cancer Center. All pts received standard-of-care anticancer therapy.

Results: We analyzed 3,211 pts (median age, 58 years; men, 29%) with informative sequencing data. Results by tumor type and molecular pathway are shown in the table. Overall, 1,193 (37%) pts had $\geq$1 actionable alterations [115 (3.6%) $\geq$4]. The most common affected pathways were PI3K, RAF/MEK, homologous recombination repair (HRR), and tyrosine kinase; 294 (9.2%) pts had alterations in $>$ 1 pathways. The median follow-up of alive patients is 7.48 years (yrs) (95%CI, 7.36-7.59). Of 3,211 pts, 1,060 (33.01%) have died. The median overall survival is 16.08 yrs (95%CI, 13.25-16.75). Of pts with breast cancer and actionable mutations, the 5-yr survival rates were: stage I-III (n = 501) 88.8%; stage IV (n = 14), 51.1% (p<.0001). Of pts with colorectal cancer and actionable alterations, the 5-yr survival rates were: stage I-III (n = 299), 76.5%; stage IV (n = 50), 15.2% (p<.0001).

Conclusions: Tumor sequencing revealed clinically relevant genomic mutations in several molecular pathways. Prospective clinical trials validating the clinical utility of tumor profiling are warranted.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group.

Funding: Hellenic Cooperative Oncology Group.

Disclosure: All authors have declared no conflicts of interest.

1877P DNA repair genetic profiling in epithelial ovarian cancer: An opportunity for clinical improvement?

J. Assis[1], S. Coelho[2], A. Nogueira[1], R. Pinto[1], M. Brandao[3], J. Dias[2], S.G.C.M. Alves[2], D. Pereira[2], R. Medeiros[1]

[1]Grupo de Oncologia Molecular e Patologia Viral - Centro de Investigação, Instituto Portugues de Oncologia Centro do Porto (IPO-Porto), Porto, Portugal, [2]Medical Oncology, Instituto Portugues de Oncologia Centro do Porto (IPO-Porto), Porto, Portugal, [3]CTSU, Institute Jules Bordet, Brussels, Belgium

Background: In a recently published systematic review and meta-analysis, we provided an updated assessment of the association between genetic polymorphisms and epithelial ovarian cancer (EOC) first-line treatment outcome. Results highlighted the role of DNA Repair mediators, namely for variants in ERCC1 and ERCC2. Therefore, this study aims to evaluate the role of ERCC1 (rs11615 and rs3212986) and ERCC2 (rs13181 and rs1799793) variants in the outcome of EOC patients.

Methods: We conducted a hospital-based study in a cohort of EOC patients submitted to platinum-based first-line treatment (n = 340). DNA was extracted from peripheral blood samples, and genotypes were determined by Real-Time PCR using validated assays. Overall survival (OS) was the primary endpoint of this analysis. Survival analyses using Kaplan-Meier method and Cox proportional-hazards model were applied and the statistical significance was set at $p < 0.05$.

Results: The definition of a genetic profile reveals that patients harboring the combination of ERCC1 rs11615 A allele/ERCC1 rs3212986 AA genotype/ERCC2 rs13181 T allele/ERCC2 rs1799793 C allele have a significantly lower survival when compared to other genotype patients (136 vs. 161 months; log-rank test, P = 0.034). Specifically, this genetic profile is associated with a poorer prognosis (26 months vs. 69 months, respectively; log-rank test, P = 0.036) and a higher risk of death (HR, 2.7; $P_{bootstrap}$=0.019) among FIGO stage IV patients.

Conclusions: In an era where DNA repair ability is stated as a major cornerstone in EOC management, the characterization and definition of a DNA repair profile might be a useful tool for EOC clinical outcome prediction. According to the results of a meta-analysis, we validate the influence of ERCC1 and ERCC2 genetic polymorphisms in the survival of EOC patients submitted to platinum-based first-line chemotherapy. Particularly, this profile seems to have a preponderant role for the subgroup of advanced disease patients. Further considerations should be applied for the functional evaluation of these mediators in this clinical setting, as they might reveal an opportunity to improve survival in a subgroup with unfavorable prognosis.

Legal entity responsible for the study: IPO-Porto.

Table: 1876P

	Total N	N with actionable alterations	%	Overall Survival	
Tumor type				Median, Years (95% CI)	5-yr OS, % (95% CI)
Breast	1,964	527	27	NR	87.8 (85.0-90.7)
Colorectal	533	359	67	NR	68.0 (63.2-73.2)
Pancreatic	188	123	65	0.82 (.65-.98)	-
Nasopharyngeal	144	77	54	8.92 (6.68-NR)	65.2 (54.7-77.7)
Brain	131	24	18	4.54 (1.69-9.71)	46.9 (29.9-73.6)
Gastric	101	11	11	4.18 (1.04-NR)	39.8 (17.8-88.9)
Biliary Tract	80	26	33	ND	
Ovarian	70	46	66	3.24 (2.18-5.32)	36.4 (24.7-53.5)
Total	3,211	1,193	37	13.23 (10.6-NR)	68.6 (65.9-71.4)
Pathway	Total tested	N with actionable alterations	%		
PI3K/AKT/mTOR	3,211	636	20	16.08 (13.23- NR)	82.3 (79.3-85.4)
MEK/RAF	3,211	459	14	6.4 (4.08-8.92)	52.3 (47.7-57.3)
HRR	3,211	260	8	7.84 (5.33-NR)	56.8 (50.7-63.5)
Tyrosine kinase	3,211	161	5	NR	69.2 (62.0-77.3)

Funding: Liga Portuguesa Contro Cancro-Centro Regional do Norte; IPO-Porto (CI-IPOP-22-2015); Fundação para a Ciência e Tecnologia (FCT).

Disclosure: All authors have declared no conflicts of interest.

1878P Strategy to improve the antitumor efficacy of dendritic cell-based nanovaccine under magnetic field control

O. Gorbach[1], N. Khranovska[1], O. Skachkova[1], M. Inomistova[1], I. Shumeiko[1], V. Orel[2]

[1]Experimental Oncology, National Cancer Institute of the MPH Ukraine, Kiev, Ukraine, [2]Research Laboratory of Medical Physics and Bioengineering, National Cancer Institute of the MPH Ukraine, Kiev, Ukraine

Background: One of the approaches for increasing DC vaccine efficacy is the direct delivery of generated DC to the regional lymph nodes and tumor site. The aim was to investigate the antitumor efficacy of DC loaded with tumor antigens and iron oxide nanoparticles (INP) under the influence of an external magnetic field.

Methods: In experimental study, 60 CBA mice were involved. Sarcoma 37 (S37) was used as experimental tumor model, and cells in lethal dose ($9*10^5$ cells per animal) were injected into the hip. DCs were obtained from syngeneic mice splenocytes and loaded by mechanically modified lyophilized Sa 37 cells (0.05 mg/ml) with Fe_2O_3 nanoparticles ($8x10^{-12}$ g/cell, Sigma-Aldrich). DC vaccine was injected intradermally 3 times with three-day interval starting on the 7^{th} day after tumor transplantation. After DC administration, animals were exposed under magnetic field for 1 hour. Tumor volume was evaluated with three days interval starting after 10 days of tumor transplantation. Tumor mass, leukocyte formula of the peripheral blood and absolute number of cells in the lymphoid organs of animals were assessed at the 25^{th} day of the experiment. The expression levels of GAPDH, FOXP3, VEGF-a, IL-10, TGF-b, IFNγ and IL-4 genes were analyzed in tumor, spleen and regional lymph nodes using a quantitative PCR method.

Results: The application of generated DCs with INP promoted a reduction of primary tumor volume compared to the control group ($p = 0{,}022$) and DC monotherapy ($p = 0.005$). DCs with INP didn't significantly effect on the hematological parameters in mice with S37. The combined effect of DCs with INP reduced mRNA expression levels of FoxP3 by 1.9 times ($p = 0.04$), VEGF-α by 2.9 times ($p = 0.02$), IL-10 by 2.9 times ($p = 0.005$) and TGF-β by 10 times ($p = 0.002$) in tumor cells compared to the control. The administration of DC vaccine with INP led to reduce tumor immunosuppression in the regional lymph nodes, namely FoxP3 mRNA level decreased in 2,4 times and Il-10 mRNA level – in 1.9 times compared to the control group, $p = 0.012$.

Conclusions: Application of DC vaccine with INP under magnetic field resulted in a pronounced antitumor effect in tumor-bearing mice.

Legal entity responsible for the study: National cancer institute of the MPH Ukraine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1879P Potential role of RICTOR copy number gain (CNG) as a key biomarker of mTOR activity: A comprehensive preclinical analysis in squamous cell lung cancer (SQLC) models

A. Gkountakos[1], S. Pilotto[2], M. Simbolo[1], C. Vicentini[1], A. Mafficini[1], A. del Curatolo[1], A. Scarpa[3], G. Tortora[2], V. Corbo[1], E. Bria[4]

[1]Department of Diagnostics and Public Health, Section of Anatomical Pathology, University and Hospital Trust of Verona, Verona, Italy, [2]Medical Oncology, University of Verona, AOUI Verona, Verona, Italy, [3]ARC-Net Research Centre and Department of Diagnostics and Public Health - Section, AOU Integrata Verona "Borgo Roma", Verona, Italy, [4]UOC Oncologia Medica, Università Cattolica del Sacro Cuore - Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy

Background: We previously performed a multi-step genomic study in almost 100 resected SQLC patients dichotomized according to the prognosis. Among the pathways with a biological impact on SQLC oncogenesis, PI3K/mTOR-Rictor emerged as a crucial axis [Pilotto WCLC 2016]. In order to explore the potentiality of mTOR inhibition, we present a set of in vitro experiments in RICTOR-aberrant SQLC preclinical models.

Methods: Next-generation sequencing (NGS), fluorescence in situ hybridization (FISH) and Western Blot were performed in 3 SQLC cell lines (H-1703, SK-Mes-1, Calu-1) for detecting CNG/protein profile of the PI3K/mTOR-Rictor components. The activity of PI3K/mTOR pathway targeted inhibitors in the SQLC cell lines was examined in short- (72 hours) and long-term (1 week) cell viability assays.

Results: NGS analysis revealed a different amount of RICTOR CNG among SQLC cell lines. FISH confirmed that H-1703 harbors the highest number of RICTOR copies (6) followed by SK-Mes-1 (4) and Calu-1 (3.5), suggesting polysomy of the short arm of chromosome 5 as the main mechanism of RICTOR gain. Although Rictor protein levels were similar among the cell lines, p-mTOR S2448 (active form of mTOR complexes) was higher in H-1703 than SK-Mes-1 and Calu-1. PI3K/mTOR inhibition proved more effective in H-1703, with lower IC50 values in short term treatment (Table). Similar findings were confirmed in long-term assays.

Table: 1879P

Drugs	H-1703	Calu-1	SK-Mes-1
		IC50 (nM)	
PF-05212384 (PI3K/mTOR inhibitor)	18	26	335
AZD-2014 (Dual mTORC1/C2 inhibitor)	145	217	215
Everolimus (mTORC1 inhibitor)	Unable determine IC50	Unable determine IC50	Unable determine IC50
MK-2206 (pan-Akt inhibitor)	Unable determine IC50	Unable determine IC50	Unable determine IC50

Conclusions: Overall, the results of our study suggest the potential implication of PI3K/mTOR-Rictor pathway in SQLC oncogenesis, thus rendering it a promising target for a targeted approach. Among the mTOR components, RICTOR CNG seems to predict a higher sensitivity to PI3K/mTOR inhibition and might represent a potential biomarker to be explored as a stratification tool in clinical trials. Confirmatory RICTOR silencing experiments are currently ongoing.

Legal entity responsible for the study: Emilio Bria.

Funding: AIRC (Associazione Italiana per la Ricerca sul Cancro).

Disclosure: All authors have declared no conflicts of interest.

1880P Final results of the phase I study in healthy volunteers of AB928, a dual antagonist of the A2aR and A2bR adenosine receptors being studied as an activator of anti-tumor immune response

L.C. Seitz[1], D. Ashok[1], M. Leleti[2], J. Powers[2], B. Rosen[2], D. Miles[2], E. Sharif[2], L. Jin[3], A. Park[1], S. Young[1], A. Rieger[4], U. Schindler[5], J. Karakunnel[4], M. Walters[5]

[1]Quantitative Biology, Arcus Biosciences, Inc., Hayward, CA, USA, [2]Chemistry, Arcus Biosciences, Inc., Hayward, CA, USA, [3]Pharmacokinetics and Drug Metabolism, Arcus Biosciences, Inc., Hayward, CA, USA, [4]Clinical Development, Arcus Biosciences, Inc., Hayward, CA, USA, [5]Biology, Arcus Biosciences, Inc., Hayward, CA, USA

Background: Adenosine suppresses anti-tumor immune responses via $A_{2a}R$ and $A_{2b}R$ receptors on intra-tumoral immune cells. This effect is mediated by increased cAMP levels and phosphorylation of the transcription factor CREB. A placebo-controlled study in healthy volunteers was conducted to assess the safety, tolerability and PK/PD (pCREB levels in blood T cells) profile of AB928, in order to select AB928 doses for the ongoing studies in cancer patients.

Methods: This placebo-controlled double-blind study had single ascending dose (SAD) and multiple ascending dose (MAD) arms. AB928 doses between 10 and 200 mg qd and 100 mg bid were evaluated. Whole blood from AB928 and placebo-treated subjects was stimulated ex vivo with the adenosine agonist NECA. Flow cytometry was used to assess levels of pCREB. AB928 plasma concentrations were determined using LC-MS-MS.

Results: The study enrolled 85 participants (randomized 3:1, active:placebo), 40 each in the SAD and MAD arms, plus 5 in a food-effect assessment cohort. The effects of 1, 5 and 10 mM NECA were assessed in whole-blood samples obtained at various time points post-dose. The PD response at each timepoint was correlated with the associated AB928 plasma levels. In all dose groups, significant inhibition at peak plasma concentrations was observed. Significant inhibition was also observed 24 hours post-dose in the higher dose groups. Final unblinded safety and PK/PD results from this study will be presented.

Conclusions: AB928 was well tolerated in this study. No stopping rules were met and dose escalation continued until maximal PD effects were observed. There was no evidence of the physiological effects associated with other adenosine receptor antagonists tested in humans. The MTD was not reached in this study. Significant inhibition of $A_{2a}R$-mediated CREB phosphorylation in blood T cells was observed in all dose groups at peak plasma concentrations, as well as at trough in the higher dose groups. The resulting PK/PD correlations were used to guide dose selection in several ongoing oncology studies, the outlines of which will be described in this presentation.

Clinical trial identification: EudraCT: 2017-002943-14.

Legal entity responsible for the study: Arcus Biosciences, Inc.

Funding: Arcus Biosciences, Inc.

Disclosure: L.C. Seitz, D. Ashok, M. Leleti, J. Powers, B. Rosen, D. Miles, E. Sharif, L. Jin, A. Park, S. Young, A. Rieger, U. Schindler, J. Karakunnel, M. Walters: Employee and stock owner: Arcus.

1881P An expression signature characterizes cancer stem cells from lung adenocarcinoma patients

A. Herreros-Pomares[1], S. Calabuig Fariñas[2], J.D. de Maya[3], E. Escorihuela[1], E. Durendez-Saez[1], A. Blasco Cordellat[4], A. Navarro[5], E. García-Del-Olmo[6], R. Lucas[7], R. Farràs[8], E. Jantus-Lewintre[9], C. Camps[10]

[1]Molecular Oncology, Fundación de Investigación Hospital General Universitario de Valencia - CIBERONC, Valencia, Spain, [2]Dept. of Pathology, Universitat de València, Fundación Investigación Hospital General Universitario Valencia-CIBERONC, Valencia, Spain, [3]Lab. de Señalización Oncogénica, Centro de Investigación Príncipe Felipe, Valencia, Spain, [4]Medical Oncology Service, Hospital General Universitario Valencia - CIBERONC, Valencia, Spain, [5]Pathology Service, Hospital General Universitario Valencia, Valencia, Spain, [6]Thoracic Surgery Service, Hospital General Universitario Valencia, Valencia, Spain, [7]Dept. of History of Science and Documentation, Universitat de València, Valencia, Spain, [8]Oncogenic Signalling Lab., Centro de Investigación Príncipe Felipe, Valencia, Spain, [9]Molecular Oncology Laboratory, Fundación Investigación Hospital General Universitario de Valencia - CIBERONC, Biotechnology Department, Universitat Politécnica de València, Valencia, Spain, [10]Molecular Oncology Laboratory, Fundación Investigación, Hospital General Universitario de Valencia - CIBERONC, Valencia, Spain, Medical Oncology Service, Hospital General Universitario de Valencia - CIBERONC Valencia, Spain, Medicine Department, Universitat de València, Valencia, Spain

Background: Treatment resistance in cancer has been linked to a population of tumor cells with self-renewal properties called cancer stem cells (CSCs). The aim of this study was to isolate and characterize CSCs from lung cancer cell lines and tumor tissue from resected non-small cell lung cancer (NSCLC) patients.

Methods: The study was performed on tumor cells from 8 resected NSCLC patients and 12 NSCLC cell lines. Suspension cultures were established for CSC isolation (3D tumorspheres), whereas differentiated tumor cells were cultured under adherent conditions (2D). In vitro differentiation, proliferation and chemotherapy resistance and in vivo tumor initiation capacity were tested. 60 CSC-related genes were evaluated by RTqPCR. Gene expression results were validated at protein level by immunoblot and IF.

Results: 8 out of 20 primary NSCLC cultures were successfully established, forming 3D tight spheroids or loose aggregates. Tumorspheres showed proper differentiation capacity, unlimited exponential growth, high resistance to cisplatin, paclitaxel, vinorelbine and pemetrexed, and great tumor initiation potential. Gene expression analysis revealed high variability between cell lines and patient cultures and that 2D cultures were more homogenous than 3D. Tight tumorspheres expressed more ECAD than loose ones. Lung tumorspheres had significantly higher expression of CSC-related genes (ALDH1A1, KLF4, NANOG, CD44, CD90, CDKN1A, JUNB, MDM2), invasion promoters (MMP9, SNAI1, ITGA6), ligands and receptors of Notch (NOTCH1, NOTCH3, DLL4, JAG1) and Wnt components (CTNNB1 and GSK3B) than their corresponding 2D cultures cells. Based on their significant and consistent overexpression in all tumorspheres: CD44, NANOG, CDKN1A, SNAI1, ITGA6 and NOTCH3 were selected to constitute a gene signature. Protein expression analyses showed overexpression of proteins encoded by the gene signature on tumorspheres from ADC patients.

Conclusions: Lung tumorspheres are a useful platform for CSCs characterization. The expression signature proposed could provide the basis for developing novel therapies for the treatment of lung ADC. Supported by grants RD12/0036/0025 from RTICC-FEDER, PI12-02838 and PI15-00753 from ISCIII.

Legal entity responsible for the study: Laboratorio de Oncología Molecular, Fundación de Investigación Hospital General Universitario de Valencia.

Funding: RTICC-FEDER and Instituto de Salud Carlos III.

Disclosure: All authors have declared no conflicts of interest.

1882P Development of primary human NSCLC patient derived xenograft and organoids models as a precision approach to tumor treatment

O.J. Juan Vidal[1], C. Gandia[2], J.M. Pardo-Sánchez[2], M. Benet[3], S. Aparisi[4], S. Palanca[5], E. Ansotegui[6], C. Jordá[7], J.A. Cerón[7], N. Mancheño[1], M. Sánchez-Céspedes[8], A. Lahoz[3], J. Carretero[4], R. Farràs[2]

[1]Medical Oncology, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [2]Oncogenic Signalling Lab., Centro de Investigación Príncipe Felipe, Valencia, Spain, [3]Biomarkers and Precision Medicine Unit, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [4]Department of Physiology, Faculty of Pharmacy, University of Valencia, Valencia, Spain, [5]Department of Clinical Analysis, Molecular Biology Unit, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [6]Servicio de Neumología, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [7]Servicio de Cirugía Torácica, Hospital Universitari i Politècnic La Fe, Valencia, Spain, [8]Cancer Epigenetics and Biology Program (PEBC), Genes and Cancer Group, Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet de Llobregat, Spain

Background: The prognosis of advanced non-small cell lung cancer (NSCLC) patients is poor. The lack of in vitro models that would faithfully recapitulate the heterogeneity of lung tumors and response to treatment is one of the reasons hampering progress in the development of new therapies. Patient-derived tumor models are becoming the standard for pre-clinical drug testing and biomarker discovery. However, the emerging technology of lung cancer organoids has not yet been broadly implemented in research and have yet to be better established. In this study, our objective was to generate and characterize a collection of NSCLC patient-derived xenograft (PDX) and tumor organoids to demonstrate their applicability to the study of lung cancer.

Methods: Surgically resected tumors were obtained from patients with stage I/II NSCLC during curative-intent surgery. Portions of the tumors were subcutaneous xenografted in NSG mice and expanded 5 passages. In addition, matched portions of tumor and adjacent non-tumor tissues were employed to develop and characterize patient-derived organoids (PDOs). Tumors grew in mice and PDOs were analyzed by histologic and molecular techniques.

Results: We describe the derivation and characterization of 8 PDX models and 20 pairs of PDOs from NSCLC tumors and adjacent non-tumor tissue. PDX could established with a succesful rate of 22,8% (8 out of 35 samples). PDX retain histologic and molecular characteristics of their donors and recapitulate the heterogeneity of human lung tumors. PDOs could be established with a success rate of 100%. We reached a successful long-term expansion of primary NSCLC cells in vitro (> 120 days). Tumor organoids displayed tumor-like cellular morphology and tissue architecture. Tumor-dependent lymphocyte infiltration were observed in these models. We assesed CD45, EpCAM, CD133, CD44 protein expression, as well as Nanog and Oct4 stem cell markers.

Conclusions: We have generated a collection of PDX and PDOs models from NSCLC tumors. These models promise to facilitate the study of cancer stem cell biology and tumor heterogeneity, and may be valuable for drug screening. These models enables the potential long term studies such as the establishment of drug resistant models.

Legal entity responsible for the study: Principe Felipe Research Center.

Funding: Instituto de Salud Carlos III (PI15/00209), co-funded by ERDF.

Disclosure: All authors have declared no conflicts of interest.

1883P PBRM1 is a novel candidate low-penetrance familial cancer predisposition gene

I. Volodin[1], V.M. Kozlova[2], K.I. Anoshkin[1], A.S. Tanas[1], D.V. Zaletaev[3], V.V. Strelnikov[4]

[1]Epigenetics Lab, Research Centre for Medical Genetics, Moscow, Russian Federation, [2]N.N. Blokhin Russian Research Center for Oncology, Moscow, Russian Federation, [3]Laboratory of Medical Genetics, Sechenov First Moscow State Medical University, Moscow, Russian Federation, [4]Epigenetics, Institute of Molecular Medicine, Moscow, Russian Federation

Background: Chromatin remodeling gene PBRM1 is frequently altered somatically in epithelioid sarcomas and clear cell renal cell carcinomas, but its germline mutation had been reported only once, in a pedigree with familial clear cell renal cell carcinoma (Benusiglio et al., 2015). We present another evidence of a cancer caused by PBRM1 germline mutation in a family with two young sibs, one of whom deceased of round cell soft tissue sarcoma 13 years old.

Methods: For search of mutations we used next generation sequencing (NGS) on Ion S5 platform. For verification of mutations identified by NGS, for mutation segregation analysis and for evaluation of allelic expression expression we used DNA and cDNA Sanger sequencing.

Results: Exome sequencing of cancer related genes identified a heterozygous germline genetic variant p.F1026L (c.3078C>G) in PBRM1 in the leucocyte DNA of the living sibling. This variant is absent from databases and bioinformatic predictors provide ambiguous estimates as to its pathogenicity. Search for this genetic variant in other family members showed that it is also being carried by the father and the older brother of the proband. Sanger sequencing of this variant in the archived tumor material of the deceased revealed its presence in the heterozygous state indicating no signs of allelic imbalance as an inactivation event that would have been consistent with Knudson's two-hit model. Yet, further examination of allelic expression in tumor revealed loss of expression of the normal allele suggesting functional loss of heterozygosity in favor of the mutant one.

Conclusions: Our finding of functional two-hit inactivation of PBRM1 in the tumour supports its role as a tumour suppressor gene. Moreover, we present a second description of PBRM1 pathogenic germline mutation, and the first to be presumably causative for a soft tissue sarcoma. Absence of any tumours in other PBRM1 mutation carriers in the family described here provides the evidence of low penetrance of this mutation.

Legal entity responsible for the study: Research Centre for Medical Genetics, Moscow.

Funding: State assignment of FASO Russia.

Disclosure: All authors have declared no conflicts of interest.

1884P Liprin-alpha4 contributes to increased proliferation and decreased chemosensitivity under hypoxia for small cell lung cancer as a downstream mediator of HIF-1alphaα

H. Onishi, A. Yamasaki, M. Kawamoto

Department of Cancer Therapy and Research, Kyushu University, Fukuoka, Japan

Background: Cancer microenvironment is extremely hypoxic condition and the analysis of cell biology under hypoxia is significantly important. Previously we have shown that leukocyte common antigen related interacting protein (liprin)-α4 could be a new

therapeutic target for pancreatic cancer. In the present study, the biological significance of liprin-α4 in small cell lung cancer (SCLC) which was one of the refractory cancers and less therapeutical options was investigated.

Methods: SCLC cell lines (SBC-3 and SBC-5) were used as target cells. Cells were cultured under normoxia (20%O_2) and under hypoxia (1%O_2). Gene inhibition was performed using small interfering RNA. Proliferation was performed by MTT assay. Invasion was estimated by matrigel invasion assay. Chemosensitivity was analyzed using CDDP and 5-FU. Mice xenograft experiments were performed using BALB/c nude mice. Twenty human SCLC specimens were used for immunofluorescent staining.

Results: 1) Expression of liprin-α4 increased under hypoxia compared to normoxia. 2) Liprin-α4 inhibition decreased proliferation in vitro under hypoxia. 3) Liprin-α4 suppression did not affect migration and invasion under hypoxia. 4) Tumor volume in mice injected with liprin-α4-inhibited SCLC cells was significantly lower than that in control mice. 5) Signaling from liprin-α4 was through MAPK signaling pathway. 6) Chemosensitivities of CDDP and 5-FU under hypoxia were significantly lower than those under normoxia. Liprin-α4 inhibition significantly enhanced chemosensitivity of CDDP under hypoxia. 7) HIF-1α regulated liprin-α4 expression in SCLC cells. 8) HIF-1α inhibition led to decreased proliferation under hypoxia. 9) HIF-1α inhibition significantly improved chemosensitivity of CDDP under hypoxia. 10) Liprin-α4 and HIF-1α expressions were observed in all patients examined in SCLC specimen.

Conclusions: These results suggest that liprin-α4 which is expressed more under hypoxia, plays a pivotal role for increased proliferation and decreased chemosensitivity under hypoxia for SCLC as a downstream mediator of HIF-1α. Inhibition of HIF-1α and Liprin-α4 could be a new therapeutic strategy for SCLC.

Legal entity responsible for the study: Kyushu University Ethics Committee.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1885P Precision medicine for patients with rare cancers: An effective strategy within the prospective MOSCATO trial

M. Abdelshafy[1], Y. El Dakdouki[1], L. Verlingue[1], A. Hollebecque[1], L. Lacroix[2], S. Postel-Vinay[1], A. Varga[1], R. Balheda[1], J-M. Michot[1], A. Marabelle[3], E. Rouleau[2], E. Solary[4], T. de Baere[5], E. Angevin[1], V. Ribrag[1], S. Michiels[6], F. André[7], J-Y. Scoazec[8], J-C. Soria[1], C. Massard[1]

[1]DITEP, Gustave Roussy Institut de Cancérologie, Villejuif, France, [2]Department of Medical Biology and Pathology, Laboratory of Translational Research and Biological Resource Center, AMMICA, INSERM US23/CNRS UMS3655, Gustave Roussy, University Paris-Saclay, Villejuif, France, [3]Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, [4]Drug Development Department, DITEP, Institut Gustave Roussy, Villejuif, France, [5]Radiation Oncology, Institut Gustave Roussy, Villejuif, France, [6]Team Oncostat, CESP, Gustave Roussy, Villejuif, France, [7]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [8]Pathology, Laboratory of Translational Research and Biological Resource Center, AMMICA, INSERM US23/CNRS UMS3655, Gustave Roussy, University Paris-Saclay, Villejuif, France

Background: MOSCATO 01 trial (NCT01566019) is a prospective molecular screening program using high-throughput molecular analysis to guide targeted therapy for patients (pts) with advanced cancers. This approach resulted in enrichment of early phase clinical trials with rare genomic alterations and rare tumors, that may lack an approved standard of care.

Methods: A retrospective clinical and molecular analysis of pts with rare tumors, enrolled in the MOSCATO 01 trial. An on-purpose tumor biopsy was performed, followed by high-throughput molecular analysis using targeted Next Generation Sequencing (NGS), comparative genomic hybridization array (CGHa) and Whole Exome Sequencing (WES) after histological control. Matched therapy was decided accordingly for pts who had targeted molecular alterations.

Results: Between December 2011 and March 2016, 122 pts with 58 different tumors types were enrolled in the MOSCATO 01 trial. Median age was 59 years (range, 19-89), median number of previous systemic therapies was 4 (range, 0–13), 51% (63/122) were women, 90% had ECOG performance 1and 2. Most prevalent histologies were adenocarcinoma of unknown primary (12%), lung NE tumor (8%) and SCC of unknown primary (5%). Most frequent actionable alterations were PIK3CA mutation (14%), ERBB2 amplification (10%), and EGFR amplification (4%). Of 122 pts, 62 (51%) harbored ≥ 1 actionable genomic alterations. Thirty pts (25%) received matched therapy. Of these, 6 had a partial response, 9 had stable disease as the best response. Overall response rate (ORR) was 20%. Median PFS2 for matched therapy was 2.8 [95% C.I (1.2 – 4.3)] versus median PFS1 for last standard line 4.6 months, $p = 0.8$. Pts harboring EGFR amplifications had the best median duration of response 9.8 months on matched therapy. Median overall survival was not significantly improved in pts who received matched therapy when compared to pts with unmatched therapy, 14.8 and 8.4 months, respectively($p = 0.1$).

Conclusions: Precision medicine using high-throughput molecular analysis of rare cancers is feasible in clinical practice and can affect their clinical outcomes. Rare tumors harboring EGFR amplification showed prolonged response to targeted treatment. Larger studies and more effective targeted molecules are still needed.

Legal entity responsible for the study: Gustave Roussy Cancer Campus.

Funding: Philanthropy.

Disclosure: All authors have declared no conflicts of interest.

1886P Streamlining multi-omic and artificial intelligence analysis through interrogative biology and baicis for translational precision medicine applications in clinical oncology

L. Rodrigues[1], M.A. Kiebish[2], G. Miller[1], L. Zhang[1], V. Vemulapalli[1], V.K. Vishnudas[3], R. Sarangarajan[3], N.R. Narain[4], V.R. Akmaev[1]

[1]Analytics, BERG, LLC, Framingham, MA, USA, [2]Precision Medicine, BERG, LLC, Framingham, MA, USA, [3]Biosystems, BERG, LLC, Framingham, MA, USA, [4]Biosystems, Analytics, & Precision Medicine, BERG, LLC, Framingham, MA, USA

Background: Despite advances in high throughput molecular technologies, increased availability of clinical information, and access to complex population level datasets, translating this information into causal and actionable clinical guidance in oncology remains a challenge.

Methods: The BERG Interrogative Biology platform deconstructs the established paradigm by using patient biology to guide the entire drug development process from R&D to clinic, leading to improved clinical outcome. In order to properly characterize the molecular phenotype of patients or disease states, this platform allows for systematic interrogation of each biological sample by high-throughput multi-omic technologies such as proteomics, lipidomics and metabolomics. This is then combined with further analytical methods that allows for assessment of sample quality through statistical, environmental/demographic influence, sample handling, and pharmacological impact markers to elucidate causal molecular signal from inherent noise.

Results: BERG ETL System uses a proprietary data-driven algorithm to automatically extract, normalize, correct eventual systematic errors, align and unify all data sources and types, outputting a harmonized molecular and/or clinical profile, which can be used for summary reports such as patient dashboards, standard analysis such as statistics and machine learning, and to be analyzed by BERG's Artificial Intelligence (AI) Technology, bAIcis. When applied to clinical trial information, bAIcis uses a multi-layer method to identify clinical and molecular markers that can stratify patients based on trial outcomes such as "Response to Treatment", "Quality of Life" or "Adverse Events" as well as identification of disease drivers.

Conclusions: Using this approach a comprehensive understanding of causal drivers, predictive biomarkers aligned with therapeutic benefit, and identification of adverse event populations in cancer indications can be elucidated. This is streamlined through an AI driven platform based on quality metric to support precision medicine in oncology drug development.

Editorial acknowledgement: Khampaseuth Thapa, Berg, LLC.

Legal entity responsible for the study: Berg, LLC.

Funding: Berg, LLC.

Disclosure: L. Rodrigues, M.A. Kiebish, G. Miller, L. Zhang, V. Vemulapalli, V.K. Vishnudas, V.R. Akmaev: Employee, and stock owner: Berg, LLC. R. Sarangarajan: Co-founder, employee and stock owner: Berg, LLC. N.R. Narain: Co-founder, President, CEO, and stock owner: Berg, LLC.

1887P Prediction of response to vemurafenib in BRAF V600E mutant cancers based on a network approach

R. Falcone[1], P. Paci[2], A. Verrienti[1], G. Fiscon[2], M. Sponziello[1], F. Conte[2], V. Pecce[1], F. Rosignolo[1], G. Grani[1], L. Lamartina[1], V. Ramundo[1], C. Durante[1], L. Farina[3], S. Filetti[1]

[1]Dipartimento di Medicina Interna e Specialità Mediche, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy, [2]Institute for Systems Analysis and Computer Science "Antonio Ruberti", National Research Council, Rome, Italy, [3]Department of Statistical Sciences, Sapienza University of Rome, Rome, Italy

Background: Selective small-molecule BRAF inhibitors are approved, alone or in combination with trametinib, for the treatment of patients with BRAF V600 metastatic melanoma and non-small cell lung cancer (NSCLC). So far, several studies showed that different histotypes of BRAF V600 mutant tumors do not respond uniformly to BRAF inhibitor vemurafenib: high response rates in hair cell leukemia and melanoma, intermediate responses in thyroid and NSCLC, low responses in colorectal cancer. Using a bioinformatics tool, we sought to elucidate, through a network unbiased approach, why different tumors harboring BRAF V600E mutation show heterogeneity in response to vemurafenib.

Methods: We exploited SWItchMiner (SWIM) software to analyze gene expression profiles available on The Cancer Genome Atlas. SWIM is able to identify a small pool of regulatory genes (switch genes), which are likely to be critically associated with drastic changes in cell phenotypes. We selected among those genes, the ones who encode for kinases. Then, we employed Geneious R11 desktop platform to identify those kinases with the maximum identity score to kinases reported as known targets of vemurafenib.

Results: Lung adenocarcinoma is the tumor with the highest number of switch genes (298) compared to its normal tissue, followed by thyroid (227) and colorectal (183) cancers. Switch genes codifying for kinases were 14, 7 and 3 respectively. We looked for

three homology sequences identified across vemurafenib targets and we found that thyroid cancer and lung adenocarcinoma have a similar number of putative targetable switch genes kinase (5-6); on the contrary, colorectal cancer has just one, with minor homology sequence.

Conclusions: Our network analysis may provide additional approaches to explore the molecular mechanisms underlying the different response to vemurafenib in BRAF V600E mutant tumors, elucidating how precision medicine cannot leave out of consideration the tumor histology. It is likely that, while different cancers share the major driver event, the response to therapy may vary based on the number of kinases with homology sequences to the druggable kinase targets. In vitro data are needed to validate this prediction.

Legal entity responsible for the study: Sapienza University of Rome.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1888P Improving value for cancer patients: A European study of outcomes in practice

R. Hazarika[1], T. Albreht[2], B. Berger[3], D. Duplay[4], L. Makaroff[5], Z. Maravic[6], R. Mortuza[7], V. Muthu[8], K. Oliver[5], R. Price[5], M.V.M. van Meerveld[5], K. Steinmann[5], A. Krukowsk[5], R. Catena[5], S. Wait[9], V. Zilli[5]

[1]Implementation & Benchmarking, International Consortium for Health Outcomes Measurement, London, UK, [2]Department of Health Care, National Institute of Public Health of Slovenia, Ljubljana, Slovenia, [3]ECCO, London, UK, [4]Healtheo360, London, UK, [5]Policy & Research, The Health Policy Partnership, London, UK, [6]EuropaColon UK, Salisbury, UK, [7]Implementation, International Consortium for Health Outcomes Measurement, London, UK, [8]Management, Marivek Ltd, Epsom, UK, [9]Research, The Health Policy Partnership, London, UK

Background: ICHOM (International Consortium for Health Outcomes measurement) and All.Can– an international multi-stakeholder initiative – are in partnership to identify and support a community of European hospitals to assess how they can optimize the efficiency of cancer care in breast and lung cancer patients.

Methods: A community of 10 hospital sites for lung cancer and 10 for breast cancer will be supported to implement and measure the ICHOM standard sets of outcomes. This community will measure clinical and patient reported outcomes and will use Time Driven Activity Based Costing to measure the cost to deliver cancer care. Guidance will also be provided to the community to support the utility of outcomes and cost data. The All.Can Patient Survey will also be deployed at the sites to obtain patient insights on sources of potential inefficiency in their care. Additional aspects of care, including intervention type and delivery of care, will also be measured based on results of an international literature review on determinants of value in the two indications. Outcome domains for collection for lung cancer patients include survival, complications, other outcomes such as treatment delays and quality of measures at the end of life. For breast cancer, the outcomes domains include survival and cancer control, disutility of care such as the impact of acute complications and degree of health. All data will be collected over a six-month period. Outcomes data will be collected on all patients with a first diagnosis of lung or breast cancer, followed up over a 6-month period, with three data collection points: (1) immediately after diagnosis, prior to treatment initiation; 3 months and 6 months after treatment initiation.

Results: Risk adjusted outcomes and costing data for the lung and breast pathways will be compared to one another to identify variation and its potential drivers. Qualitative interviews and insights from the All.Can Patient Survey will be used to identify barriers and enablers to value measurement and innovative value improvement strategies.

Conclusions: Findings will guide All.Can policy recommendations to improve the efficiency of cancer care.

Legal entity responsible for the study: International Consortium for Health Outcomes Measurement (ICHOM).

Funding: Bristol-Myers Squibb (main sponsor), Amgen, MSD and Johnson & Johnson (sponsors).

Disclosure: All authors have declared no conflicts of interest.

1889P High-throughput screening of new drugs targeting lung CSCs

H.A. Amado Labrador[1], E. Jantus-Lewintre[2], S. Calabuig Fariñas[3], C. Aguilar-Gallardo[4], J. Murga[5], E. Munera-Maravilla[6], E. Durendez-Saez[4], M. Mosqueda[6], E. Escorihuela[4], F. Zhang[6], E. Masiá[7], N. Dong[6], R. Guijarro[8], C. Camps[9]

[1]Fundación Carolina/BBVA, Molecular Oncology Laboratory, Fundación de Investigación Hospital General Universitario de Valencia, Valencia, Spain, [2]Molecular Oncology Laboratory, Fundación para la Investigación Hospital General Universitario de Valencia-CIBERONC, Biotechnology Department, Universitat Politécnica de València, Valencia, Spain, [3]Pathology Department, Universitat de València, Molecular Oncology Laboratory, Hospital General Universitario de Valencia - CIBERONC, Valencia, Spain, [4]Molecular Oncology Laboratory, Fundación de Investigación Hospital General Universitario de Valencia - CIBERONC, Valencia, Spain, [5]Departamento de Química Inorgánica y Orgánica, Universidad Jaume I, Castellón, Spain, [6]Molecular Oncology Laboratory, Fundación de Investigación Hospital General Universitario de Valencia, Valencia, Spain, [7]Laboratorio de Polímeros Terapeúticos, Centro de Investigación Príncipe Felipe, Valencia, Spain, [8]Medicine Department, Universitat de València, Thoracic Surgery Department, Hospital General Universitario de Valencia, Valencia, Spain, [9]Medicine Department, Universitat de València, Medical Oncology, Consorcio Hospital General Universitario de Valencia -CIBERONC, Valencia, Spain

Background: Non-small cell lung cancer (NSCLC), the most common subtype of lung cancer, is characterized by low response rates and a poor prognosis. The majority of patients are diagnosed in advanced stages, where chemotherapy remains the gold standard of treatment. However, the resistance has been associated to cancer stem cells (CSCs), a highly tumorigenic subpopulation of cells with the ability to grow as spheres in non-adherent conditions. The aim of this study was to discover novel therapeutic strategies through screening platforms in order to target CSCs population.

Methods: High-throughput screening with commercial chemical libraries (Prestwick and Myria) was performed, comparing cytotoxic effect in monolayer cells vs. lung-tumorspheres derived from 8 resected NSCLC patients and 11 NSCLC cell lines. Compounds were added per triplicates at different concentrations (0.01 to 50 μM). Cell viability was measured after 48h using MTS Assay. Consecutively, 8 tumors were induced by inoculating resected NSCLC patient and H1650 lung-tumor-spheroids in NOD/SCID mice. Selected drugs were administered intraperitoneally (3 times a week, 100 mg/kg). Characterization of the inhibition pathway involved in the mechanism of action of these drugs was performed by RT-qPCR.

Results: Three drugs of the commercial chemical libraries (DSF, Compound 1 and Compound 2) were identified with greater cytotoxic potential against lung tumorspheres, compared to a poor or null effect on monolayer cells. These results were validated in vivo, which demonstrated the capacity of these drugs to inhibit tumor growth in mice treated respect to the control (Table). We are currently characterizing the signaling pathways involved in the mechanism of action of these drugs.

Conclusions: Our findings reveal that these drugs can inhibit CSCs like properties, as evidenced in the lung tumorspheres in vitro and in vivo assays. Therefore, these compounds could be a promising targeted therapy as potential inhibitors of lung CSCs.

Table: 1889P Percentage of tumor reduction in the mice treated respect to the control

Mice (Line/Patient)	Tumor Volume (mm^3)	Tumor Reduction (%)
H1650_CNT	1593,11	
H1650_DSF	541,44	66.02
H1650_Compound 1	483,72	69.64
H1650_Compound 2	276,98	82.62
Patient_CNT	1645,68	
Patient_DSF	490	70,23
Patient Compound 1	721,56	56,16
Patient Compound 2	1020	38,02

Legal entity responsible for the study: Fundación para la Investigación Hospital General Universitario de Valencia.

Funding: Supported by ISCIII (P12-02838 / FIS P15-00573).

Disclosure: All authors have declared no conflicts of interest.

1890TiP RING observational trial to compare T790M mutation testing in blood by different methodologies

B. Garcia-Pelaez[1], E. Jantus[2], A. Romero[3], M-A. Molina[4], A. Blasco Cordellat[5], C. Perez-Barrios[3], R. Rosell[6], C. Camps[7], M. Provencio Pulla[8]

[1]Laboratory of Oncology/Pangaea Oncology, Quiron-Dexeus University Hospital, Barcelona, Spain, [2]Molecular Oncology Department, Hospital General Universitario Valencia, Valencia, Spain, [3]Liquid Biopsy Laboratory, H. Univ. Puerta De Hierro, Majadahonda, Spain, [4]Quirón Dexeus University Hospital, Pangaea Biotech S.L., Barcelona, Spain, [5]Medical Oncology , Hospital General Universitario Valencia, Valencia, Spain, [6]Cancer Biology & Precision Medicine Program, Germans Trias i Pujol Science Inst., Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Barcelona, Spain, [7]Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain, [8]Servicio de Oncología Médica, Hospital Universitario Puerta de Hierro, Madrid, SpainKeyword: NSCLC, T790M, EGFR, TKI, resistance, blood

Background: EGFR- mut NSCLC patients benefit from EGFR-TKIs therapy. However, most patients relapse within 1 to 2 years. In 40-60% of the cases, the mechanism of resistance is the emergence of the EGFR p.T790M mutation, and third generation TKIs have shown efficacy in this setting. The availability of new biopsies at relapse to TKIs is limited and guidelines recommend testing for the p.T790M in blood at relapse to TKIs, and rebiopsy only in case of a negative result. Several blood based methodologies for EGFR-mut detection have been developed, including some NGS approaches, but comparison studies are limited. We aim to evaluate the agreement, specificity and sensitivity of methodologies available for T790M testing in liquid biopsies and to determine the best pre-analytical conditions for T790M mutation identification.

Trial design: The RING is a non-PAS, non-interventional, cross-sectional, diagnostic study that will enroll 75 patients from different Spanish institutions. Blood samples will be collected at the time of progression to first and second generation TKIs, and sent to the laboratories participating in the study. Three DNA extraction procedures will be tested; Maxwell® RSC cfDNA (Promega), the QIAamp® Circulating Nucleic Acid Kit (Qiagen) and automatic extraction using Qiasymphony® (Qiagen). The presence of the p.T790M in the purified DNA will be tested by 7 methodologies, namely cobas® EGFR Mutation Test v2 (Roche Diagnostics), Therascreen EGFR Plasma RGQ PCR Kit (Qiagen), QuantStudio® 3D Digital PCR System (Applied Biosystems), a 5′-nuclease real-time PCR (Taqman®) assay in presence of PNA, BEAMing digital PCR (Sysmex Inostics), NGS with the Oncomine® panel for Ion Torrent (Thermofisher) and NGS with the Lung Cancer Panel for GeneReader® (Qiagen). The kappa coefficient values and its corresponding 95% confidence intervals (95% CI) will be used to assess the agreement between methodologies and the Intraclass Correlation Coefficients (ICC) and Bland & Altman plots to evaluate the concordance between quantitative methodologies. Finally, we calculate that 40 patients will have a re-biopsy mutation T790M analysis, which will be considered the gold standard to estimate the sensitivity and specificity of each method.

Legal entity responsible for the study: Spanish Lung Cancer Group / Grupo Español de Cancer de Pulmon (Slcg/Gecp).

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii670–viii682, 2018
doi:10.1093/annonc/mdy304

TUMOUR BIOLOGY AND PATHOLOGY

1892O Molecular characterization of epithelioid sarcoma (ES) tumors derived from patients enrolled in a phase II study of tazemetostat (NCT02601950)

S. Daigle[1], S. Stacchiotti[2], P. Schöffski[3], V. Villalobos[4], G. Cote[5], R. Chugh[6], T.W-W. Chen[7], T. Jahan[8], E.T. Loggers[9], A. Italiano[10], A. Gupta[11], M. Agulnik[12], S. Attia[13], R.L. Jones[14], B.A. van Tine[15], G.D.D. Demetri[16], A. Clawson[1], M. Roche[1], S. Blakemore[1], M. Gounder[17]

[1]Clinical, Epizyme, Cambridge, MA, USA, [2]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy, [3]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium, [4]Medical Oncology, University of Colorado, Denver, CO, USA, [5]Medical Oncology, Massachusetts General Hospital, Boston, MA, USA, [6]Medical Oncology, Michigan Medicine Comprehensive Cancer Center, Ann Arbor, MI, USA, [7]Medical Oncology, National Taiwan University Hospital, Taipei City, Taiwan, [8]Medical Oncology, University of California, San Francisco, CA, USA, [9]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [10]Early Phase Trials Unit, Institute Bergonié, Bordeaux, France, [11]Department of Hematology and Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [12]Hematology/Oncology, Northwestern Memorial Hospital, Chicago, IL, USA, [13]Oncology, Mayo Clinic, Jacksonville, FL, USA, [14]Medical Oncology, The Royal Marsden Hospital and Institute for Cancer Research, London, UK, [15]School of Medicine, Washington University in St. Louis, St. Louis, MO, USA, [16]Ludwig Center at Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA, [17]Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

1893PD A joint metabolic profile of plasma and tissue samples or discovering novel biomarkers in breast cancer

N. Harada, H. Tada, M. Miyashita, Y. Hamanaka, A. Sato, T. Ishida

Department of Breast and Endocrine Surgical Oncology, Tohoku University Hospital, Sendai, Japan

1894PD Single-cell RNA sequencing of triple negative breast cancer patient-derived xenograft reveals distinct cellular populations spatially mapped to histological sections

C. Martinez Ramirez[1], H. Kuasne[2], M. Park[2], D. Zuo[2], C. Kleinman[3], Y. Yang[4], A. Blanchet-Cohen[4], P. Savage[5], J. Ragoussis[6]

[1]Pathology, McGill University, Montreal, QC, Canada, [2]Goodman Cancer Research Centre, McGill University, Montreal, QC, Canada, [3]Lady Davis Research Institute, Jewish General Hospital, McGill University, Montreal, QC, Canada, [4]Human Genetics, McGill University, Montreal, QC, Canada, [5]Experimental Medicine, McGill University, Montreal, QC, Canada, [6]Genome Québec Innovation Centre, McGill University, Montreal, QC, Canada

1895PD **Homology-directed repair (HDR)-defective lung adenocarcinomas (LUACs) in circulating tumor DNA (ctDNA)**

N. Karachaliou[1], M. Lefterova[2], J.F. Draper[3], M-A. Molina[4], I. Chaib[5], R. Palmero[6], A. Taus[7], S. Viteri[8], M. González Cao[8], M. Majem Tarruella[9], E. Carcereny Costa[10], T. Moran[10], J. Garde Noguera[11], E. Felip Font[12], S. Olsen[13], M. Jackson[14], M. Sampayo[15], I. Faull[16], D. Dix[3], R. Rosell[17]

[1]Institute of Oncology Rosell, University Hospital Sagrat Cor, Grupo QuironSalud, Barcelona, Spain, [2]Clinical Laboratory, Guardant Health, Redwood City, CA, USA, [3]Clinical Data Management, Guardant Health, Redwood City, CA, USA, [4]Quirón Dexeus University Hospital, Pangaea Oncology S.L., Barcelona, Spain, [5]Laboratory of Cellular and Molecular Biology, Health Sciences Research Institute of the Germans Trias i Pujol Foundation (IGTP), Badalona, Spain, [6]Hospital Duran i Reynals, Catalan Institute of Oncology, Bellvitge, Spain, [7]Medical Oncology, Hospital del Mar, Barcelona, Spain, [8]Medical Oncology, QuironSalud Dexeus University Institute, Barcelona, Spain, [9]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [10]Medical Oncology, Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain, [11]Oncology, Hospital Arnau de Vilanova, Valencia, Spain, [12]Medical Oncology Service (Lung Cancer Unit), Vall d'Hebron University Hospital, Barcelona, Spain, [13]Oncology, Guardant Health, Redwood City, CA, USA, [14]Statistics, Guardant Health, Redwood City, CA, USA, [15]Statistical Expert Trial Management, Medica Scientia Innovation Research – MEDSIR, Barcelona, Spain, [16]Business Development & Medical Affairs, Guardant Health, Barcelona, Spain, [17]Cancer Biology & Precision Medicine Program, Germans Trias i Pujol Science Inst., Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

1896PD **Joined analysis of sarcomatoid carcinoma (SC) mutational profiles: Comparison of lung versus head and neck cancer**

N. Pecuchet[1], R. Touachi[2], A. Ben Lakhdar[3], V. Fallet[4], N. Rabbe[5], H. Blons[6], A. Lemoine[7], M. Antoine[8], S. Tenam[9], P. Laurent-Puig[10], M. Wislez[11]

[1]UMRS-1147, Paris Descartes University, Paris, France, [2]Head and Neck Cancer Department, Gustave Roussy Institute Gustave Roussy Cancer Campus, Villejuif, France, [3]Pathology, Gustave Roussy Institute Gustave Roussy Cancer Campus, Villejuif, France, [4]Thoracic Oncology, APHP, CancerEst, Tenon University Hospital, Paris, France, [5]GRC n°04, Theranoscan, APHP, CancerEst, Tenon University Hospital, Paris, France, [6]Biochimie UF de Pharmacogénétique et Oncologie Moléculaire, Hopital European George Pompidou, Paris, France, [7]Biochemistry, Hopital Paul Brousse - Paris Sud Hospital, Villejuif, France, [8]Department of Cytology and Pathology, APHP, CancerEst, Tenon University Hospital, Paris, France, [9]Head and Neck Cancer Department, Gustave Roussy Cancer Campus, Villejuif, France, [10]UMRS-1147 - Department of Biochemistry, Pharmacogenetic and Molecular Oncology Unit, Paris Descartes University - Georges Pompidou European Hospital, Paris, France, [11]Pneumology, GRC n°04, Theranoscan, APHP, CancerEst, Tenon University Hospital, Paris, France

1897PD Differential expression of immune checkpoints (PD-L1, HHLA2, B7x and B7H3) and their association with driver mutations in pulmonary sarcomatoid carcinoma (PSC)

H. Cheng[1], J. Sharma[1], C. Su[2], S. Li[3], X. Zang[4], R. Perez-Soler[1], B. Halmos[1], A. Borczuk[5]

[1]Medical Oncology, A. Einstein College of medicine, Bronx, NY, USA, [2]Internal Medicine, A. Einstein College of Medicine, Bronx, NY, USA, [3]Internal Medicine, Jacobi Medical Center, Bronx, NY, USA, [4]Microbiology and Immunology, Montefiore Medical Center Albert Einstein College of Medicine, Bronx, NY, USA, [5]Pathology, Weill Cornell Medicine, New York, NY, USA

1898P The role of SWI/SNF chromatin remodelling complex ATPase subunit - BRM in TNBC

I. Jancewicz[1], N. Rusetska[1], A. Armatowska[2], M. Stachowiak[1], K. Pogoda[3], A. Niwińska[3], W. Olszewski[4], Z.I. Nowecki[3], T.J. Sarnowski[5], E. Sarnowska[1], J.A. Siedlecki[1]

[1]Department of Molecular and Translational Oncology, The Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland, [2]Faculty of Chemistry, Warsaw University of Technology, Warsaw, Poland, [3]Department of Breast Cancer and Reconstructive Surgery, The Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland, [4]Department of Pathology, The Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland, [5]Department of Protein Biosynthesis, Institute of Biochemistry and Biophysics Polish Academy of Sciences, Warsaw, Poland

Background: Triple negative breast cancer (TNBC) is a BC subtype featured by lack of estrogen and progesterone receptor and HER2. It is an aggressive type linked with poor prognosis and chemotherapy-resistance. Cancer malignancy can be caused by epithelial-mesenchymal transition (EMT). It allows cells' phenotype change and is driven by proteins such as Twist, ZEB, SNAIL and SLUG. SWI/SNF chromatin remodeling complexes (CRCs) modify chromatin structure, hence changing expression patterns. Disruption of their stoichiometry can lead to development of many types of cancer including BC. This work is focused on the role of BRM – the catalytic subunit of SWI/SNF CRCs in the TNBC development.

Methods: 102 paraffin embedded tissue samples were analysed by immunohistochemistry (IHC). In vitro analysis was performed on MDA-MB-231 and MCF7 cancer cell lines using Western Blot, coimmunoprecipitation (Co-IP) and bimolecular fluorescence complementation (BiFC).

Results: Upon IHC analysis of data available for TNBC patients we identified subgroups based on BRM level in cancer samples (high >90% and low <30% expression). In patients with low BRM level the higher number of lymph node metastasis was observed. Moreover, these patients exhibited significantly higher number of brain and liver metastasis but no metastasis to lung. On the contrary patients with high BRM level had metastasis located mostly in lung. Additionally, the group of patients with low BRM level had higher amount of vimentin in cancer cells, providing a likely explanation for the higher number of lymph node metastasis. Moreover, using Co-IP and BiFC the direct interaction between SNAIL and SLUG proteins (EMT drivers) with SWI/SNF CRC subunits was found. The in vitro overexpression of SNAIL in MDA-MB-231 cell line caused BRM protein level downregulation. The inhibition of proteasome in this cell line resulted in the upregulation of BRM protein, suggesting the link between SNAIL, SLUG, BRM and proteasome in EMT.

Conclusions: Malignancy of TNBC might be dependent on BRM - SWI/SNF CRCs and its direct connection with EMT. SNAIL and SLUG, overexpressed during EMT, might influence the stoichiometry of SWI/SNF CRC in BC cells leading to development of aggressive TNBC. BRM protein level may have a predictive value for place of metastasis.

Legal entity responsible for the study: The Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology in Warsaw.

Funding: Ministry of Science and Higher Education of Poland, grant No. DI2014 022944 and National Science Center of Poland, grant No. UMO-2016/23/N/NZ1/01138 and No. UMO-2014/15/B/NZ5/03532.

Disclosure: All authors have declared no conflicts of interest.

1899P Fluoropyrimidine and inflammatory genes promoter methylation in Egyptian CRC patients

M.A. Fouad, S.E. Salem, M.M. Hussein, A.N. Zekri, D.M. Badr, H.F. Hafez, E. Eldesouky, S.A. Shouman

Cancer Biology, National Cancer Institute-Cairo University, Cairo, Egypt

Background: Methylation of CpG islands in the promoter region of a gene is commonly associated with gene silencing and frequently observed in colorectal cancer (CRC) disease. Fluoropyrimidine (FP) based therapy received as single agent or in combination is still the backbone in CRC treatment according to the stage of the disease at diagnosis.

Methods: This prospective study was conducted on 43 Egyptian CRC patients and 32 healthy individuals. Baseline whole blood samples were collected from the patients and after 3 and 6 months of FP based therapy. Methylation specific PCR (MS- PCR) was performed for FP metabolizing genes: thymidylate synthase (TS), thymidine phosphorylase (TP), dihydropyrimidine dehydrogenase (DPD), and for the inflammatory gene: cyclooxygenase-2 (COX-2). Genes expression were calculated as fold change relative to healthy control by real time PCR.

Results: TS gene was unmethylated in 90.7 % of CRC patients who had upregulation of TS gene (median= 23.43 folds). TP gene was fully methylated in all CRC patients and upregulated by a median of 22 folds. Significant DPD down-expression ($\leq$ 0.3 folds) was found in 58.8 % CRC patients with full DPD gene promoter methylation ($P < 0.001$) while significant COX-2 down-expression ($\leq$ 5.86 folds) was encountered in 25.5 % CRC patients with partial promoter gene methylation ($P = 0.006$), and significantly down-expressed in 35.3 % of CRC patients with full methylation ($P = 0.002$).TS, DPD and COX-2 genes expression were significantly increased with FP therapy while TP expression was significantly decreased but FP therapy did not change the form of promoter genes methylation.

Conclusions: Both DPD and COX-2 genes expression were dependent on the methylation status of their promoter regions. FP therapy affects FP metabolizing and inflammatory genes expression but not the methylation status of genes promoter.

Legal entity responsible for the study: Egyptian National Cancer Institute, Cairo University.

Funding: Egyptian National Cancer Institute, Cairo University.

Disclosure: All authors have declared no conflicts of interest.

1900P Real-world prospective data of small biopsy samples for tumor PD-L1 expression in non-small cell lung cancer

K. Morikawa, A. Tsunoda, T. Inoue, M. Mineshita

Division of Respiratory Diseases, St. Marianna University School of Medicine, Kawasaki, Japan

Background: PD-1 antibody has been effective in patients with PD-L1-positive advanced NSCLC. However, surgically resected specimens or core-needle biopsy samples were used to estimate drug potency in past clinical trials.

Methods: The aim is to prospectively investigate small sample reliability for NSCLC to determine the PD-L1 expression status. We prospectively enrolled patients who underwent diagnostic biopsy by any procedures (bronchoscopy, CT/US-guided core-needle) from 2017.3 to 2018.3. Pathologically confirmed NSCLC PD-L1 expression was evaluated in our institution using companion diagnostic PD-L1 IHC. We evaluated: 1) the total number of tumor cells and sample size; 2) compared PD-L1 expression for each procedure using tumor proportion score: TPS (50%≦, 1～49%, <1%), 3) the concordance rate of PD-L1 expression status by biopsy and surgical materials.

Results: 137 cases of PD-L1 expression were evaluated. 112 cases were sampled by bronchoscopy (98 TBBs using BF-1T260/P260F in 23/75 cases, 20 TBNAs), and 25 cases

of CT or US-guided core-needle biopsy. The TPS (50%≦ / 1∼49% / <1% / undiagnosed) for total cases was 31/29/37/3% respectively which was similar to the past report. In histological subtype, TPS for adenocarcinoma (n = 82) were 28/27/43/2% and squamous cell carcinoma (n = 49) were 35/35/27/4% respectively. TPS for TBBs using BF-P260F (thin bronchoscopy) were 20/33/43/4% and TBBs using BF-1T260 (normal bronchoscopy) were 48/22/30/0%. TPS for TBNAs were 50/25/25/0% and CT or US-guided sample showed 37/21/37/5%. Four cases were not able to be diagnosed for TPS because we couldn't obtain enough tumor cells (less than 100 tumor cells) for diagnosis of TPS. The concordance rate of PD-L1 expression status by biopsy and surgical materials was 83.3% for comparison of 24 cases.

Conclusions: Utilizing smaller samples to evaluate PD-L1 expression, the frequencies of TPS were comparable to past clinical trials which used larger samples for evaluating TPS. In this study, the larger samples showed higher PD-L1 expression than smaller samples due to their containing more squamous cell carcinoma cases or advanced stage. The concordance rate of PD-L1 expression for surgically resected tissue and biopsy sample was relatively good in our institution.

Clinical trial identification: UMIN000027030.

Legal entity responsible for the study: Kei Morikawa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1901P ATM as a DNA damage response protein in uveal melanoma: Association with clinicopathological factors and prognostic outcome

J. Jha[1], M.K. Singh[2], N. Pushker[1], S. Sen[2], S. Kashyap[2]

[1]Ophthalmology, All India Institute of Medical Sciences, New Delhi, India, [2]Ocular Pathology, All India Institute of Medical Sciences, New Delhi, India,

Background: Uveal melanoma (UM) is an intraocular malignancy commonly arising from choroid which can cause visual loss or metastasis. Till date, there is no current study available on UM with respect to ATM (Ataxia Telangiectasia Mutated) protein that induces DNA damage response. Several studies revealed that loss of nuclear ATM (nATM) in various cancers like pancreatic, colorectal, gastric cancer leads to poor prognosis. This signifies ATM protein as a prognostic biomarker for cancer progression. Therefore, the aim of the study is to detect the expression/localization of ATM protein in uveal melanoma patients.

Methods: Expression of nATM was investigated on 69 formalin fixed paraffin embedded choroidal melanoma samples by immunohistochemistry and validated by western blotting. Results were then correlated with clinical and histopathological parameters. To determine the prognostic significance, Kaplan–Meier analysis and multivariate analysis by Cox's Proportional Hazards Model was performed.

Results: There was a male preponderance in our study. Histopathological high-risk factors were identified in 30/69 (43.5%) cases. Loss of nATM was found in 65.2% of the cases. Loss of nATM was statistically significant with epithelioid cell type, high pigmentation, LTD >10mm, HRFs>1, tumour height and advanced tumour staging ($p < 0.05$). On multivariate analysis, advanced tumour staging found out to be an independent prognostic factor.

Conclusions: Our data suggest that loss of nATM protein might serve as a potential prognostic marker in the pathogenesis of uveal melanoma and leads to increased risk of metastasis. These findings demonstrate an important role of ATM protein and may have a therapeutic potential in uveal melanoma. However, further studies are required in a larger cohort of patients with longer follow up and translational validation needs to be performed.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1902P BRCA mutation and castration-resistant prostate cancer

L.V. Spirina

Laboratory of Tumor Biochemistry, Tomsk Cancer Research Institute RAMS, Tomsk, Russian Federation

Background: Mutations of BRCA genes are an independent poor prognostic factor in the development of prostate cancer. It is known that the mutations BRCA1 / 2 are most often associated with the AKT / m-TOR signaling cascade hyperactivation. The purpose was to study the AKT/m-TOR pathway components in castration-resistant prostate cancer patient, depending on the presence of the BRCA mutations.

Methods: 40 patients with prostate cancer, 15 patients with castration-resistant prostate cancer and 20 patients with benign hyperplasia are enrolled in the investigation. The expression of AKT, c-Raf, GSK-3, PDK1, and m-TOR, 70-S64, E-BP1 was determined by real-time PCR. The BRCA 1/2 mutation was determined in allele-specific PCR in real time.

Results: Activation of the AKT / m-TOR signaling cascade was detected in prostate cancers. The high levels of AKT and m-TOR expression were revealed. The increase in the level of phosphatase PTEN was found in benign hyperplasia and cancer tissues. The level of mRNA 4E-BP1 was decreased in castration-resistant prostate cancer patients. At the next stage of the study, the incidence of inherited BRCA1 / 2 mutations were studied in patients with castration-resistant cancer. The BRCA1-5382insC mutation was detected in 3 patients (20%), BRCA1-4153delA – in 5 patients (33%), BRCA1-185delAG – in 2 patients (13%), BRCA1-T300G – in 2 patients (13%) and BRCA2-6174del – in 4 patients (27%). BRCA1-deficiency activates the AKT oncogenic pathway, one of the most common alterations associated with human malignancy. Mutation of BRCA1 gene increases the phosphorylation and the kinase activity of AKT. The decreased AKT expression in cancers was found in patients with BRCA1-5382insC mutation. Mutation of BRCA1-4153delA increased expression of 70S, m-TOR, in the presence of BRCA1-T300G - increased PTEN. The inherited BRCA2-6174del mutation was correlated with the increased expression of AKT.

Conclusions: Therefore, the development of PCa is accompanied by activation of this signaling cascade, even more pronounced in the presence of mutations BRCA2-6174del, BRCA1-4153delA, BRCA1-T300G. It should be noted that the frequency of occurrence of these mutations varies from 13 to 33%. At the same time, a greater accumulation of hereditary mutations BRCA1-4153delA and BRCA2-6174del was noted.

Legal entity responsible for the study: Tomsk National Research Medical Center.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1903P Prevalence of KRAS mutation subtypes and MSI status in pancreatic cancer

P. Gultawatvichai[1], I. Puthawala[2], K. Tomaszewicz[3], V.G. Bathini[1], L. Hutchinson[3]

[1]Hematology-Oncology, University of Massachusetts Medical Center UMass Memorial Medical Center, Worcester, MA, USA, [2]Internal Medicine, University of Massachusetts Medical Center UMass Memorial Medical Center, Worcester, MA, USA, [3]Pathology, University of Massachusetts Medical Center UMass Memorial Medical Center, Worcester, MA, USA

Background: KRAS is the most prevalent driver mutation in pancreatic ductal adenocarcinoma (PDAC) which impacts cell differentiation, proliferation, migration and apoptosis. KRAS subtypes may have prognostic significance but this finding remains uncertain. Microsatellite Instability / mismatch repair deficiency (MMR) has also been reported in PDAC but at a low frequency (0.8%) and these patients are eligible for immunotherapy. This study investigates the effect of KRAS subtype on survival rate and the prevalence of mismatch repair deficiency in our patient cohort.

Methods: 91 patients enrolled from 2005 to 2012 with biopsy proven PDAC of all stages. All clinical data were collected from the medical records of each patient. Next generation sequencing was performed on all 91 samples. We also evaluated MMR expression in all resection specimens who underwent adjuvant treatment. Statistical analysis: Data were summarized as descriptive analysis statistics and analyzed using unpaired t-test. Overall survival (OS) was measured from the date of diagnosis to last known follow up or date of dead from disease.

Results: The most common type of mutation in all stages is KRAS (95%). KRAS mutation subtypes in the order of frequency were: G12D, G12V, G12R, Q61H, Q61L and G12C. Among codon 12 mutations, G12V showed the best OS at 20.12 months. Mutations in codon 61 carry better OS compared to codon 12 by 24 months ($P = 0.0002$, 95% CI 11.85 to 37.03). The staining for MMR status was performed on 30 of 91 specimens and all were mismatch repair protein proficient (analogous to MSI-stable [MSS]).

Conclusions: The prevalence and distribution of KRAS mutations from our study is similar to previous reports. Patients with a KRAS codon 61 mutation had better OS than with a codon 12 mutation. Interestingly, Q61 variants are far less common than the G12 variants which may explain why most of the pancreatic patients have an aggressive disease course. Our results support the conclusion that MMR defects are uncommon in PDAC. Germline mutation analysis could be considered to find other targetable mutations found in hereditary cancer syndromes such as BRCA1/2 or PALB2.

Legal entity responsible for the study: Lloyd Hutchinson.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1904P Molecular signature in malignant pleural mesothelioma (MPM): Preliminary data of Italian RAMES study

F. Zanelli[1], M. Pagano[1], C. Bonelli[1], R. Gnoni[1], L. Boni[2], G.L. Ceresoli[3], M. Larocca[1], M. Tiseo[4], P. Zucali[5], F. Grosso[6], F. Cappuzzo[7], A. Ciarrocchi[8], F. Torricelli[9], C. Pinto[1]

[1]Oncology Unit, AUSL di Reggio Emilia-IRCCS, Reggio Emilia, Italy, [2]Istituto Toscano Tumori, Clinical Trial Coordinating Center, AOU Careggi, Florence, Italy, [3]Oncology, Humanitas Gavazzeni, Bergamo, Italy, [4]Medical Oncology, AOU di Parma, Parma, Italy, [5]Oncology, Humanitas Clinical and Research Hospital, Rozzano, Italy, [6]Oncology/ Hematology, Ospedale di Alessandria, Alessandria, Italy, [7]Dipartimento di Oncologia Medica, Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy, [8]Laboratory Research, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy

Background: MPM is a highly aggressive pleural tumor associated with asbestos exposure. The ability to analyze entire genomes opens the door to identification of new treatments.

Methods: RAMES is a ongoing phase II study to evaluate the efficacy and the safety of the addition of ramucirumab to gemcitabine as the second-line treatment in 160 pts with MPM. We designed a custom panel covering 1040 amplicons spanning 33 genes frequently altered in MPM. To establish the genetic asset of MPMs we used an amplicon-based next generation sequencing approach.

Results: To date, 40 FFPE mesothelioma cancer tissues were successfully sequenced A total of 2930 variants passing quality filters were detected. Focusing on potentially functional alterations, polymorphisms and non-coding variants were excluded, leaving 143 alterations in 23 of the analyzed genes. Of these, 59.4% (85/143) were missense mutations, 22.4% (32/143) lead to frameshift alteration of the gene sequence, 13.3% (19/143) were splice variants, while the remaining 4.9% (7/143) were start loss, stop gain alterations and deletion. 97.5% of patients (39/40) displayed at least one mutation, while the average number of mutations per sample was 3.6 (range 0-8), confirming the high mutational load of these tumors. The most frequently altered genes identified were PIK3CA (62.5%), RDX (40%), MXRA5 (20%), BAP1 (15%), NF2 (15%). Molecular analyses have been correlated with Histology and Stage (thoracic vs extrathoracic MPM). We found the following NF2, PIK3CA, RDX altered genes in 9 biphasic tumor and MXRA5, NF2, PIK3CA, RDX, CUL1, BAP1, NF2, TAOK1 altered genes in 31 ephitelioid tumor. We observed a significant correlation between mutations in RDX gene (23.1%) and extrathoracic MPM. CUL1 and RDX genes were found in pts with progression free survival $\geq$6 months from prior treatment.

Conclusions: This preliminary data supports the generation of a genetic signature based on tumor mutational status useful to discriminate MPM with different clinicopathological features and possible correlation with treatment choice.

Legal entity responsible for the study: AUSL-IRCCS Reggio Emilia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1905P N-Myc and STAT interactor (NMI) as a key determinant of chemosensitivity in breast cancer: Proteomic-based computing network mapping and in vivo verification with a mouse model

H. Lee[1], K-M. Lee[2], D. Han[3], H. Ryu[4]

[1]Radiation Oncology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Biomedical Research Institute, Seoul National University Hospital (SNUH)-Yongon Campus, Seoul, Republic of Korea, [3]Proteomic Core Facility, Seoul National University Hospital (SNUH)-Yongon Campus, Seoul, Republic of Korea, [4]Pathology and Proteomic Core Facility, Seoul National University Hospital (SNUH)-Yongon Campus, Seoul, Republic of Korea

Background: We targeted NMI based on our previous proteomics analysis using FFPE breast cancer samples with neoadjuvant settings and text-mining analytics to verify NMI as a target agent to overcome chemoresistance through in vitro and in vivo studies.

Methods: Quantitative proteomics was analyzed for three different breast cancer cell lines with NMI gene silencing. We performed computation pathway enrichment based on domain knowledge for text-mining and bioinformatics tools to identify critical pathways related to chemotherapeutic sensitivity. A total of 8 breast cancer cell lines with or without endogenous chemoresistance were enrolled to define the important pathways and molecules in determining chemosensitivity through cell-titer glo assay, FACS, 3D spheroid and invasion assay, ROS assay by DCFDA and Mitotracker. Interaction network analyses were investigated to define the signaling pathway landscapes with public network databases and bioinformatic network evaluations. To verify the chemosensitive roles of NMI in vivo setting, we are conducting animal tests and immunostaining in human breast cancer samples where the patients received neoadjuvant chemotherapy.

Results: A total of 972 were confirmed to be significantly altered proteins after NMI gene silencing. A vast number of cell cycle-related proteins, which were downregulated considerably in NMI suppressed group led us to verify NMI's biological function on chemosensitivity through molecular biology-driven assays. Cell-titer glo assay and FACS revealed significantly induced cytotoxicity and apoptosis in both hormone receptor positive and negative groups without NMI gene after treatment with three different chemotherapeutic agents. The 3D-spheroid assay demonstrated a reduced spheroid formation in the case group. DCFDA and Mitotracker assay revealed increased intracellular and intramitochondrial ROS levels. We built biological network models based on in-silico and biology-driven assays. Currently, we are conducting in vivo validation using an animal test model and human samples.

Conclusions: Our biological evidence for NMI can provide novel insights to overcome chemo-resistance in breast cancer.

Legal entity responsible for the study: Han Suk Ryu.

Funding: This research was suppoorted by a grant of the Korea Health technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea.

Disclosure: All authors have declared no conflicts of interest.

1906P Lung cancer predisposition in women with previous breast cancer identified by whole exome sequencing

F. Grossi[1], C. Genova[1], D. Cittaro[2], S. Bonfiglio[2], S. Boccardo[1], I. Vanni[1], M. Mora[3], M.G. Dal Bello[1], F. Biello[1], E. Rijavec[1], C. Sini[1], G. Rossi[1], M. Tagliamento[1], A. Alama[1], G. Burrafato[1], G. Barletta[1], A. Ballestrero[4], S. Coco[1]

[1]Lung Cancer Unit, Ospedale Policlinico San Martino, Genoa, Italy, [2]Centre for Translational Genomics and Bioinformatics, IRCCS San Raffaele Scientific Institute, Milan, Italy, [3]Pathology Unit, Ospedale Policlinico San Martino, Genoa, Italy, [4]Department of Internal Medicine, University of Genoa, Genoa, Italy

Background: Women treated for breast cancer (BC) are at risk to develop a subsequent lung cancer (LC; relative risk ranging from 1.38 to 5.05), especially in case of smoking history and if adjuvant radiation (aRT) was administered for BC. We hypothesized that genetic variants might predispose patients (Pts) to develop LC after BC. Our aim was to perform whole exome sequencing (WES) to identify genes associated with such predisposition.

Methods: 28 women with diagnosis of LC after BC (Study Population, SP) were enrolled, as well as 32 women treated for BC and with no secondary cancer after a follow-up $\geq$10 years (control population; CP). DNA was extracted from tumors and normal tissue samples from both SP and CP. Libraries were prepared with Agilent SureSelect All Exon kit and sequenced on Illumina HiSeq2500. Variant calling was performed with FreeBayes software.

Results: The median age of SP at BC diagnosis was 63.5 years (range: 47-76); the median interval between diagnosis of BC and occurrence of LC was 4.5 years (range: 0-11). 13 Pts (46%) were never-smokers and, among the 21 Pts who had received aRT, 13 (62%) developed ipsilateral LC. At somatic analysis, no common mutation among known driver genes was shared between each BC and LC pair in SP Pts. WES performed on BC and LC samples identified two mutational signatures (S1 and S2). S1 (C>T substitutions) was observed in all BC samples and 16/28 (57%) LC samples and was more frequent in never-smokers (11 vs. 5 Pts) and among Pts who developed ipsilateral LC after aRT (10 vs. 6 Pts). S2 (C>A transversions) was observed in 12/28 LC samples (43%) and was strongly associated with smoking habit (10 vs. 2 Pts). When compared with COSMIC libraries, S2 results were similar to COSMIC 4, common in LC samples collected from smokers. Since S1 was largely shared between paired BC and LC samples, we explored the eventuality of a genetic predisposition to S1-related malignancies with a gene-based burden test over rare germline variants in normal tissue of S1-LC Pts compared with CP Pts; 249 candidate genes were identified (FDR<0.05).

Conclusions: Our data identified two mutational signatures underlying the LC development. Germline analysis suggests that genetic variants may contribute to increase the risk of LC after BC.

Legal entity responsible for the study: Ospedale Policlinico San Martino.

Funding: Italian Ministry of Health (GR-2011-02350922).

Disclosure: F. Grossi: Honoraria: BMS, MSD, AstraZeneca, Pierre Fabre, Boehringer Ingelheim, Pfizer, Celgene, Amgen, Roche. C. Genova: Honoraria: AstraZeneca, Boehringer Ingelheim, BMS, MSD, Roche. G. Barletta: Employee: AstraZeneca. All other authors have declared no conflicts of interest.

1907P Discordance of the PAM50 intrinsic subtypes compared with IHC-based surrogate in breast cancer patients: Potential implication of genomic alterations of discordance

Y.H. Park, H.K. Kim, J.H. Cho

Internal Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: In recent decades, 5 intrinsic molecular subtypes have been characterized according to variation in gene expression patterns of breast cancer. However, in real-world practice, immunohistochemistry (IHC)-based classification such as estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor (HER2) are routinely used. We aimed to analyze the discordance between IHC-based surrogate subtyping and PAM50 intrinsic subtypes and to assess overall survival (OS) according to discordance.

Methods: A total of 607 patients were analyzed. Hormone receptor (HR) was evaluated by IHC and HER2 by IHC and/or FISH. PAM50 intrinsic subtypes were determined according to 50 cancer genes using NanoString nCounter Analysis System. In addition, we used Ion Ampliseq Cancer Panel v2 to identify the genomic alteration related with discordance between IHC subtype and PAM50 intrinsic subtype. The Kaplan-Meier method was used for estimation of OS.

Results: The majority of patients were HR + (343/607, 56.5%) by IHC and luminal A/B (283/607, 46.6%) by PAM50. We matched concordant tumor as luminal A and HR+/HER2-, luminal B and HR+/HER2+, HR-/HER2+ and HER2-enriched, TNBC and Normal- or Basal-like. 233 patients (38.4%) were discordant between IHC-based subtypes and PAM50 intrinsic subtypes. The discordant patients were mostly HR + (176 of 234, 75.2%) and 12.4% (29 of 234) were HER2+. Using targeted sequencing with Ampliseq, we detected somatic mutation related discordant breast cancer including VHL gene in HR+/HER2- group (31% in concordant group, 0% in discordant group, P = 0.03) and IDH and RET genes (7% vs. 12%, P = 0.02, 0% vs. 25%, P = 0.02, respectively) in TNBC group. In survival analysis, among the patients with HR+, basal-like group by PAM50 showed significantly inferior OS compared with other intrinsic subtypes (p = 0.010).

Conclusions: A substantial portion of patients showed discrepancies between IHC-based subtypes and PAM50 intrinsic subtypes in our study. The survival analysis demonstrated that current IHC-based classification could misdirect treatment and result in poorer outcomes. Current guidelines of IHC for ER, PR, and HER2 would better be updated accordingly.

Legal entity responsible for the study: Yeon Hee Park.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1908P Impact of invasive lobular carcinoma in Latin American breast cancer patients' disease-free survival: The new paradox

D. Flores-Díaz[1], C. Arce Salinas[1], L. Flores[2], F. Lara[1], J.A. Matus Santos[3], J.E. Bargallo Rocha[3], V. Perez[3], N. Reynoso-Noveron[4], P.A. Cabrera[3], A. Mohar[4]

[1]Breast Medical Oncology, Instituto Nacional de Cancerología, Mexico City, Mexico, [2]Epidemiology Department, Instituto Nacional de Salud Publica, Mexico City, Mexico, [3]Breast Cancer Department, Instituto Nacional de Cancerología, Mexico City, Mexico, [4]Epidemiology Breast Cancer Unit, Instituto Nacional de Cancerología, Mexico City, Mexico

Background: Traditionally invasive lobular breast carcinoma (LBC) has been considered a good prognosis histology. However, it has a unique molecular pathogenesis and different genomic profile. Our objective was to establish whether there is a difference in disease-free survival (DFS) between LBC and ductal carcinoma.

Methods: We evaluated a cohort of 5185 breast cancer patients with lobular and ductal carcinoma (DC) treated the at National Cancer Institute Mexico between 2006 and 2016. We compared presentation variables using the chi squared test. A Cox proportional hazards regression model was constructed to evaluate disease-free survival.

Results: With a median of 60 months follow-up, patients with LBC were older ($p < 0.001$), more frequently patients with Ki67 <18% (40.2% vs 28.6% $p < 0.001$), had lower nuclear grade ($p < 0.001$), and predominantly hormone receptor positive disease (77.9% vs 56.9% $p < 0.001$). Nevertheless, LBC patients had a higher recurrence rate (25.2% vs 21.1% p = 0.011). For both LBC and DC patients, factors that negatively influence 5-years DFS in the univariate analysis were stage III (71.9% vs 78.9% $p < 0.001$), Ki67>18% (83.3% vs 93.1% p = 0.016), low nuclear grade (82.1% vs 95.9% $p < 0.001$), triple negative (46.7% vs 71.8% p = 0.002), and Her2 positive (72.4% vs 84.5% p = 0.023). In the multivariate analysis patients with stage III, (OR 10.8, 95%CI 5.9–19.9), high nuclear grade (OR 1.5, 95%CI 1.0-2.4), Ki67 >18 (OR 1.5, 95%CI 1.1–1.9), triple negative phenotype (OR 2.7, 95% CI 1.1-6.6) and lobular carcinoma (OR 1.8, 95%CI 1.1-2.7) are independent negative factors for DFS.

Conclusions: The presence of lobular invasive carcinoma is an independent negative factor for DFS. Despite the high rate of good prognosis elements in pathological reports, lobular carcinoma seems to be another disease and we need to evaluate deeply new and old treatment strategies to provide better disease control. Particulary in clinical stage III, Latin America has a challenge to be aware of it.

Legal entity responsible for the study: Instituto Nacional de Cancerología, Mexico.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1909P Clinical validation of an NGS-based assay for the detection of BRCA1 and BRCA2 variants in Chinese patients with breast cancer or ovarian cancer

G. Zhu[1], H. Ge[2], X. Li[2], L. Ruan[1]

[1]Medical Oncology, Amoy Diagnostics Co., Ltd., Xiamen, China, [2]NGS, Amoy Diagnostics Co., Ltd., Xiamen, China

Background: Variation in BRCA1 and BRCA2 genes are associated with the development of hereditary breast cancer and ovarian cancer (HBOC) and sensitivity to poly ADP-ribose polymerase inhibitors (PARPi). A genetic testing assay based on next-generation sequencing (NGS) method, named AmoyDx BRCA1 and BRCA2 Mutation Detection Kit (ADx-BRCA NGS kit), has been developed for the detection of BRCA1/2 variants. The present study evaluated the clinical performance of the ADx-BRCA NGS kit in detecting BRCA variants in peripheral blood-derived DNA.

Methods: A cohort of 1,341 peripheral blood samples from Chinese patients were analyzed for BRCA1/2 variation using ADx-BRCA NGS kit, including 1,035 patients with breast cancer and 306 with ovarian cancer. BRCA MASTR Dx assay (Multiplicom) was used as a reference method to test the same cohort. ADx-BRCA NGS kit allows identification of variants in complete coding regions of BRCA1/2 genes which are also covered by the reference method, and 22 additional UTR regions beyond the coverage of the reference assay. The concordance of BRCA variation detected with ADx-BRCA NGS kit was calculated compared to the reference assay.

Results: In this study, all the 1,341 samples were successfully detected and the classification for BRCA1/2 variants identified by ADx-BRCA NGS kit in breast and ovarian cancer is listed in the table. Using BRCA MASTR Dx assay as relference, the overall concordance of BRCA variation status determined by ADx-BRCA NGS kit was 99.92% (1,286/1,287). In addition, 54 samples were excluded from the analysis due to the variation detected in the UTR regions that were not covered by reference method.

Table: 1909P Classification for BRCA1/2 variants detected by ADx-BRCA NGS kit

Class	Definition	Variant amount in breast cancer	Variant amount in ovarian cancer	Total
5	Definitely pathogenic	63 (6.09%)	73 (23.86%)	136 (10.14%)
4	Likely pathogenic	33 (3.19%)	6 (1.96%)	39 (2.91%)
3	Uncertain	101 (9.76%)	40 (13.07%)	141 (10.51%)
2	Likely benign	213 (20.58%)	53 (17.32%)	266 (19.84%)
1	Benign	625 (60.38%)	134 (43.79%)	759 (56.6%)
Total		1,035	306	1,341

Conclusions: ADx-BRCA NGS assay has shown a high concordance rate of 99.92% compared to the BRCA MASTR Dx assay, demonstrating that it is a highly accurate method for the detection of BRCA1/2 variants and can be used to screen patients with germline BRCA mutations.

Legal entity responsible for the study: Amoy Diagnostics Co., Ltd.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1910P Correlation beetween the expression of androgens receptor (RA) and histopathological characteristics and survival parameters of breast cancer

I.D. Sillero[1], A. López González[1], L.F. Sanchez Cousido[1], M. López-Flores[1], E. Honrado Franco[2], L. Lopez Gonzalez[3], O. Sanz[4], C. Castañón López[1], A. García Palomo[1]

[1]Oncología Médica, Complejo Asistencial Universitario de León, León, Spain, [2]Pathology, Complejo Asistencial Universitario de León, León, Spain, [3]Radiology, Complejo Asistencial Universitario de León, León, Spain, [4]General Surgery, Complejo Asistencial Universitario de León, León, Spain

Background: Clinical trials have attempted to demonstrate a correlation between the expression of androgen receptor (RA) and the prognosis of breast cancer. We have analyzed a sample of women with diagnosis of triple negative breast cancer (TN) in order to establish their prognostic value.

Methods: We retrospectively analyzed a cohort of women diagnosed of early stage TN breast cancer in the Universitary Hospital of León from 2008 to 2013. Our first end point was to establish a correlation between RA expression, clinical parameters, immunohistochemical characteristics and PFS and OS.

Results: A total of 58 women with TN breast cáncer were included. From the total number of biopsies, 20% expressed RA, and the 80% of this subgroup had an apocrine histology. The RA expression was associated to a favourable grade (G) :(RA + G3: 45.5% vs. RA - G3 79%, p = 0.05); smaller size (11.1% T1, 77% T2 .11.1% T3-T4), and lower percentage of Ki-67: (mean in RA + 23.6% ± 5 vs 41.4% ± 3, p = 0.005). There was also a trend towards association with premenopausal status (60% vs 40% postmenopausal p = 0.02) and axillary involvement at the time of diagnosis (65% N1-2 vs. 35% N0 p = 0.045). Regarding OS and PFS, we did not find statistical significant differences between RA positive and negative tumors (p = 0.89 and p = 0.34 respectively).

Conclusions: The RA expression in TN breast cancer is associated with more favourable histopathological characteristics except the axillary involvement. Although most of our cases were N+, we did not find a worse prognosis in these patients. It is possible that with the antiandrogenic therapy a better survival could be obtained, which would justify the design of clinical trials.

Legal entity responsible for the study: CAULE.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1911P Metabolic syndrome in breast cancer patients: An observational study

S. Khare

General Surgery, PGIMER, Chandigarh, India

Background: With significant increase in the prevalence of overweight population in India, there might be a similar increase in the prevalence of metabolic syndrome. Positive association between metabolic syndrome in Indian subjects, if any, may translate into significant changes in the risk factors for breast cancer and may have a significant impact on the incidence and mortality related to breast cancer in India. Hence, we undertook this study to find any correlation between metabolic syndrome and breast cancer.

Methods: We did a prospective study from August, 2016 to July, 2017. Measurements of height, weight, BMI and waist circumference and fasting blood sugar, fasting triglycerides, fasting HDL and HBA1c were done. Metabolic syndrome was defined according to International Diabetes Federation consensus statement 2006. TNM staging, type and grade of tumour, hormone receptor status, Her2 neu status and Ki67 index along with other known risk factors of breast cancer like age at menarche, age at first child birth (FCB), breastfeeding, presence or absence of family history of breast cancer and mammographic density were recorded. K-S test was used to check the normality of the data. Student's t test and Mann Whitney U test, Chi Square test or Fisher exact test (whichever was applicable) was used for comparison.

Results: Total of 305 patients were recruited into the study with 191 (62.6%) patients having metabolic syndrome. The mean age was of 50.7±12.4 years. There was no correlation of metabolic syndrome to any of the known risk factors (Age, age at menarche, age at FCB, early menarche, parity, no breast feeding, breast density on mammography or family history of breast cancer). Patients with metabolic syndrome were found to be less likely to have hormone receptor positive tumours ($p = 0.025$), more likely to have Her2 positive tumours ($p = 0.011$). They were also more likely to have Her2 enriched and basal like subtype and less likely to have Luminal A and B subtypes ($p = 0.027$). There was no correlation between metabolic syndrome and T, N, M or overall staging. It also had no relation to type of tumour (IDC vs No IDC), grade or Ki67.

Conclusions: Metabolic Syndrome may emerge as a significant prognostic factor in breast cancer in the future.

Legal entity responsible for the study: Department of General Surgery, PGIMER, Chandigarh.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1912P The prognostic value of different molecular subtypes of breast cancer in relation to enhancer-of-zeste homologue 2 expression

Z. Sanaat, R. Dolatkhah

Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran

Background: Studies have shown that Enhancer-of-zeste homologue 2 (EZH2) plays an important role in carcinogenesis in the breast cancer, and invasion and progression of the disease. We aimed to assess the prognostic value of different molecular subtypes of breast cancer in relation to EZH2 expression.

Methods: We performed a cross-sectional analytical research study on 100 breast cancer women. Survival analysis was then performed using the Kaplan–Meier method, with log-rank tests to assess statistical significance between groups. To assess the effects of variables on OS and DFS, a Cox proportional-hazard model was then used to give adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: Samples were collected for 100 women with breast cancers, with follow-up data collected over a 5-year period. The mean age was 51.5 ± 9.54 years (range, 34–75 years), By molecular subgroup, 43% had luminal A tumors, 41% had luminal B tumors, 9% had HER2 tumors, and 7% had TNBC tumors. Overall, 74% had high EZH2 expression, which was most common for the luminal A subtype (43.2%) and least common for the TNBC subtype (8.1%). There was no significant correlation between subgroups by EZH2 expression ($P = 0.33$).

Conclusions: In conclusion, although our results provide some interesting insights, there remains controversy about the prognostic value of different molecular subtypes of breast cancer in relation to EZH2 expression. Given that there are very few studies on this topic, we advocate further research with larger sample sizes and the inclusion of molecular techniques.

Editorial acknowledgement: This study was conducted as part of a fellowship thesis for Dr Boostani (thesis no 94/5-9/30). Dr Robert Sykes (www.doctored.org.uk) provided technical editing services for the final drafts of this manuscript.

Legal entity responsible for the study: The study protocol was approved by the ethics committee of Tabriz University (permit no. 5/d/988072).

Funding: Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

Disclosure: All authors have declared no conflicts of interest.

1913P A guided and personalised treatment in metastatic breast cancer: Optimisation of gene and protein expression in tumor tissue

E. Seront[1], S. Lejeune[1], B. Petit[1], V. Samartzy[2], S. Sauvage[3], J-F. Laes[3]

[1]Medical Oncology, Centre Hospitalier Jolimont-Lobbes, Haine Saint Paul, Belgium, [2]Gynecology, Centre Hospitalier Jolimont-Lobbes, Haine Saint Paul, Belgium, [3]Scientific, OncoDNA, Gosselies, Belgium

Background: The better understanding of the signaling pathways involved in cancer has led to the use of targeted therapies, such as everolimus (E), a mammalian target of rapamycin (mTOR) inhibitor and palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in the treatment of metastatic breast cancer (mBC). However, treatment response is variable, and resistance occurs systematically. We hypothesised that the combination of gene sequencing and protein expression analysis could help, in a patient, to identify resistance mechanisms occurring on a specified treatment as well as to determine potential further treatments.

Methods: We studied paired-biopsies performed in a 69-year-old woman patient with mBC who achieved a durable (16 months) partial response to E-exemestane association. Biopsy 1 was performed before E initiation and biopsy 2 at the progression on E. Analyses were realised with OncoSTRAT&GO™, from OncoDNA company, which combines sequencing of oncogenic genes panel and expression analysis of proteins that could be targeted by current antitumoral agents.

Results: Biopsy 1 revealed PIK3CA(E542K) gene mutation and a high expression of phospho 4EBP1, an effector of mTOR, reflecting an excessive activation of the mTOR pathway that explains the E sensitivity. Biopsies 1 and 2 showed a high expression of phospho-retinoblastoma (pRb), reflecting a continuous cell cycle activation by CDK4/6. Palbociclib was thus initiated in association with letrozole at the progression on E and resulted in a rapid and long-duration (17 months) partial response. In the paired biopsies, the tyrosine kinase receptor cMET was not detected on biopsy 1, but was highly expressed in biopsy 2, suggesting that cMET could play a role in the development of resistance to E. In this context, we are currently treating our patient with cabozantinib (cMET inhibitor). Response profile will be further specified.

Conclusions: These gene and protein expressions reflect correctly the efficacy of targeted therapies this patient received. PIK3CA mutation was associated with E sensitivity and pRb with impressive response to palbociclib. cMET could play a role in the development of resistance to E and its inhibition should be evaluated in mBC.

Legal entity responsible for the study: Centre Hospitalier de Jolimont.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1914P HER2 staining intensity has prognostic impact on patients with HER2 type invasive breast cancer

H. Yi-Hsuan[1], L. Yen-Shu[2], H. Chih-Yi[3], T. Ling-Ming[2]

[1]Department of Surgery, Cardinal Tien Hospital, New Taipei, Taiwan, [2]Department of Surgery, Taipei Veterans Hospital, Taipei, Taiwan, [3]Department of Pathology, Taipei Veterans Hospital, Taipei, Taiwan

Background: Human epidermal growth factor receptor 2 (HER2) is a key marker for breast cancer and HER2-targeted therapy has improved the prognosis for patients with HER2 overexpressed breast cancer. HER2 positivity is defined as HER2 protein overexpression measured by immunohistochemistry (IHC) or HER2 gene amplification evaluated by in situ hybridization (ISH). As the protein expression of HER2 IHC 3+ is higher than that of HER2 IHC 2+, we suppose patients with HER2 IHC 3+ tumor would have better response to anti-HER2 therapy, and their prognosis would better than that of HER2 IHC 2+ tumor. This study aimed to evaluate whether the degree of HER2 IHC positivity affected the outcome of early breast cancer.

Methods: Clinicopathological information of 785 consecutive cases of HER2+ early breast cancer who underwent surgery at Taipei Veterans General Hospital, Taiwan, ROC from 2007 October to 2015 December were retrieved from the medical records. Survival curves were plotted by Kaplan-Meier method, and their differences were calculated by log-rank test. Cox regression model was used to evaluate the hazard of recurrence and death, and the influences of the age of patients, stage, hormonal receptor status, anti-HER2 treatment were adjusted.

Results: Recurrence-free survival of cases with HER2 IHC 3+ tumor was significantly better than that of cases with HER2 IHC 2+ tumor ($p = 0.018$). Multivariate Cox regression revealed the hazard ratios of cases with HER2 IHC 3+ was significant smaller than those with HER2 IHC 2+ in both RFS ($p = 0.001$) and OS ($p = 0.007$).

Conclusions: We confirmed that the intensity of HER2 IHC provided prognostic information for HER2 positive breast cancer. The prognosis of HER2 IHC 3+ cases was significantly better than that of HER2 IHC 2+ and ISH amplified cases. Accurate HER2 testing is important to maximize the benefit of anti-HER2 therapy.

Legal entity responsible for the study: Tseng Ling-Ming.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1915P Does the minimal axillary approach lead to loss of prognostic factors in breast cancer?

R.A. de Araujo[1], C.P. Nascimento[2], C.L.P. Da Cunha[2], E.D.C. Marinho[2], E.R.T. Mosca[2], F.A.C. Da Luz[2], P.F.R. Delfino[2], R.M. Antonioli[2], T.R. Mendes[2], M.J.B. Silva[3]

[1]Oncologia Clínica, COT - Centro Oncológico do Triângulo, Uberlandia, Brazil, [2]Hospital do Câncer em Uberlândia, Universidade Federal de Uberlândia, Uberlândia, Brazil, [3]Instituto de Ciências Biomédicas, Universidade Federal de Uberlândia, Uberlândia, Brazil

Background: There are several factors for metastasis in breast cancer, such as tumor size (T) and lymph node involvement (N). In this study was investigated the association of T and N with metastasis in breast cancer patients treated in the Oncology Sector of a public Hospital of Minas Gerais.

Methods: Observational and retrospective study. A total of 1671 medical records of women with breast cancer treated in the period of 1981-2013 were analyzed, of which 797 were excluded for lack of pathologic data or by being diagnosed in advanced stage. Fisher's exact test or χ^2 were performed.

Results: As expected, the positivity of lymph node metastasis increased with tumor size: of the Tis patients, 5.55% were N + (3.7% N1, 1.85 N2); of T1, 25.29% were N + (21.01% N1, 4.28% N2); of T2, 51.45% were N + (37.21% N1; 9.88% N2; 4.36% N3); of T3, 77.05% were N + (55.74% N1; 18.03% N2; 3.28% N3); and of T4, 80% were N + (48.57% N1; 17.14% N2; 14.29% N3). When analyzed by T, decreased odds of metastasis in Tis (OR = 0.3435; p = 0.0197) and T1 (OR = 0.3805; p < 0.0001) were observed, while increased odds in T2 (OR = 1.469; p = 0.0364), T3 (OR = 2.114; p = 0.0081) and T4 (OR = 4.222; p < 0.0001). When analyzed by N, decreased odds of metastasis in N0 (OR = 0.1587; p < 0.0001) was observed and increased odds in N1 (OR = 2.56; p < 0.0001), N2 (OR = 3.703; p < 0.0001) and N3 (OR = 4.328; p = 0.0002). Overall, N+ had an increased odd of metastasis when compared with N- (OR = 6.321; p < 0.0001) patients. Increased odds only in T1N + (OR = 9.49; p < 0.0001) and T2N + (OR = 3.557; p < 0.0001) was observed when compared with their N- counterparts. Moreover, a borderline increase in the odds (OR = 3.667; p = 0.0533) was observed in T1N2 compared with in T1N1, but not in T2 (p = 0.9190) nor T3 (p = 0.4639) patients.

Conclusions: Lymph node involvement (N) is a greater risk factor for metastasis than tumor size (T). Adjuvant therapy is based on T, N and molecular subtype. In the minimal axillary approach by sentinel lymph node (SL) the pathologic analysis of this unique sample, and maybe including two other lymph nodes, have a great prognostic weight, mainly in early stage. These data corroborate the lack of necessity in dividing, as formerly, between the 12 or more dissected lymph nodes in a clinically negative axilla.

Legal entity responsible for the study: Grupo Luta Pela Vida.

Funding: Grupo Luta Pela Vida.

Disclosure: All authors have declared no conflicts of interest.

1916P The influence of the surgical approach in women diagnosed with breast neoplasia

R.A. de Araujo[1], C.P. Nascimento[2], C.L.P. Da Cunha[2], E.D.C. Marinho[2], E.R.T. Mosca[2], F.A.C. Da Luz[2], P.F.R. Delfino[2], R.M. Antonioli[2], T.R. Mendes[2], M.J.B. Silva[3]

[1]Oncologia Clínica, COT - Centro Oncológico do Triângulo, Uberlandia, Brazil, [2]Hospital do Câncer em Uberlândia, Universidade Federal de Uberlândia, Uberlândia, Brazil, [3]Instituto de Ciências Biomédicas, Universidade Federal de Uberlândia, Uberlândia, Brazil

Background: Although recent years have seen improvement in systemic therapies and radiotherapy, the surgical approach is still a keystone in oncologic treatment. In this study we investigated the association between surgical margin status and surgical approach with disease progression and death of breast cancer patients treated in the Oncology Sector of a Public Hospital of Minas Gerais.

Methods: Observational and retrospective study: A total of 1979 medical records of women with breast cancer treated in the period of 1981 to 2013 were analyzed. The surgical approach and surgical margin were obtained from anatomopathological reports. Of the total, 987 were excluded for lack of pathologic data, being diagnosed at stage IV or pathogical 0 stage.

Results: Of the subtotal, 992 medical records reported the surgery approach (radical or breast-conserving), and 905 reported surgical margins, of which 110 had positive margin and 795 negative margin. The median age was of 55 y.o. (27-91). It was observed that 49.69% (n = 493) of surgeries were breast-conserving. No association between surgical approach and local relapse (p = 0.2672) was observed. However, increased odds of surgical margin impairment (OR = 1.531; p = 0.0395) and decreased odds of distant relapse (OR = 0.4068; p < 0.0001) and death (OR = 0.1455; p < 0.0001) was observed for breast-conserving surgeries compared with radical surgeries. No association between surgical margin and local relapse was observed (p = 0.1063). However, patients with positive surgical margin had greater odds of distant relapse (OR = 1.940; p = 0.0052) and death (OR = 2.002; p = 0.0494). When analyzed by pathological stage (I-III), it was observed that positive surgical margin increased the odds of distant relapse in stage II (OR = 2.280; p = 0.00499) and III (OR = 2.820; p = 0.0132) patients.

Conclusions: Although an association between radical surgery and death was observed, factors such as tumor complexity and locally advanced tumor could be involved. However, it is noteworthy that positive surgical margin increased the odds of distant relapse, mainly in stage III patients, and death. These data corroborate the fact that the surgical approach is still a keystone in breast cancer treatment and it has a strong impact in patients with locally advanced tumors.

Legal entity responsible for the study: Grupo Luta Pela Vida.

Funding: Grupo Luta Pela Vida.

Disclosure: All authors have declared no conflicts of interest.

1917P Use of comparative proteomics to identify potential cisplatin-resistance mechanisms in neuroblastoma

M.A. Merlos Rodrigo, H. Buchtelova, V. Strmiska, Z. Heger, V. Adam

Chemistry and Biochemistry, Mendel University in Brno, Brno, Czech Republic

Background: Neuroblastoma (Nbl) is an embryonal tumour, originating from progenitor cells of the sympathetic nervous system, and is the most common extra-cranial solid tumour of childhood. Cisplatin is one of the most commonly used drugs in the treatment of Nbl. Unfortunately, the development of resistance against this cytotoxic agent limits its clinical use. We aimed to gain further understanding of the mechanisms underlying development of cisplatin resistance using an in vitro cell line model.

Methods: Cytotoxicity of cisplatin, carboplatin and oxaliplatin in neuroblastoma UKF-NB-4 and UKF-NB-4^{CDDP} cells cultured in the exponential growth was determined. Peptide separations were carried out on an Easy-nLC 1000 nano system. MS analysis was performed using a Q-Exactive MS. MS data were analyzed with Proteome Discoverer (version1.4.1.14) using standardized workflows. The mass spectrum *.raw file was searched against the human SwissProt 57.15 database (20266 sequences protein entries) using MASCOT search engine (version 2.3, Matrix Science).

Results: The two cell lines that were used were the following: cisplatin-resistant UKF-NB4CDDP and UKF-NB4 cell lines. We proved decreased sensitivity of line UKF-NB-4^{CDDP} to cisplatin and crossresitance to carboplatin and oxaliplatin. Out of a total 1802 identified proteins, 1448 were common expressed in two datasets. A total of 281 significant protein expressions were exclusively registered in the UKF-NB4CDDP cell line and 73 proteins were exclusively identified in UKF-NB4 cell line. UKF-NB-4^{CDDP} and UKF-NB-4 cell lines showed overexpression of trafficking of transport in two datasets: comparison between of UKF-NB-4^{CDDP} and UKF-NB-4 cell lines and proteins exclusive identified in UKF-NB-4^{CDDP}. Exosome vesicles assay showed increase of vesicles in UKF-NB-4^{CDDP} cell lines.

Conclusions: The Orbitap MS results could shed some light on the proteins involved in inducing resistance to cisplatin in cancer cells. These data strongly suggest that exosomes potently induce properties of Nbl cells and their chemoresistance to cisplatin and reinforces the potential benefit of trafficking of biological material across membranes in cancer.

Legal entity responsible for the study: Mendel University in Brno, Czech Republic.

Funding: AZV project 15-28334A and Erasmus+: Staff Mobility - European Commission.

Disclosure: All authors have declared no conflicts of interest.

1918P Acquired resistance mechanism of osimertinib targeting EGFR in human lung cancer

V. Ciaramella, C.M. Della Corte, G. Barra, R. Di Liello, G. Viscardi, M. Orditura, E. Martinelli, F. Ciardiello, F. Morgillo

Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: Significant progress has been achieved by the development of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) targeting EGFR mutations in non-small cell lung cancer (NSCLC), however the acquisition of resistance to these agents are always the main cause of disease progression. Osimertinib (AZD9291), an oral potent drug, has developed as 3rd generation EGRF-TKIs with activities against sensitising mutations and the EGFR Thr790Met resistance mutation, which account for about 50% of the mechanisms of acquired resistance to 1st or 2nd generation EGFR-TKIs.

Methods: We developed in vitro model of acquired resistance to EGFR-inhibitors by treating human NSCLC cell lines with Osimertinib. PC9 and H1975 cell lines, which were initially sensitive to Osimertinib treatment (IC50: 0.1 and 0.5 μM, PC9 and H1975, respectively), became resistant after 8 months of continuous treatment reaching an IC50 ≈ 20 μM. This phenomenon was accompanied by visible morphological changes of the cells that acquire the typical characteristics of mesenchymal cells.

Results: We verified if this morphological change is translated into a functional change through the activation of specific pathways; protein lysates from harvested resistant cells showed higher levels of phosphorilation of EGFR, AKT and MAPK proteins than parental cell lines. We next examined whether resistant cell lines exhibit molecular changes known to occur during Epiteliali-to-Mesenchymal Transition (EMT) and we

found a significant expression of mesenchymal protein like Vimentin, Snail and Slug in Osimertinib-resistant cells as compared to with Osimertinib-sensitive cells.

Conclusions: This data, indicates the importance of EMT as a crucial event in the acquisition of resistance to third-generation EGFR-TKIs inhibitors and suggests new opportunities to design new treatment strategies in lung cancer.

Legal entity responsible for the study: Università degli Studi della Campania Luigi Vanvitelli.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1919P Interaction of oncostatin M and its receptor OSMR promotes gastric cancer progression via STAT3/FAK/Src signaling

L. Su, X. Wu, J. Li, Z. Yu, B. Liu

Surgery, Shanghai Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China

Background: Gastric cancer (GC) is one of the deadliest cancers in the world. With its lacking of early diagnostic methods, metastasis and recurrence lead to a low 5-yeard survival rate. Discovering mechanisms of gastric cancer and thus developing new strategies for gastric cancer diagnosis and therapy is urgent for clinicians and scientists. OSM receptor (OSMR) is a member of the interleukin 6 (IL-6) receptor family and transduces signaling events induced by its major ligand OSM. Interaction between OSMR and OSM plays key roles in inflammation, hematopoiesis, and development, and is increasingly being recognized as an important contributor to cancer progression. However, the role of OSM-OSMR interaction on GC is still not known.

Methods: Expression of OSM receptor (OSMR) was performed by RT-PCR, immunohistochemistry and Western Blot in gastric cancer tissues and cell lines. The malignant effects of OSM-OSMR interaction on gastric cancer cells in vitro and in vivo were examined.

Results: OSMR is highly expressed in GC tissues and cell lines, and OSMR levels are positively associated with age, T stage, tumor size, lymph node metastasis, TNM stage, Lauren Classification and poor prognosis. In GC cells that overexpress OSMR, recombinant human OSM (rhOSM) treatment promotes cell proliferation, migration, invasion, EMT in virto, as well as tumorigenesis and peritoneal metastasis in vivo. These multiple pro-malignant effects induced by OSM-OSMR interaction are mediated by activation of STAT3/FAK/Src signaling pathway. Specific inhibition of OSM-OSMR interaction by silencing OSMR expression significantly inhibits STAT3/FAK/Src activation, leading to reduced cell proliferation, migration, invasion and EMT.

Conclusions: OSM-OSMR interaction contributes to the progression of GC through the activation of t STAT3/FAK/Src signaling pathway and OSMR could be a potential target for gastric cancer treatment.

Legal entity responsible for the study: Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

Funding: This study was supported by grants from National Natural Science Foundation of China (No.81272749, No.81572798 and No.91529302), and Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20152505).

Disclosure: All authors have declared no conflicts of interest.

1920P Role of pioglitazone on gene/protein expression profile, bioenergetics and TGFβ/SMAD signaling pathway in NSCLC

R. Di Liello, G. Viscardi, V. Ciaramella, G. Barra, G. Esposito, M. Fasano, F. Ciardiello, F. Morgillo

Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: Pioglitazone is an antidiabetic drug of the Thiazolidinediones (TZDs) class that acts as ligand for PPAR-γ, a member of peroxisome proliferator activated receptors (PPARs), that regulates lipid and glucose cell metabolism. Prior studies in in vitro and in vivo models of non-small cell lung cancer (NSCLC) showed that PPAR-γ modulation affects cancer cells proliferation and differentiation but few reported studies have investigated molecular pathways involved in the potential role of PPAR-γ agonists as anti-cancer agents.

Methods: NSCLC cell lines H460 and H1299, were treated with different doses of Pioglitazone. Anti-proliferative effect was determined by MTT, colony-forming assay and flow-cytometry. Protein expression was detected by Western Blot analysis while functional mitochondrial measurements were performed with SeaHorse© stress test. Finally, cell lines samples were analyzed with a cDNA microarray assay.

Results: Pioglitazone significantly reduces cell proliferation and invasion with an IC_{50} of 1-5 μM. Analysis of apoptosis confirmed the data. Western blot analysis demonstrated a dose-related reduction of Survivin and phosphorylated proteins of MAP kinase pathway and cDNA microarray expression profiling showed a down-regulation of MAPK, Myc and RAS genes. Oxygen Consumption Rate (OCR) and proportional Glut-1 protein expression reduction of treated cells demonstrated cell bioenergetics modulation. Interestingly cDNA microarray analysis showed that also TGFβ pathway is regulated by Pioglitazione through pTGFβR1 and pSMAD3 down-regulation and consecutive up-regulation of total TGFβR1.

Conclusions: Pioglitazone regulates NSCLC cell lines proliferation and bioenergetics. Moreover, affecting TGFβ/SMAD signaling pathway, it could have a role in epitelial-to-mesenchymal transition (EMT) and cancer invasive phenotype development. These results encourage the study of PPAR-γ agonists as anti-cancer agents and promote research to explore the mechanisms beyond their activity in NSCLC models.

Legal entity responsible for the study: Università degli Studi della Campania "Luigi Vanvitelli".

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1921P Somatostatin receptor 2 expression and clinical significance in pulmonary lymphoepithelioma-like carcinoma

S. Han[1], J. Yeong[2], C.X. Lim[3], M-K. Ang[1], W.T.D. Lim[1], C.K. Toh[1], Q.S. Ng[1], D.S. Tan[1], T.K.H. Lim[2], J.H. Loh[2], A. Tanako[2], R. Kanesvaran[1], W.L. Tan[1], T. Rajasekaran[1], W. Nei[4], A. Jain[1]

[1]Division of Medical Oncology, National Cancer Centre Singapore, [2]Department of Pathology, Singapore General Hospital, Singapore, [3]Medical Oncology, National Cancer Centre Singapore, [4]Division of Radiation Oncology, National Cancer Centre, Singapore

Background: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare Epstein-Barr virus (EBV) associated cancer, histologically indistinguishable from nasopharyngeal carcinoma (NPC). Somatostatin receptor type 2 (SSTR2) is a bonafide theranostic target in neuroendocrine tumour. It is also demonstrably expressed in NPC, with autoradiography and positron emission tomography (PET). SSTR2 expression has not been reported in PLELC. In this study, we aimed to investigate SSTR2 expression and its co-localization with EBV positive PLELC cells using immunohistochemistry (IHC); and to investigate the clinical significance of SSTR2 in PLELC.

Methods: Clinical demographics including age, gender, TNM staging, EBV titre, smoking status, survival and treatment regime were collected. Archival formalin fixed, paraffin embedded (FFPE) tissue from patients diagnosed with PLELC between 2003 and 2016 at National Cancer Centre Singapore were retrieved and studied retrospectively. IHC staining for SSTR2 and Epstein-Barr encoding region in-situ hybridisation (EBER-ISH) were performed using a dual-staining technique.

Results: We report clinical data and dual staining from 20 PLELC patients. The median age at diagnosis was 56.5; 80% (16/20) of the patients were female; all non-smokers (except 3 with unknown status); 55% (11/20) of the patients had stage IV disease and the rest stage I-IIIB. High serum EBV titres were also noted in PLELC patients. Sixteen out of 20 patients (80%) stained positive for SSTR2 on IHC. SSTR2 expression co-localised with EBER positive cells. Nine out of 11 (82%) patients with stage IV PLELC stained positive for SSTR2 while 7 out of 9 (78%) stage I-III disease stained positive. Two year OS by SSTR2 status is 100% in SSTR2 negative and 65.2% (CI 35.1, 84.0) in SSTR2 positive patients, $p = 0.467$ by Log Rank Test. Two year OS by stage is 85.7% (CI 33.4, 85.7) for stage I-III and 63.6% (CI 29.7, 84.5) for stage IV disease, $p = 0.014$.

Conclusions: In PLELC, high levels of SSTR2 IHC expression is reported with co-localisation with EBV infected cells. A high proportion of stage IV patients have SSTR2 positive tumours. These patients have limited treatment options. This study opens up the possibility of using SSTR2 theranostics for these patients.

Legal entity responsible for the study: National Cancer Centre Singapore.

Funding: National Cancer Centre Singapore Research Fund.

Disclosure: All authors have declared no conflicts of interest.

1922P The role of neurotrophic factors in nerve-cancer crosstalk

A. Planken[1], L. Truu[2], K. Oselin[1], V. Valvere[1]

[1]Department of Oncology and Hematology, North Estonia Medical Centre Foundation, Tallinn, Estonia, [2]Department of Bioenergetics, National Institute of Chemical Physics and Biophysics, Tallinn, Estonia

Background: "Nerve-cancer crosstalk" has been suggested as an important mechanism of tumor growth and dissemination. Cells in the cancer microenvironment secrete biomolecules which induce neoneurogenesis, while tumor cells utilize nerves for dissemination to other organs, thru a process of perineural invasion. The molecular basis for this crosstalk has remained unclear and no targeted approaches against these mechanisms exist. The current study evaluates the neuronal effects of cancer from the viewpoint of neurotrophic growth factors (NTFs). We screened various tumors for changes in gene expression of NTFs, in order to characterize the role of these factors in human cancers.

Methods: TNTF gene expression data was assesed from the Cancer Genome Atlas (TCGA) and GTEx transcriptomic databases for 33 cancers, totaling to 9736 tumor and 8587 normal samples. Data was analyzed by Gene Expression Profiling Interactive Analysis software (http://gepia.cancer-pku.cn/index.html), as transcripts per million using the log2 FC cutoff of 1 and by ANOVA. qRT-PCR for NTFs MANF and CDNF from patients with colorectal (CRC) and breast cancer (BC) was performed. Trizol and Qiagen RNeasy Mini Kit was used for RNA extraction, cDNA was synthesized using

High Capacity cDNA RT-kit and TaqMan® qRT-PCR analysis was done with Roche LightCycler 480 system. Data was analyzed by the 2-ΔCT method and the unpaired Student t-test.

Results: The expression levels for the 3 NTFs: mesencephalic astrocyte-derived neurotrophic factor (MANF), cerebral dopamine neurotrophic factor (CDNF) and growth differentiation factor (GDF15) were profiled from the TCGA and GTEx databases. MANF RNA was upregulated in 9 different cancers, CDNF was up- in 1 and downregulated in 5 cancers and GDF15 was up- in 14 and downregulated in 3 cancers. qRT-PCR for MANF and CDNF from 52 patients with CRC showed that MANF is significantly upregulated 2-fold ($p < 0.001$) in CRC as compared to controls from the same patients, and upregulation was already seen in tumor-nearby samples. The analysis of RNA samples from 38 BC patients showed significant down-regulation for CDNF ($p < 0.05$).

Conclusions: These results support the hypothesis that NTFs indeed play a role in tumors and provide the basis for the need of further study for these factors within the cancer paradigm.

Legal entity responsible for the study: Anu Planken.

Funding: The Archimedes Foundation.

Disclosure: All authors have declared no conflicts of interest.

1924P Glutathione S-transferase M subfamily in TMZ-resistant glioblastoma cells

S.Y. Cheng[1], W-F. Chen[2], Z-H. Wen[3]

[1]Doctoral Degree Program in Marine Biotechnology, National Sun Yat-sen University, Kaohsiung, Taiwan, [2]Department of Neurosurgery, Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [3]Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan

Background: Glioblastoma multiforme (GBM), the most aggressive central nervous system cancer, is highly angiogenetic and infiltrative with high potential of resistance to chemotherapy and radio therapy. The median survival of primary GBM patients is approximately 14.6 months, despite patients receiving aggressive treatment with surgery, radiotherapy, and alkylating chemotherapy drugs such as temozolomide (TMZ). Some research results point out more than 90% of patients show no response after the second cycle of current GBM chemotherapy. Glutathione S-transferase (GST) is an important detoxification protein family that highly correlates with drug inactivation and multidrug resistance.

Methods: In our study, we generated TMZ-resistant glioblastoma GBM8401 cells (GBM8401-TMZ-R) over a 130-day period. We compared TMZ resistance level in TMZ-sensitive cell lines U87MG, A172 and GBM8401 with TMZ-resistant cell lines GBM8401-TMZ-R, T98G and U138 through cell toxicity assays and O-6-Methylguanine-DNA Methyltransferase (MGMT) expression. Moreover, we investigated the mRNA profiles of GBM8401, GBM8401-TMZ-R, and T98G cells by using next generation sequencing (NGS) for analyzing.

Results: We found GBM8401-TMZ-R cells with significantly higher MGMT expression and increased TMZ tolerance. GSTM subfamily proteins, which are located in human chromosome 1, showed different basal expressions in the GBM cell lines we tested. Surprisingly, GBM8401-TMZ-R cells showed higher GST activity and increased GSTM1 and GSTM5 protein levels than GBM8401. GBM8401-TMZ-R cells also displayed higher glycolytic capacity in a Seahorse extracellular flux (XF) analyzer. We also analyzed the expression of GST subfamilies and drug resistance-related genes by NGS.

Conclusions: From these results, we theorized that certain GST proteins may play a key role in TMZ-resistant glioblastoma cells. We hope this study will provide potential therapeutic targets for TMZ-resistant GBM patients.

Legal entity responsible for the study: National Sun Yat-sen University.

Funding: Ministry of Science and Technology, R.O.C (Taiwan).

Disclosure: All authors have declared no conflicts of interest.

1925P Combining 2D angiogenesis and 3D osteosarcoma microtissues to improve vascularization

H.M. Chaddad

Regenerative Nanomedecine, Faculté de Médecine de Strasbourg, Strasbourg, France

Background: The number of patients suffering from cancers worldwide is increasing, and one of the most challenging issues in oncology continues to be the problem of developing active drugs economically and in a timely manner. Considering the high cost and time-consuming nature of the clinical development of oncology drugs, better pre-clinical platforms for drug screening are urgently required. So, there is a need for high-throughput drug screening platforms to mimic the in vivo microenvironment. Angiogenesis is now well known for being involved in tumor progression, aggressiveness, emergence of metastases, and also resistance to cancer therapies.

Methods: In this study, to better mimic tumor angiogenesis encountered in vivo, we used 3D culture of osteosarcoma cells (MG-63) that we deposited on 2D endothelial cells (HUVEC) grown in monolayer. Combination 2D HUVEC/3D MG-63 was characterised by Indirect immunofluorescence, scanning electron microscopy, optical microscopy and mRNA expression (qPCR).

Results: We report that endothelial cells combined with tumor cells were able to form a well-organized network, and those tubule-like structures correspond to new vessels infiltrating tumor spheroids. These vessels presented a lumen and expressed specific markers, such as CD31 and collagen IV. The combination of 2D endothelial cells and 3D microtissues of tumor cells also increased expression of angiogenic factors as VEGF, CXCR4 and ICAM1.

Conclusions: The cell environment is the key point to develop tumor vascularization in vitro and to be closer to the tumor encountered in vivo.

Legal entity responsible for the study: Inserm 1260, Regenerative nanomedecine.

Funding: Agence Nationale de la Recherche, ANR.

Disclosure: The author has declared no conflicts of interest.

1926P Survival analysis of sorafenib in hepatocellular carcinoma patients with microvascular invasion after hepatectomy

Z. Zhang, Y. Huang, Y. Zhou, J. Yang, K. Hu, Z. Wang

Department of Hepatobiliary Surgery, Xiangya Hospital of Central South University, Changsha, China

Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer. The recurrence rate after hepatectomy remains high, which seriously affects the prognosis. Microvascular invasion (MVI) has been proved to be an independent risk factor for the recurrence of liver cancer. If patients with MVI can receive timely and effective treatment, it will help reduce the recurrence rate, and prolong the survival time. The aim of the study was to analyze the effect of sorafenib on the clinical outcomes in HCC patients with MVI after hepatectomy.

Methods: Patients with HCC who underwent hepatectomy and were pathologically diagnosed as MVI at the research center between January 2009 and December 2016 were retrospectively analyzed. Patients were divided into sorafenib group and control group according to whether or not sorafenib (Nexavar®) was taken after surgery. Sorafenib was administered orally, 0.4 g each time, twice daily. Follow-up was performed after hepatectomy. The recurrence-free survival (RFS) and overall survival (OS) were observed. Associated factors were analyzed using univariate and multivariate COX regression.

Results: This study included 16 patients in the sorafenib group and 33 patients in the control group. There was no significant difference in age, gender, hepatitis B surface antigen level, preoperative prethrombin time (PT), BCLC stage, preoperative a-fetoprotein level, maximum tumor diameter, and tumor number (all $P < 0.05$). The RFS and OS were both longer in the sorafenib group (both $P < 0.05$). The three-year RFS rates of the sorafenib group and the control group were 9 (56.3%) and 8 (24.2%), respectively, with significant difference ($P = 0.027$). The three-year OS rates of the sorafenib and control group were 13 (81.3%) and 13 (39.4%), respectively, with significant differences ($P = 0.006$). The results of multivariate COX regression indicated that preoperative PT and sorafenib treatment were the independent associated factors for RFS and OS.

Conclusions: The use of sorafenib after hepatectomy in HCC patients with MVI can prolong survival time.

Legal entity responsible for the study: Zhiming Wang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1927P FAM115c that upregulates proliferation and invasion under hypoxia could be a predictive biomarker for pancreatic cancer

K. Saeki[1], H. Onishi[2], Y. Oda[3], M. Nakamura[4]

[1]Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [2]Department of Surgery and Oncology, Kyushu University Hospital, Fukuoka, Japan, [3]Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [4]Department of Surgery and Oncology, Kyushu University Hospital, Fukuoka, Japan

Background: In pancreatic cancer whose microenvironment is extremely hypoxic, the analysis of signal transduction under hypoxia is thought to be important. Recently, we have found that the expression of TRP channel-associated factor family, FAM115c, increased under hypoxia in pancreatic cancer. In the present study, the biological significance of FAM115c was investigated in pancreatic cancer, and whether FAM115c could be a new therapeutic target for pancreatic cancer was evaluated.

Methods: Three pancreatic ductal adenocarcinoma cell (PDAC) lines (ASPC-1, SUIT-2, and PANC-1) were cultured under normoxia (20%O_2) and under hypoxia (1%O_2) and were used as target cells. Inhibition or overexpression of FAM115c was performed using FAM115c siRNA and plasmid, respectively. Expression of FAM115c was analyzed by qRT-PCR, western blot and immunohistochemical staining (IHC). Proliferation

was performed by MTT assay. Migration was estimated using time-lapse imaging analysis. Mice xenograft experiments were performed using BALB/c nude mice. Forty surgically resected human pancreatic cancer specimens were used for qPCR experiment and IHC.

Results: 1) Expression of FAM115c increased in PDAC under hypoxia compared to normoxia. 2) FAM115c suppression significantly increased migration and invasion in PDAC under hypoxia. 3) FAM115c inhibition significantly increased proliferation in vitro in PDAC under hypoxia. 4) FAM115c overexpression led to decreased proliferation, migration and invasion in PDAC under hypoxia. 5) Tumor volume in mice injected with FAM115c-inhibited PDAC was significantly higher than that in control mice. 6) Signaling from FAM115c was through PI3K and MAPK signaling pathways. 7) FAM115c expression was observed in all 40 patients examined by IHC. 8) In qPCR experiment FAM115c expression correlated with better prognosis in patients with pancreatic cancer.

Conclusions: These results suggest that FAM115c upregulates proliferation and invasion in pancreatic cancer under hypoxia and that FAM115c may be a predictive biomarker for better prognosis of patients with pancreatic cancer. FAM115c gene transfer may be a new therapeutic strategy for pancreatic cancer.

Legal entity responsible for the study: Graduate School of Medicine, Kyushu University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1928P Pathologic assessment following neoadjuvant immunotherapy or chemotherapy demonstrates similar patterns in non-small cell lung cancer (NSCLC)

A. Weissferdt[1], B. Sepesi[2], A. Pataer[2], N. Kalhor[1], C.A. Moran[1], W.N. William[3], X. Le[3], B. Glisson[3], F. Skoulidis[3], G. Blumenschein[3], J. Zhang[3], M. Altan[3], D. Rice[2], R. Mehran[2], J.J. Lee[4], A. Vaporciyan[2], D.L. Gibbons[3], S.G. Swisher[2], J.V. Heymach[3], T. Cascone[3]

[1]Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Thoracic/Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [4]Biostatistics, MD Anderson Cancer Center, Houston, TX, USA

Background: Neoadjuvant chemotherapy (CT) and immunotherapy (IT) are associated with features of pathologic treatment response (PTR) in NSCLC. Comparison of such features in NSCLC following neoadjuvant CT, IT or upfront surgical resection is lacking. Nivolumab (N) and/or N plus ipilumumab (NI) are being investigated in resectable NSCLC (NCT03158129). We analyzed the histopathologic patterns of CT- and IT-treated NSCLC vs untreated surgically resected tumors.

Methods: Histopathologic assessment of untreated, CT- and IT-treated NSCLC was performed (n = 30, 10/group). Hematoxylin and eosin-stained tumor sections were scored for parameters of PTR: percentage of viable tumor, fibrosis, and necrosis; inflammation, tertiary lymphoid structures (TLS), macrophages, lymphovascular invasion (LVI), cholesterol clefts (CC), giant cells (GC) and neovascularization (NV) were reported as a score (0-3). Values for each variable were expressed as a mean (± SD). Statistical comparison between two groups was calculated with unpaired two-sided t-test. Significance was defined as p-value <0.05.

Results: CT and IT were associated with significantly less viable tumor cells (p = 0.04 and p = 0.02, respectively), IT with more fibrosis (p = 0.04) and CT with more CC (p = 0.03) than untreated tumors. Trends towards higher amounts of inflammation, macrophages and CC were seen in IT-treated compared to untreated tumors. CT had a trend towards more fibrosis and GC compared with untreated NSCLC (Table).

Table: 1928P Summary of PTR parameters

	Untreated	CT-treated	IT-treated
Viable tumor	67.7%	42.4%*	37.5%*
Fibrosis	26.6%	46.6%	52.3%*
Necrosis	5.6%	11.0%	10.1%
Inflammation	1.46	1.54	1.87
TLS	0.80	1.00	1.00
LVI	0.23	0.16	0.33
Macrophages	0.12	0.94	1.17
CC	0.13	0.92*	1.04
GC	0.40	0.80	0.70
NV	0	0	0

*p-value <0.05

Conclusions: Neoadjuvant CT and IT are associated with similar histopathological changes compared to untreated tumors but with lower proportions of viable tumor and higher degrees of fibrosis. Neoadjuvant treatment is also associated with a trend towards higher amounts of inflammation, macrophages, CC and GC. Analysis of a larger cohort, including comparison of N- vs NI-treated tumors (estimated n = 80) is ongoing and will be presented in due course.

Clinical trial identification: NCT03158129.

Legal entity responsible for the study: University of Texas MD Anderson Cancer Center.

Funding: The University of Texas MD Anderson Lung Cancer Moon Shot Program, Bristol-Myers Squibb.

Disclosure: B. Glisson: Research funding to institution: Medimmune, Pfizer, ISA Pharmaceuticals, Abbvie. G. Blumenschein: Consulting/advisory role: Bristol-Myers Squibb, Bayer, Clovis, Merck, Celgene, AbbVie, ARIAD; Research funding: Bristol-Myers Squibb, Novartis, Xcovery, AstraZeneca, Adaptimmune, Immatics, Macrogenetics, Bayer, Merck, Celegene, Genentech, GlaxoSmithKline, Kite Pharma; Travel, accomodations, expenses: BMS, AbbVie, Merck. J.V. Heymach: Advisory board: Bristol-Myers Squibb; Research/Grant: Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1929P Tumor-infiltrating CD3+ lymphocytes and ICOS+ T-cells predict a favorable survival in resected esophageal squamous cell carcinoma

M.H. Hong[1], S-J. Shin[2], Y-L. Choi[3], B.C. Cho[1], H.R. Kim[1]

[1]Department of Internal Medicine, Yonsei Cancer Center Yonsei University, Seoul, Republic of Korea, [2]Department of Pathology, College of Medicine, Hanyang University, Seoul, Republic of Korea, [3]Department of Pathology, Samsung Medical Center, Seoul, Republic of Korea

Background: The prognosis of advanced esophageal squamous cell carcinoma (ESCC) is extremely poor. With an increasing potential of immune checkpoints modulators in oncology, the aim of the current study was to assess the extent of tumor-infiltrating lymphocyte (TIL) and expression and significance of various immune checkpoints in the resected ESCC.

Methods: Total 396 patients who underwent radical surgery for ESCC between 2005 and 2013 were included. Using immunohistochemistry (IHC) with tissue microarray, type of T-cells including CD3, CD8, and Foxp3 T-cell and the expression of checkpoints including programmed cell death-ligand 1 (PD-L1), programmed cell death-1 (PD-1), inducible co-stimulator (ICOS), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and mucin-dominant containing-3 (TIM-3) was manually scored. Outcome measures included recurrence-free survival (RFS) and overall survival (OS). The expression was defined as high density when the expression level was above the median value/4HPFs (high-power fields).

Results: With median follow-up period of 24.8 months, 32.6% of recurrence and 45.7% of death occurred. Patients with a high frequency of CD3+ TILs (n = 198) demonstrated a significant longer RFS (hazard ratio [HR] = 0.61, P = 0.0005) and OS (HR = 0.59, P = 0.0005). High ICOS expression group (n = 184) displayed longer RFS (HR = 0.72, P = 0.021) and OS (HR = 0.67, P = 0.007) than low ICOS expression group. Regarding PD-1 expression, the RFS (HR = 0.67, P = 0.004) and OS (HR = 0.66, P = 0.006) were significantly better in high expression group (n = 179). In multivariate Cox analyses, high CD3+ TIL and ICOS were also indicated as an independent prognostic factor for better PFS (HR = 0.59, P < 0.001 and HR = 0.64, P = 0.002, respectively) and OS (HR = 0.48, P < 0.001 and HR = 0.60, respectively) and high TIM-3 expression in immune cells was related to the shorter RFS (HR = 1.46, P = 0.020) and OS (HR = 1.54, P = 0.013). Even though various cut-off applied, the expression of PD-L1 in tumor or immune cells failed to report any association with prognosis.

Conclusions: Our analysis involving TMA and IHC of multiple immune checkpoints in resected ESCC suggests that CD3+ TILs and ICOS+ T-cells might be a favorable prognostic factor.

Legal entity responsible for the study: Min Hee Hong.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1930P Chemokine receptor CXCR7 expression, function and clinical implications in head and neck squamous cell carcinoma

M-W. Lee[1], N. Kim[2], S. Kim[2], M. Joo[2], H. Ryu[1], H.J. Lee[2]

[1]Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea, [2]Departments of Internal Medicine and Medical Science, College of Medicine, Chungnam National University, Daejeon, Republic of Korea

Background: The atypical chemokine receptor, CXCR7, has been shown to play an important role in the progression of several types of cancer. However, there have been few reports on the biological role of CXCR7 in head and neck squamous cell carcinoma

(HNSCC). In this study, we investigated the functional role of CXCR7 and the underlying molecular mechanism of disease progression in HNSCC.

Methods: We examined the association between CXCR7 expression and clinicopathological characteristics in 103 cases of HNSCC using tissue microarrays by immunohistochemical staining. The biological roles of CXCR7 and CXCR7-mediated signaling pathways were investigated in HNSCC cell through CXCR7 overexpression and treatment of SDF-1α, a major ligand of CXCR7, as well as knockdown of CXCR7 in vitro and in vivo.

Results: CXCR7 was differentially expressed in human HNSCC tissues. High expression of CXCR7 was significantly related to depth of tumor invasion ($P = 0.007$), lymph node metastasis ($P = 0.004$), and tumor stage ($P = 0.02$). Overexpression of CXCR7 dramatically enhanced cell migration and invasion in HNSCC cells in vitro, and promoted lymph node metastasis in vivo. CXCR7 knockdown using siRNA in HNSCC cells recovered the cell migratory and invasive behavior of HNSCC cells. CXCR7 overexpression also induced the epithelial-mesenchymal transition. Vimentin, Slug, and Twist were increased but E-cadherin and Ep-CAM were decreased by CXCR7 expression. Akt phosphorylation and Smad2 signaling activation were induced in HNSCC cells with CXCR7 overexpression. Treatment with a PI3K inhibitor reduced Slug and Twist levels while suppression of Smad2 signaling by siRNA reduced Akt phosphorylation, as well as Slug and Twist. Furthermore, inhibition of Smad2 decreased tumor cell migration and invasion in HNSCC.

Conclusions: CXCR7 expression was associated with an aggressive tumor behavior in HNSCC. CXCR7 contributed to cell migration and invasion of HNSCC cell through the Smad2/Akt signaling axis in vitro, and was involved in lymph node metastasis in vivo, suggesting that CXCR7 might be a therapeutic target for the treatment of HNSCC.

Legal entity responsible for the study: Hyo Jin Lee.

Funding: Cancer Research Institute of CNU.

Disclosure: All authors have declared no conflicts of interest.

1931P Assessment of PD-1/PD-L1 colocalization in hepatocellular carcinoma (HCC) using bright-field double labeling and quantitative digital image analysis

T. Mrowiec[1], F. Wilm[1], E. Frick-Krieger[1], M. Silva[1], L. Terracciano[2], I. Dussault[3], C. Ihling[1]

[1]Clinical Biomarkers & CDx Department, Merck KGaA, Darmstadt, Germany, [2]Department of Pathology, University of Basel, Basel, Switzerland, [3]Clinical Biomarkers, Immuno-Oncology, EMD Serono, Billerica, MA, USA

Background: Tumors may suppress host defenses by activating immune checkpoints (eg, the programed cell death [PD-1/PD-L1] pathway). Colocalization (CL) is a requirement for PD-1/PD-L1 interaction. PD-1/PD-L1 CL in tissue sections, as determined by immunohistochemistry (IHC), may be an indicator of PD-L1/PD-1 pathway activity.

Methods: We assessed CL of PD-L1 and PD-1 in situ by applying a novel duplex bright-field IHC technique on 49 formalin-fixed, paraffin-embedded HCC samples using digital image analysis (DIA; Definiens Tissue Studio®) to determine the percentage of single PD-1^+ and PD-$L1^+$ cells, PD-L1/PD-1 double-labeled cells, and PD-1^+ cells adjacent to ≥ 1 PD-$L1^+$ cells.

Results: All cases showed typical HCC morphology (low- to high-grade trabecular [4/49], pseudoglandular [1/49], solid [40/49], clear cell [2/49], or desmoplastic [2/49]). PD-L1 was largely observed in immune cell infiltrates. On average, 2.6% ± 3.6% (median, 1.5%) of the cells (immune + tumor) within the tumor area were PD-1^+, and 4.3% ± 5.5% (median, 1.9%) were PD-$L1^+$. There was considerable variation among samples in the number of PD-1^+ (range, 0.05%-21.2%) and PD-$L1^+$ (range, 0.2%-30.3%) cells. In 18/49 cases (37%), the number of PD-1^+ cells exceeded the number of PD-$L1^+$ cells; in 31/49 cases (63%), the number of PD-L1+ cells exceeded the number of PD-1^+ cells. PD-1/PD-L1 double-stained cells were present in 31/49 cases (63%), and 1.6% ± 4.1% (median, 0.13%) of the cells were double labeled, with considerable intersample variation (range, 0.5%-22.9%). Finally, 10.5% ± 8.03% (median, 9.4%) of PD-1^+ cells were in the immediate vicinity of a PD-$L1^+$ cell (range, 1.1%-43.3%).

Conclusions: By combining a novel duplex bright-field IHC technique with DIA, we quantitated the number/distribution of PD-1^+ and PD-$L1^+$ cells in HCC. Variation in the numbers of PD-1^+ and PD-$L1^+$ cells, and PD-1^+ cells with $\geq$1 PD-$L1^+$ adjacent cells, in HCC was seen. Future studies can use these techniques to explore the predictive potential of PD-L1/PD-1 expression in patients who are being considered for immunotherapy. Our proof of concept results suggest that the methods may also be applied for other tumors.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: T. Mrowiec, F. Wilm, E. Frick-Krieger, C. Ihling: Employment: Merck KGaA. M. Silva: Employment: Merck KGaA; Equity ownership: Merck KGaA. L. Terracciano: Consultancy: Merck KGaA. I. Dussault: Employment: EMD Serono.

1932P Pulmonary tumor thrombotic microangiopathy (PTTM): 24 case series and its criteria for pathological diagnosis

N. Sato[1], T. Tasaki[1], H. Noguchi[1], K. Irie[2], T. Nakayama[1]

[1]Department of Pathology, University of Occupational and Environmental Health, Kitakyushu, Japan, [2]Department of Diagnostic Pathology, Kitakyushu General Hospital, Kitakyushu, Japan

Background: PTTM is a fatal complication of malignancy causing progressive pulmonary hypertension (PH) or right heart failure. It is considered as a rare disease, but a growing number of cases have been reported. The pathogenesis is hypothesized that widespread cancer emboli in microscopic pulmonary arteries activate fibrocellular intimal proliferation and thrombosis. Adenocarcinomas, especially gastric ones, are the major cause. Pathological diagnosis of PTTM is apparently easy. However, microscopic pulmonary tumor emboli are a sporadic finding of cancer patients, which can resemble PTTM when followed by intimal changes and other pulmonary diseases. The increase of misdiagnosis is a concern as PTTM becomes better known. The purpose of this study is to build diagnostic criteria of PTTM.

Methods: 24 cases diagnosed as PTTM in multiple institutions were collected and classified into two groups; (1) a definite group ($n = 13$), those who had been clinically diagnosed as PH, and (2) a suspicious group ($n = 11$), those who revealed respiratory symptoms but lacked clinical assessment of PH. As a control group, autopsy cases with PTTM-like lesions but who were lacking progressive respiratory symptoms were selected ($n = 7$). PTTM-like lesions in these groups was observed and counted.

Results: The numbers of PTTM-like lesions (fibrocellular intimal proliferation and thrombi with tumor cells) in the definite and non-PTTM group were 26.5-68.8 and 0.5-5.9/cm^2 area of lung specimen. In definite cases, peripheral arterioles smaller than 150 μm in diameter were predominantly involved. In the suspicious group, 7 of 11 cases had as many lesions (25.4-68.9/cm^2) in small arterioles as in the definite cases, while the remaining 4 had as few lesions (1.3-9.6/cm^2) as the non-PTTM group. Lymphangitis carcinomatosa was seen in these 4 cases.

Conclusions: We suggest that the pathological criteria of PTTM is as follows: 1) fibrocellular intimal proliferation and thrombi with tumor cells 2) involvement of microscopic pulmonary arteries and arterioles, predominantly small ones in alveolar septa (<150 μm in diameter), and 3) the innumerable spreading of more than approximately 100 lesions/5 cm^2 area of lung specimen.

Legal entity responsible for the study: Naoko Sato.

Funding: A Grant-in-Aid for the Promotion of Occupational Health for the Post Graduate Student of the University of Occupational and Environmental Health.

Disclosure: All authors have declared no conflicts of interest.

1933P Autofluorescence: A new marker for identifying cancer stem cells (CSCs) in primary tumors

M. López Gómez[1], E. Casado[1], M. Muñoz[2], S. Alcalá[3], J. Moreno-Rubio[4], S. Salinas[2], F. Zambrana[1], A.M. Jiménez-Gordo[1], B. Sainz Jr[3]

[1]Medical Oncology/Precision Oncology Laborary, Infanta Sofia University Hospital, San Sebastian De Los Reyes, Spain, [2]Pathology, Hospital Universitario Infanta Sofía, San Sebastian De Los Reyes, Spain, [3]Biochemistry, Universidad Autónoma de Madrid, Madrid, Spain, [4]Precision Oncology Department, Infanta Sofia University Hospital, San Sebastian De Los Reyes, Spain

Background: CSCs, specifically their involvement in tumor progression and chemoresistance, represents one of the cornerstones of current cancer research. CSCs autofluorescence analysis has proven to be an accurate method to detect these cells in tumor tissues, offering an ideal setting to study the prognostic and predictive implications of this marker. More importantly, it also offers a new scenario for the development of personalized screening platforms, which could be widely universalized in the hospital setting. However, a straightforward and reproducible model for the identification and isolation of autofluorescent CSCs is still lacking.

Methods: Fresh tissues from 97 resected tumors were analyzed over 24 months. The percentage of CSCs in primary tumors was analyzed using autofluorescence, the result of Riboflavin accumulation in discrete cytoplasmic vesicles over expressing the ATP-dependent transporter ABCG2. These results were correlated with the established CSCs markers CD133 and CD90. Fumitremorgine C (FTC), a specific inhibitor of ABCG2, was used to verify the specificity of the autofluorescence observed.

Results: Autofluorescent cells (AC) in the epithelial cell compartment (EpCAM+) of the tumors analyzed were identified in 60% of the samples, primarily in gastrointestinal tumors (e.g. colon, gastric, rectal). AC also co-expressed other established CSC markers, such as CD90. Autofluorescence disappeared when tumoral cells were incubated with FTC confirming that the autofluorescence observed was ABCG2-dependent.

Conclusions: CSCs can be efficiently identified and isolated from gastrointestinal tumors using autofluorescence. The simplicity of this method would allow for its applicability to the broader scientific community in order to investigate the behaviour of CSCs in tumor progression and drug resistance. Moreover, upon their isolation, AC could be used in screening platforms to assess the chemoresistance of CSCs, thus allowing for the development of new molecular targeted therapies.

Legal entity responsible for the study: Hospital Universitario Infanta Sofía.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1934P NACC1 as a target of microRNA-331-3p regulates cell proliferation in urothelial carcinoma cells

K. Morita[1], T. Fujii[2], K. Shimada[3], H. Itami[1], K. Hatakeyama[1], M. Miyake[4], K. Fujimoto[4], C. Ohbayashi[1]

[1]Diagnostic Pathology, Nara Medical University, Nara, Japan, [2]Clinical Pathology, Nara Medical University, Nara, Japan, [3]Diagnostic Pathology, Nara City Hospital, Nara, Japan, [4]Urology, Nara Medical University, Nara, Japan

Background: microRNA (miRNA) constitutes a class of small non-coding RNAs, which are involved in cell proliferation, differentiation, and progression of tumors. miRNAs and their target molecules are utilized for molecular diagnosis of urothelial carcinoma. Nucleus accumbens-associated protein 1 (NACC1), one of several transcription factors, is constitutively expressed in the urothelium, wherein it regulates cell growth, senescence, autophagy, epithelial-mesenchymal transition. We previously reported that NACC1 is the target molecule of miR-331-3p and is associated with cell proliferation in prostate and cervical cancer.

Methods: Functional experiments involving miR-331-3p and its target molecule, NACC1, was analyzed using urothelial carcinoma (UC) cell lines, T24, UMUC6, and KU7. Quantitative reverse transcription polymerase chain reaction, and immunostaining were performed to evaluate the expression of miR-331-3p and NACC1 in UC derived from transurethral resection of bladder tumor (TUB-Bt) specimens.

Results: The MTS assay revealed that cell proliferation was significantly reduced after transient transfection of miR-331-3p precursor and/or NACC1 siRNA in UC cells. Cell senescence via cell cycle arrest at the G1 phase was induced by NACC1 inhibition. Immunohistochemistry with TUR-Bt specimens revealed that greater than 90% of both UC and normal urothelial cells were positive for NACC1 in contrast to no or limited expression in squamous cell carcinoma of the esophagus, cervix, and oral cavity. The NACC1 expression profile is not significantly associated with the pathological parameters including the pT stage.

Conclusions: The present results suggest that NACC1 regulated by miR-331-3p contributes to cell proliferation and is a new potential target molecule for the diagnosis and treatment of UC.

Legal entity responsible for the study: Nara Medical University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1935P Somatic-stem transition of tumor cells is a key link in the metastasis

N.V. Litviakov[1], M.K. Ibragimova[1], E.M. Slonimskaya[2], E.G. Skurikhin[3], M.M. Tsyganov[1], O.V. Pershina[3], I.V. Deriusheva[1], P.V. Kazantseva[2]

[1]Laboratory of Oncovirology, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation, [2]General Oncology, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation, [3]Laboratory of Regenerative Pharmacology, Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russian Federation

Background: Hypothesis: Non-stem (differentiated and progenitor) cancer cells can form metastases by performing a reverse transition to cancer stem cells (CSC) in organs under the influence of cytokines (SST - Somatic-Stem Transition). The ability to SST is acquired in the course of evolution and is ensured by ectopic expression of several stemness genes (such as SOX2, OCT3/4, MYC, KLF4, NOTCH1, NANOG ...), due to amplifications in chromosomal regions of their localization (3q, 5p, 6p, 7q, 8q, 13q, 9p, 9q, 10p, 10q21.1, 16p, 18chr, 19p). If there are no amplifications in the tumor, it is not capable of SST and will not metastasize.

Methods: Breast cancer cells of two patients were used to induce a SST. One patient had amplifications of 3q, 6q, 8q, 9q, 10q22.1 in the tumor, in which the SOX2, MYC, KLF4, NOTCH1, NODAL genes were localized. The other patient had no amplifications of stemness genes in the tumor. Magnetic separation was used to extract populations of $EpCAM^+CD44^-$ tumor cells of both patients. SST was IL6-induced. Following this, the content of $EpCAM^+CD44^+CD24^-$ CSC was evaluated via flow cytometry, the increase in the number of cells after 3 passages, and the induction of mammospheres were measured.

Results: Under the influence of IL6, CSC emerged in the population of $EpCAM^+CD44^-$ tumor cells with amplifications, the number of cells after 3 passages increased by a factor of 33, and mammospheres of 7-15 cells were induced. While SST was not induced in the population of $EpCAM^+CD44^-$ tumor cells taken from the patient with no amplifications, the number of cells after 3 passages was increased only by a factor of 5 and no mammospheres were formed. Prospective trials: in 11 breast cancer patients with stemness genes amplifications in the tumor, neoadjuvant chemotherapy (NAC) eliminated the clones with amplifications. All patients have a metastatic-free survival. 11 patients had no amplifications and they did not undergo NAC. All patients had100% survival. 9 patients had no amplifications of their stemness genes before the treatment, and NAC induced their occurrence, 90% of the patients developed metastases.

Conclusions: We showed an SST in $EpCam^+CD44^-$ tumor cells, the importance of amplifications of stemness genes loci for its induction, and the importance of amplifications of stemness genes for metastasis.

Legal entity responsible for the study: Cancer Research Institute, Tomsk National Research Medical Center RAS, Russia.

Funding: The Russian Science Foundation grant 17-15-01203.

Disclosure: All authors have declared no conflicts of interest.

1936P Survival effect of lncRNA-X expression in EGFR-mutant adenocarcinoma

Y. Nakano[1], K. Isobe[1], A. Kakimoto[1], H. Kobayashi[1], K. Kaburaki[1], G. Sano[1], S. Sakamoto[1], Y. Takai[1], N. Tochigi[2], T. Mikami[3], A. Iyoda[4], S. Homma[1]

[1]Respiratory Medicine, Toho University Medical Center Oomori Hospital, Tokyo, Japan, [2]Surgical Pathology, Toho University Medical Center Oomori Hospital, Tokyo, Japan, [3]Pathology, Toho University School of Medicine, Tokyo, Japan, [4]Chest Surgery, Toho University Medical Center Oomori Hospital, Tokyo, Japan

Background: Long non-coding RNAs (lncRNAs) are RNAs longer than 200 nucleotides that do not code for protein. Recently, the lncRNA-X was implicated in physiological and pathological processes such as proliferation, invasion, and metastasis. However, the roles of lncRNA-X in epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma are poorly understood.

Methods: qRT-PCR was used to measure lncRNA-X expression in 5 lung cancer cell lines (A549, H1299, PC9, H4006, H1975). Non–small cell lung cancer (NSCLC) cells with knockout of lncRNA-X were generated with a CRISPR-Cas9 system and used to investigate the effect of lncRNA-X on gefitinib-induced cell death in an MTT assay. We studied 21 patients with recurrent postoperative EGFR-mutant lung adenocarcinoma (exon 19 deletion in 11, L858R in 8, G719C in 2) treated with gefitinib during the period from January 2008 to January 2018. Relative quantification of lncRNA-X expression on real-time PCR analysis of formalin-fixed paraffin-embedded slides of surgical specimens was used to determine lncRNA-X expressions in tumors and adjacent normal tissues.

Results: lncRNA-X expression was greater in the cell lines harboring EGFR exon 19 deletions and L858R (PC-9, H4006, H1975) than in those without EGFR mutation (A549, H1299) ($p < 0.001$). H1299 cells with lncRNA-X knockout were more sensitive to gefitinib. lncRNA-X expressions were significantly greater in NSCLC tumors than in adjacent normal tissues ($p < 0.01$). Patients with high lncRNA-X expression in tumors had significantly shorter progression-free survival (PFS) after gefitinib therapy and overall survival than did those with low expression (median PFS: 304 vs 1125 days, $p = 0.046$; MST: 1271 vs 1876 days, $p = 0.014$).

Conclusions: lncRNA-X expression in EGFR-mutant adenocarcinoma is associated with shorter overall survival and shorter PFS after gefitinib therapy.

Legal entity responsible for the study: Toho University School of Medicine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii683–viii688, 2018
doi:10.1093/annonc/mdy276

CANCER NURSING: CANCER NURSE ROLES

CN1 Evaluation of an education programme on compassion fatigue: Turkish oncology-haematology nurses' perspectives

T. Pehlivan, P. Güner
School of Nursing, Koc University Hospital, Istanbul, Turkey

CN2 The efficacy of nurse-led clinic

C. Allan
Oncology and Metabolism, Weston Park Hospital Cancer Research Centre, Sheffield, UK

CN3 Introducing the role of the advanced clinical practitioner in haematology and oncology

M.N. Fowler
Oncology and Haematology, Heartlands Hospital-Heart of England NHS Foundation Trust, Birmingham, UK

CN4 Nurse navigators in thoracic oncology: A qualitative study of German nurses' attitudes to nursing role expansion

L. Hagelskamp[1], S. Berger[2], M. Villalobos[1], M. Thomas[1], M. Wensing[2], C. Mahler[2]
[1]Thoracic Oncology, Thoraxklinik Heidelberg, Heidelberg, Germany, [2]General Practice and Health Services Research, University Hospital Heidelberg, Heidelberg, Germany

CN5 Patients: Power sources for cancer nurses

C. Beisel

Paediatric Oncology, Haematology and Immunology, Heidelberg University Hospital, Heidelberg, Germany

Background: It's obvious that cancer nurses have to deal with a lot of different burdens during their everday work. These burdens are obvious and very well known. If one has an overall view at cancer nursing staff at a ward one will recognise two huge groups: Beginners, which passed their exam recently and colleagues, that are working with cancer patients for more than 15 years and often until retirement. The question which arises is therefore why can these "senior nurses" resist these strains and stay healthy?

Methods: Study of literature focussing on • spiritual, physical and psychological needs • groups (especially cancer nurses) that are known for be on stress • published European Standards regarding physical burden at workplace Own empiric cases from working life, which had a lasting influence Informal interviews with colleagues.

Results: The intensity of work has increased in most clinics: pressure on time, more severe ill patients, complexicity of treatment. The working conditions deteriorated considering payment, job confidence, team work and support. Nevertheless, cancers nurses do stay in their workplace for a very long time because of • spiritual background, rituals and general upbringing • resilience • inspiring contacts and interaction with their patients.

Conclusions: With all the burden of and to the care of the patients and their relatives: it is more than coping with their needs. They also give back enormous energy, provided one give space to the moving moments and allow it to draw strength from this particular source.

Legal entity responsible for the study: Cordula Beisel.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

CN6 BRAF/MEK-inhibition for patients with metastatic melanoma: Towards patient-centered care

J.J. Koldenhof[1], S.C. Vervoort[1], C.A. Nierop[2], K.P. Suijkerbuijk[1]

[1]Medical Oncology, University Medical Center Utrecht, Utrecht, Netherlands, [2]Master Advanced Nursing Practice, HU University of Applied Sciences, Utrecht, Netherlands

Background: The incidence of melanoma – the deadliest form of skin cancer - is steadily increasing. Over the last few years, treatment options for inoperable or metastatic melanoma have increased. Treatment with BRAF/MEK-inhibitors (BMi) induces fast responses in the large majority of patients with BRAF-mutant melanoma. As a result, BMi are often used as a palliative treatment for patients with aggressive metastatic melanoma. A successful palliative treatment - a treatment in which life is prolonged and the patient experiences an acceptable quality of life - requires intensive support. Nursing interventions are aimed at empowering people and helping them to achieve, maintain or (re)acquire their independence. This Dutch study was set up to collect building blocks in order to develop an evidence-based nursing intervention that supports patients during palliative treatment with BMi.

Methods: Using the van Meijel model, a problem analysis, a literature review, a patient needs analysis and a current practice analysis, were performed. A literature search was performed to collect available, appropriate interventions. Nationwide questionnaires – in patients as well as in nurses - were used to gain insight into patient needs and the current practice.

Results: The problem analysis and results of the literature review showed that patient education, disease and/or treatment related symptoms and support with self-management are key components during treatment with BMi in adult patients with metastatic melanoma. When considering nursing care, the available literature focusses on promoting adherence in particular.

Conclusions: Treatment with BMi is a life-prolonging treatment. As a result, medication adherence seems more important in relation to symptom burden and quality of life than to the effectiveness of the treatment alone. In conclusion, future nursing interventions should not only focus on treatment adherence, but also on quality of life and quality of dying, with respect to the patient's needs and wishes.

Legal entity responsible for the study: Jose Koldenhof.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN7 Perceptions of rural nurses extending their role to administer chemotherapy

Q. Alnasser[1], K. Cameron[2], J. Prouse[3]

[1]Oncology/Nursing Development and Saudization, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [2]Nursing Development, Adelaide University, Adelaide, Australia, [3]Oncology Department, Royal Adelaide Hospital, Adelaide, Australia

Background: Nurses in rural regions of South Australia are currently administering chemotherapy in centres where this was not previously the case. To prepare these nurses; a state-wide chemotherapy education and assessment programme was implemented in 2013. This research project explored the perceptions of nurses working in level-one rural centres administering low-risk chemotherapy protocols. The study explored how registered nurses who administer chemotherapy in low-risk chemotherapy services in rural SA perceive their expanded roles and whether they felt equipped with the knowledge and skills required to undertake them.

Methods: This is a qualitative study. Individual interviews were conducted with eight registered nurses working in low-risk chemotherapy centres in rural settings. The data analysis methods were based on critical social theory.

Results: Four main categories of findings are identified: 1) role extension, preparedness and self-confidence; 2) chemotherapy services in rural areas; 3) power relationships, referrals and knowledge sustainability; and 4) communication with other cancer settings and professionals. Overall, participants highly valued the service as valuable support for rural patients with cancer, but they identified areas of concern, including the rural nurses' roles in cancer care, the need to maintain knowledge and skills and to establish their role in referral and follow-up processes.

Conclusions: Participants expressed their perceptions of their role. Then, through critical theory, their voices were revealed, expressing their needs and suggestions for changing and improving their role and the service.

Editorial acknowledgement: Way With Words.

Legal entity responsible for the study: University of Adelaide.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN8 AYA cancer nursing, an emerging sub-speciality: The first book about AYA cancer nursing, edited and authored by nurses

S. Smith

Nursing and Clinical Services, Teenage Cancer Trust, London, UK

Background: During the last twenty years, adolescents and young adults with cancer have gained increased attention in healthcare. The body of knowledge is growing accordingly. Nurses who have led the way amongst the now widening circle of professionals engaged in providing specialist care for young people with cancer are now ready to describe their contributions within education, clinical nursing, rehabilitation, research and leadership.

Methods: To provide healthcare professionals with knowledge about the distinct developments made within AYA cancer nursing internationally a book entitled Nursing Adolescents and Young Adults with Cancer. Developing knowledge, competence and best practice is under production.

The book is based on international collaboration between the publisher Springer, the two editors and an authorship of nurses with thorough knowledge and expertise in AYA cancer care from the Netherlands, Belgium, Australia, Ireland, Norway, Denmark and England.

Results: The book will be published by Springer in 2018. It contains chapters describing 1) The history of the speciality and AYA nursing competence development, 2) Approaches, Interventions and Innovations in AYA cancer nursing and 3) Aspects and challenges for future AYA cancer nursing.

Conclusions: The authors offer insights into the development of AYA cancer care; why it matters; how it should be delivered; and how it might be done better – and with recognition of the unique needs and wants of each young person at the centre of it all.

Legal entity responsible for the study: Publishing company Springer.

Funding: Publishing company Springer.

Disclosure: The author has declared no conflicts of interest.

CN9 Nurse led follow-up for CML patients on oral cancer treatment

S. De Wilde, J. De Munter, M. Quaghebeur, D. Mazure, A. De Pauw, B. Casteels
Hematology, University Hospital Ghent, Ghent, Belgium

Background: Chronic myeloid leukemia (CML) is a bone marrow disorder accounting for 15% of newly diagnosed leukemia in adult patients (Rychter A et al. 2017 & Trivedi D et al. 2014). The introduction of tyrosine kinase inhibitors (TKIs) has changed the CML treatment significantly. Patients' concerns have shifted from reduced life expectancy to management of long-term toxicities and improvement of quality of life (QoL) (Isfort S & Brümmendorf TH 2018). In 2016 Moulin et al. showed that closely monitoring patients affects adherence. Poor adherence is associated with greater overall health care utilization and medical costs in CML (Jabbour EJ et al. 2012). An increase in the patient health is expected from improvements in adherence.

Methods: After receiving information from the doctor, patients remember approximately half of the information provided (Hillen MA et al. 2015). The hematology department in UZ Ghent has an interdisciplinary approache to CML patients. In a nurse led consultation patients who start with TKIs receive additional written information. The purpose is to reduce the information gap and manage patients concerns. Over time the nurse led consultation transforms to monthly telephone follow-up. This includes the assessment of the patient's condition, adverse events (AEs) and the influences on their QoL. Individual nurse led consultation supports a solid health care provider-patient relationship, offers patient tailored care and is ideally placed to detect psychological and social problems. Referral to other health care providers must always be based on shared decision making.

Results: The aim is to educate the patients and offer psychosocial support. By creating a strong health care provider-patient relationship the goal is to make sure the patient feels free to talk about any issues. This also empowers the patient, improves adherence and helps to detect and control AEs prematurely.

Conclusions: An interdisciplinary approach and establishing a care pathway is a necessity to streamline the patient treatment process. A more structured questionnaire is needed to improve the telephone nurse led follow-up and the handover to the doctor. After implementing such a structured tool the effectiveness of the project must be reviewed by using questionnaires that assess the adherence and QoL.

Legal entity responsible for the study: Universtiy Hospital Ghent.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN10 Introducing a new role in cancer care, coordinating contact nurses: Patient-reported evaluation

B. Westman[1], H. Ullgren[2], L. Sharp[3]
[1]Stockholms Läns Landsting, Regional Cancer Center Stockholm Gotland, Stockholm, Sweden, [2]Theme Cancer/ Regional Cancer Center, Karolinska University Hospital-Solna, Stockholm, Sweden, [3]Cancer Care Improvments, Regional Cancer Center Stockholm Gotland, Stockholm, Sweden

Background: According to the Swedish National Cancer Plan, every cancer patient is entitled to supportive care strategies such as a contact nurse (CN) and a written care plan (IWCP). The National Cancer Plan also highlights the importance of patient's right to actively participate in care planning and decision-making regarding their care. A new cancer nursing role, coordinating contact nurses (CCN)s, was initiated in the Stockholm-Gotland region, Sweden 2015. The CCNs, with an overarching leading role in the cancer process, work on a regional level with co-operation between different care-givers aiming to reduce inadequate continuity and fragmentation in cancer care and improve person-centered care. The CCNs are also supposed to support CNs with implementation of IWCPs and routines for safe handover procedures where the patient actively is involved in the process. We have evaluated the impact of CCNs from a patient perspective with baseline and follow-up data. The aim was to evaluate the usefulness of the new role from the patients' perspective.

Methods: Data was collected through a project-specific questionnaire (including questions on information exchange, continuity, patient involvement, collaboration and communication) from patients diagnosed in 2014 ($n = 869$), before the implementation of the CNN role, and follow-up data from patients diagnosed in 2016 ($n = 1003$).

Results: Patients report significantly higher access to CN (2014 53%, 2016 66%, $p = <0.0001$) and IWCP (2014 40%, 2016 54%, $p = 0.0001$) after the introduction of the CCN role. Patients also report higher satisfaction with their involvement on decisions in care (2014 29%, 2016 34%, $p = 0.042$).

Conclusions: Experiences so far are that the CCNs have a unique opportunity to impact and improve cancer care which has been difficult previously for the clinical staff.

Legal entity responsible for the study: Bodil Westman, Regional Cancer Centre, Stockholm Gotland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN11 The role of the nurse in the detection of geriatric frailty and the risk of chemotherapy toxicity in elderly patients with cancer: Preliminary study

E. Mahía[1], G. Simó[1], E. Heras[2], M. Pascual[2], F. Cobo[1], J. Pujadas[1], S. Albiol[1]
[1]Oncology-Hematology Unit, Servei Andorra Atenció Sanitaria, Escaldes-Engordany, Andorra, [2]Internal Medicine Service, Servei Andorra Atencio Sanitaria, Escaldes-Engordany, Andorra

Background: The increase in life expectancy along with the higher incidence of cancer with age motivates the need for a model of care to optimize the management of elderly patients with cancer and avoid complications associated with treatment. We used two questionnaires: the G8 Oncodage that screens frail elderly patients and the Hurria that predicts the risk of chemotherapy toxicity; both are vulnerability screening tools that help establish the most appropriate treatment in oncogeriatric patients. We present our initial experience with this approach in a single institution in Andorra.

Methods: From November, 2017 to April, 2018, the oncology nurse evaluated twenty-six patients with cancer $\geq$70 years of age. The tools used are short questionnaires (8 items in the G8 and 16 items in the Hurria), clear, simple and quick to perform. They are always used before starting the treatment. Patients with scores G8 $>$ 14 and Hurria $<$ 6 are considered fit for standard oncologic management. Patients with scores G8 $\leq$ 14 or Hurria $\geq$ 6 are considered at risk of vulnerability and then an integral geriatric assessment (CGA) is performed. The care plan is established by a multidisciplinary care team.

Results: Twenty-six patients were evaluated, with a majority of males (81%) and the average was 75.9 years (range 70-86 years). A score G8 $\leq$ 14 or Hurria $\geq$ 6 occurred in 24 (92.31%) and 22 (84.62%) patients, respectively, 5 were women and 19 men. Two patients with low risk of chemotherapy toxicity (1 woman and 1 man), 15 patients with moderate risk (3 women and 12 men) and 7 at high risk (1 woman and 6 men) were detected. 24 patients were referred to the gerontologist for CGA. Half of patients received a modified treatment.

Conclusions: According to preliminary results, the use of the two questionnaires would allow to select those patients who could benefit from CGA and a personalized treatment. The study proposes a model of nurse-led oncogeriatric screening that could offer objective and useful information in the decision making of the therapeutic plan in elderly patients with cancer. Due to the limited number of patients included, it is necessary to continue the longitudinal and prospective study to draw definitive conclusion.

Legal entity responsible for the study: Servei Andorra Atenció Sanitaria.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN12 Systemic anticancer therapy administration safety

S. Toland[1], A. Simons[2]
[1]Oncology, Birmingham City University, Birmingham, UK, [2]Birmingham City University, Birmingham, UK

Background: SACT safety in administration and waste disposal Our original article explored the immediate adverse effects experienced by nurses during the administration of systemic anti-cancer therapy (SACT), specifically cytotoxic chemotherapy, and whether closed systems are being used tominimise exposure risk. Many SACT agents are known to be carcinogenic, teratogenic and mutagenic and this has led to concerns relating to the increased number of healthcare workers potentially exposed to these agents.

An anonymous online survey was designed, made up of four questions, to elicit whether adverse effects were experienced by nurses during preparation, administration or following administration of chemotherapy. A total of 46% of respondents stated that they experienced some form of adverse effect either during preparation, administration or following administration of SACT. More formal research is required in this area to explore the relationship between exposure to SACT and perceived adverse effects in healthcare workers administering SACT. As a follow up to this survey, we are going to develop a further survey to elicit healthcare professionals awareness of SACT exposure risk, education / training provision and current practices in relation to SACT administration and waste disposal.

Methods: In our original study, a short anonymous online survey was designed made up of four questions to elicit whether adverse effects were experienced by nurses during preparation or administration or following administration of chemotherapy. This was distributed via social media and networking contacts. For our follow-up survey, we will replicate this method, including questions about awareness, education / training and current practice in relation to SACT administration and waste disposal

Results: of the original study were obtained through the questionnaire responses which were analysed and presented using a quantitative approach. The follow up survey will require a mixed methods approach to analysis to elicit greater depth of information from participants.

Conclusions: Following quantitative analysis of our original survey, we concluded that further research was required in this area, hence the need for additional data collection via a further online survey.

Legal entity responsible for the study: Samantha Toland and Alison Simons.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN13 Increasing incidence and prevalence of immune-related adrenal insufficiency in patients with cancer: The role of the nurse practitioner for early recognition and management

C. Roth, M. Labots, A.J. Eertwegh

Medical Oncology, Vrije University Medical Centre (VUMC), Amsterdam, Netherlands

Background: Immune checkpoint inhibitors have improved the outcome of patients with advanced cancer significantly over the last decade. Disadvantageous effects of these novel treatments include auto-immune toxicities, named immune-related adverse events (irAEs), that most commonly affect the skin, gastrointestinal tract, liver and endocrine glands. Immune-related endocrine toxicities that involve the pituitary gland or adrenal glands may cause adrenal insufficiency (irAI), which can be life-threatening if not early recognized and managed.

Due to the expanding number of novel immunotherapies and indications, the number of patients with irAI will increase. We report a clinically applicable algorithm, with a key role for the nurse practitioner (NP), to manage irAI and to improve safety using a system-focused approach.

Methods: A collaboration between NP, oncologists and endocrinologists, taking input and perspectives from patients into account, was used to develop consensus regarding irAI management. Based on literature, institutional experience and group consensus, a clinically applicable algorithm was created.

Results: Team members were educated on algorithm application and to improve safety. The NP was the first point of call and coordinated collaboration between patient, medical specialists and family physician. The NP was appointed a key role for patient education and information. Patients were educated to recognize symptoms of adrenal insufficiency and react promptly by increasing the dose of the corticosteroid substitution therapy. Patients were encouraged to contact the NP in case of problems or questions about the prophylactic dose of corticosteroids for stressful events.

Conclusions: Due to the increased use and the long-term efficacy of immune checkpoint inhibitors in patients with cancer, the incidence and prevalence of immune-related adrenal insufficiency (irAI) will increase. The here reported algorithm provides a streamlined approach for the management of irAI that is expected to improve safety and quality of life of patients.

Legal entity responsible for the study: Van den Eertwegh AJM.

Funding: Has not received any funding.

Disclosure: M. Labots: Advisory board: BMS. J. Eertwegh: Advisory boards: BMS, Merck, Roche, Novartis, Amgen; Study grant: Roche. All other authors have declared no conflicts of interest.

CN14 Experiences from a new advanced cancer nursing role in Sweden: An analysis based on EONS Cancer nursing education framework using the Delphi method

H. Ullgren

Theme Cancer/Regional Cancer Center, Karolinska University Hospital, Stockholm, Sweden

Background: A new advanced nursing role - Coordinating contact nurse (CCN) were implemented as a pilot in 2015, aiming to improve care transitions, collaboration and communication between different teams, as well as strengthening the nurses and clinicians in the whole team. The CCNs has a regional role over one patient trajectory within the Stockholm-Gotland region. When interviewing patients at start of the project, many patients wished for more support regarding coordination and felt they had to be responsible themselves for important clinical information exchange. Collaboration and communication between the teams within the acute hospitals different disciplines, as well as acute and palliative care (PC) were sub-optimal, and it affected for example emergency admissions from PC to acute care. A baseline survey was performed before implementation of the CCN project. It showed that some of the supportive care resources were accessible for only half of the patients.

Methods: Experiences from this new role are currently analyzed, based on the 8 modules included in EONS Cancer Nursing Education Framework. Data is analyzed using the Delphi process including different groups of staff and patient representatives.

Results: Preliminary results show that the CCN role cover all 8 modules in the framework and indicate that the CCN role fulfill the criteria described for advanced cancer nursing roles. The practice competencies have been useful both in recognizing what cancer nurses do, and highlights areas in need of development.

Conclusions: Patient-reported evaluation of the CCN role is needed and ongoing. Preliminary data shows significant improvement in areas such as perceived information about self-care and access to supportive care. This new advanced cancer nursing role could contribute to improved experiences and outcome for cancer patients. If formally established, the CCN role could be an important clinical career opportunity for Swedish cancer nurses.

Legal entity responsible for the study: Helena Ullgren, Regional Cancer Centre Stockholm Gotland, Sweden.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

CN15 Opinions and experiences of patients receiving oral chemotherapy: A qualitative study

S. Kutlutürkan[1], Ö. Yurtal[2], K. Kirca[3]

[1]Nursing, Gazi University, Ankara, Turkey, [2]Nursing, Gazi Üniversitesi Sağlik Uygulama ve Araştirma Merkezi Gazi Hastanesi, Ankara, Turkey, [3]Nursing, Kirikkale University, Kirikkale, Turkey

Background: The importance of oral chemotherapy in cancer patients is increasing day by day. Oral chemotherapy drugs provide many advantages in terms of social and economic. The desired impact in oral chemotherapy treatment can be achieved with patient adherence. The aim of this study was to investigate the opininons and experiences of who are receiving oral chemotherapy.

Methods: This research was designed as a qualitative study. The study is conducted on eighteen patients who were admitted to the oncology clinic of a university hospital in January 2018. The patients who agreed to participate in the study were included in the study. There is no limitation in the type of cancer disease in the practice of the study. In this study a semi structured interview form was used, this form created as a result of review of the literature. Data were collected through face-to-face individual interviews. All interviews were recorded with voice recorder with permission from the patients. The data obtained from the interviews were transcripted after each interview and evaluated with the thematic content analysis method.

Results: As a result of the content analysis identified five main themes. These themes were prescribing oral chemotherapy, administering oral chemotherapy, side effects and control of oral chemotherapy, approach of health professionals, support of family and relatives. In the interviews, the majority of patients were using capecitabine as oral chemotherapy. Patients stated that health professionals for drug use may differ in their recommendations. patients stated that they had problems such as constipation, nausea / vomiting, change of taste, fatigue and mouth instability, and that information on side effect control was made by the physician at the beginning of the treatment.

Conclusions: Interdisciplinary approaches are needed to increase compliance of patients with treatment, to monitor treatment side effects and to ensure safe use of medications. It is necessary for nurses to take an active role in patient education and counseling in order to determine the weaknesses and opportunities for recovery of patients during oral chemotherapy.

Legal entity responsible for the study: Sevinç Kutlutürkan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN16 Introducing cancer nurse led consultations to improve sexuality & fertility outcomes for adolescents and young adults (AYAs) with an hematological disease

J. De Munter[1], S. De Wilde[2], M. Quaghebeur[2]

[1]Cancer Centre, Ghent University Hospital, Ghent, Belgium, [2]Hematology, Ghent University Hospital, Ghent, Belgium

Background: With improving survival rates among AYAs with cancer, sexuality and fertility are important quality of life (QoL) concerns before, during and after treatment. Healthcare providers aren't always knowledgeable about infertility risks associated with prescribed therapies. Cancer nurses are often the first professionals to identify and address sexuality concerns. Different barriers are the reason of not addressing sexuality concerns and fertility preservation options prior treatment. It is crucial that AYAs are well informed prior treatment to support them in their decision-making about fertility preservation options.

Methods: An Interdisciplinary team developed an evidence-based care pathway for Hodgkin's disease. Healthcare providers from different staffs shared knowledge, expertise and skills to have positive impact on young patients survivorship outcomes. Standard infertility counselling was included prior to treatment for AYAs and a nurse led consultation prior therapy gives the opportunity to discuss important topics such as sexuality.

Results: Implementation a care pathway increased the awareness about discussing sexuality and fertility preservation options among all healthcare providers within the haematology department. Collaboration between fertility specialists, physicians and cancer nurses will improve reproductive outcomes in AYA cancer care. Systematic feedback after fertility preservation procedures is helping to reduce reproductive concerns. Discussing sexuality during a nurse led consultation results in a better understanding of the effects of the disease and treatment and will improve QoL.

Conclusions: Cancer nurses have a key role in discussing sexual concerns. A cancer nurse led consultation through the whole treatment process allows patients the opportunity to discuss sexual issues and concerns. Knowing that they can have their questions answered, makes them feel more confident and comfortable during treatment. Multidisciplinary care pathways are needed to establish systems to ensure that fertility is adequately addressed and comprehensive fertility counselling is offered to all AYAs prior to therapy and during survivorship.

Legal entity responsible for the study: University Hospital Ghent.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN17 Standardising the psychosocial assessment of oncological patients at Donostia university hospital

E. Uranga, A. Valverde, M.A. Landa, M.J. Esnaola, L. Basterretxea, G. Agirre, O. Aizpurua, A. Barrio, M. Centeno, I. Delgado, G. Jauregui, L. Moreno, M. Murguiondo, J. San Francisco, H. Telleria

Oncology, Hospital Donostia, San Sebastian, Spain

Background: A cancer diagnosis often causes an emotional impact with signs of anxiety, uncertainty and subjective discomfort. It is necessary to identify and assess emotional discomfort to offer quality treatment articulated around the patient and his / her demand. The design of a questionnaire that is easy to use and understand, allows the detection of patients susceptible to referral to the Psycho-oncology Unit (POU) The POU consists of a Psychiatrist and a Nurse with specific training in Psycho-oncology.

Methods: Prepare a PAQ that includes: Evaluation of emotional distress assisted by visual analogue scales (VAS); Modified Gijón scale (sociofamilar assessment scale); previous use of psychoactive drugs - Include PAQ in the first nursing visit - Quick referral to POU - Interview with psycho-oncology nurse - Valuation, diagnosis and treatment planning by POU - Data recording.

Results: Patients with a positive PAQ are referred to the POU where the liaison nurse performs an interview with the patient and / or family. The nurse collects data on psychobiography, oncological disease, psychic sphere, frequent affections, previous contacts with psychologists / psychiatrists and treatments with psychoactive drugs. The POU will offer the patient the most appropriate resource for their needs (Psychotherapy, Psychopharmaceuticals, Social Work Service).

Conclusions: The inclusion of the PAQ in the first visit of nursing allows the detection and early treatment of disorders in the psychosocial area. We achieve an optimal use of resources, a greater adherence to the proposed oncological treatment, alleviate problems that are found throughout the oncological treatment and improve the quality of life of our patients by reducing emotional discomfort.

Legal entity responsible for the study: Hospital Universitario Donostia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN18 Are there differences between nurses' and patients' perceptions of cancer patients' quality of life in Greece?

M. Lavdaniti, E. Gogou, G-C. Karagiannidou, M. Delibaltidou, E. Zioga, K. Marmara, E.C. Fradelos

Nursing, Alexander Technological Educational Institute, Thessaloniki, Greece

Background: Cancer and its treatment affect negatively patients' quality of life. Nurses and their perceptions about patient quality of life should be vital in order to provide high-quality care and increase patients' QoL. The aim of this study is investigate nurses' and patients' perceptions about cancer patients' quality of life.

Methods: This was a non-experimental and descriptive study. It was conducted in two large hospitals in a major Northern Greek city. The subjects were 50 pairs of cancer patients and their nurses. Patients and nurses had completed the Greek Version of the World Health Organization quality of life (WHOQoLBREF) questionnaire, separately

Results: The majority of patients was female (50%) with mean age 59.8 years (S.D. 15.1). Regarding nurses' demographic characteristics 88% was female with mean age 45.8 years (S.D. 8.8). According to the patients' perceptions the mean of physical health domain was 14.8 (S.D. 3.2), psychological domain was 15.1 (S.D. 2.6), social relationships domain was 14.2 (S.D. 3.7) and environment domain was 15.7 (S.D. 2.3). The corresponding scores of nurses were 12.6 (S.D. 1.9), 12.9 (S.D. 2.6), 13.1 (S.D. 3.4), 14.1 (S.D. 2.9) respectively. Wilcoxon test was shown statistically significant differences between patients' perceptions and nurses' perceptions in 3 domains (physical health ($p = 0.001$), psychological domain ($p = 0.001$), environment domain ($p = 0{,}003$) except from social relationships. Specifically, the quality of life was scored lower by nurses than the corresponding drawings of patients. Additionally, correlation was found between the time which nurse spends with patients and psychological domain ($r = 0.313$) and environment domain ($r = 0.372$) respectively.

Conclusions: There were differences between Greek cancer patients and their nurses about cancer patients QoL. The results of the present study stress the need for further research in order to increase nursing understanding about patients' life and enhance holistic nursing approach.

Legal entity responsible for the study: Alexander Technological Educational Institute-1, Research Laboratory "Care in Adult Cancer Patients".

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN19 How an empowerment program can touch cancer survivor's life by improving post-traumatic growth?

Y.S. Uzar Ozcetin

Psychiatry Nursing, Hacettepe University Faculty of Nursing, Ankara, Turkey

Background: Cancer experience can cause traumatic symptoms with higher levels of stress. Although cancer has been traditionally seen as a destructive illness, in recent years, this perspective has been abandoned, and it is being argued that coping with cancer and developing growth is possible. Research in this area has supported this new perspective, and the results have shown that cancer does not always contain traumatic effects and people can also have positive attainments during this process. Re-meaning of life during cancer process enables posttraumatic growth (PTG), which improves interpersonal relations, inner resurgence, and deeper spirituality.

Methods: Researcher has studied on an empowerment program in her PhD thesis and keeps working on this area. Hence, the aim in this study is to point out the effects of an empowerment program to improve PTG of cancer survivors. Literature review and sharing experience in such works.

Results: Having resilience in cancer experience help people to understand the value of life, find new meanings, determine the priorities in life, and reach spiritual well-being. Re-meaning of life during cancer process enables posttraumatic growth, which improves interpersonal relations, inner resurgence, and deeper spirituality. In this regards, using an empowerment program can be an effective way in helping the participants recognize the nature of the problem in their life, and created a safe and therapeutic environment to improve their social skills. Also, such programs refer to the use of not only intrinsic sources, such as self-efficacy and self-esteem, but also extrinsic ones, such as social support and social coherence. On the other hand, providing supportive activities/programs are valuable to help them learn from others who had similar experiences; in this way, they can feel understood, accept the process with its positive and negative consequences, and have better coping strategies.

Conclusions: Empowerment program could improve both PTG in cancer survivors and nurses caring for cancer survivors can use such programs to improve PTG and resilience, in addition to the usual medical care in cancer. By this way, cancer survivor can have enough psychological support which usually forgotten among routine medical care.

Legal entity responsible for the study: Yeter Sinem Üzar Özçetin.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

CN20 Organising a general oncology nursing outpatient clinic

C. Lundgren[1], A. Lagerquist[1], M. Högman[2], U. Östlund[3]

[1]Oncology, Sjukhus Gävle, Gävle, Sweden, [2]Medical Sciencies, Uppsala University, Uppsala, Sweden, [3]Centre for Research and Development, Region Gävleborg, Gävle, Sweden

Background: The complexity of living with, being treated for or dying from cancer present numerous issues and needs for patients and their families. Many those are appropriately dealt with based on oncology nursing. Despite this most general oncology outpatient clinics in Sweden are physician-led. The development of general nurse-led cancer care services has been suggested to improve the care of cancer patients. Consequently a general oncology nursing outpatient clinic has been implemented. The aim of this study was to describe the feasibility of organizing an oncology nursing outpatient clinic, its implementation and outcomes.

Methods: This study had a descriptive multi methods design. Qualitative data to describe nurses, physicians and managers perspectives was collected and analysed with qualitative content analysis. Quantitative data was collected for referral, for patients' problems being within nurses' competences and for patient views of the quality of the care they received.

Results: The oncology nursing clinic became a valid complement to the existing organisation. The use of the nursing competence in a more structured way resulted in greater possibilities for patients to get relevant care for their problems. The continuity of and access to care improved. Experiences from patients can be summarised as better quality care. The implementation of the clinic was described as a way of "putting the right competence in the right place". The clinic was both part of the oncology team and had an autonomic function. For most of the patients problems presented the nurses could independently solve them, for some they had to contact the oncologist. Before the implementation of the clinic most expectations were high and at the follow-up mostly described as fulfilled. The implementation can be seen as a process with some difficulties that had to be solved but the use of the clinic has constantly increased over time.

Conclusions: The implementation of a general oncology nursing outpatient clinic is a feasible way to improve patient care. Due to the positive results the clinic is now a permanent part of the organisation. The implementation process could have been improved as it took nearly a year to get the oncology nurse outpatient clinic to run efficiently.

Legal entity responsible for the study: Ulrika Östlund.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN21 Job content of advanced practice nurses in Flanders

E. Decoene[1], A. Van Hecke[2]

[1]Cancer Center, Ghent University Hospital, Ghent, Belgium, [2]Public Health - UCVV Nursing Science, University Ghent, Ghent, Belgium

Background: Current evolutions in medicine, the emphasis on cost-effectiveness in healthcare and the increase of complex healthcare needs addressed the need for highly educated and specialised nurses, such as advanced practice nurses (APN). By means of scientifically specialised knowledge, skills and competences, APN should enhance expansion, advancement and innovation in nursing care.

Methods: A cross sectional design was used to explore the job content performed by APN. 58 APN in Flemish hospitals participated. A validated self-reported questionnaire was used, combined with non-participant observational data (40 days).

Results: APN in Flanders are mainly experts in the domain of oncology, pain and wound care. Based on the self-reported data, the job content of APN is diverse and is linked with the APN roles as described by Hamric. 94.8% are involved in professional development and teaching of nurses in the hospital. 65.5% develops a nursing consultation and 63.8% performed these consultations autonomously. Medical delegated tasks are performed to a lesser extent. 87.9% of APN reads and evaluates scientific literature to enhance evidence based nursing in practice. Initiating and executing domain-specific nursing research is performed by 70.7%. 91.4% participates in quality improvement projects in their specific domain. APN actively participate in international and national professional organizations. There is a limited participation in working groups within governmental agencies, national and international advisory boards. Based on observational data, APN spent the following working percentages to: clinical expert (33,2%), educator (11,7%), innovator and implementation (7,3%), research (7,2%), leader and policy advisor (5,1%) and facilitator in ethical decision making (0,1%).

Conclusions: APN are 'young' professionals, in age and in working experience in the specialist domain. They are less involved in policy-making and work related to extramural activities. The focus is mainly on clinical expert care. Although APN can significantly contribute to high-quality, evidence-based patient care by providing training and coaching to nurses, initiating and guiding quality projects, conducting research and translating research findings into practice, there is room for further growth.

Legal entity responsible for the study: University Ghent, Department of Nursing Science.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN22 Developing and testing a theory-based e-learning intervention to enhance healthcare professional's self-efficacy when supporting parents newly diagnosed with cancer who have dependent children

C.J. Semple[1], E. McCaughan[2]

[1]Institute of Nursing and Health Research/Cancer Services, Ulster University/South Eastern Health and Social Care Trust, Belfast, UK, [2]Institute of Nursing and Health Research, Ulster University, Coleraine, UK

Background: Families impacted by parental cancer need advice from healthcare professionals on how to communicate this devastating news to their children and support them while having treatment. Despite the evident need, this support is often inadequate, due to lack of confidence and training for healthcare professionals. To address this gap, a theory-based e-learning intervention has been development using a 'person-based approach', aimed at enhancing healthcare professionals' self-efficacy when supporting parents newly diagnosed with cancer who have dependent children.

Methods: Using the person-based approach two qualitative focus groups (n = 23) were conducted at the planning phase, with frontline oncology professionals. During the development phase, an iterative approach was adopted incorporating 'think aloud' interviews (n = 14) for usability testing, hence moving between data collection, analysis and modifications of the e-learning intervention. The data was analysed using thematic analysis.

Results: Drawing upon existing evidence and data generated from the two focus groups at the planning phase, an e-learning prototype was developed. Three cycles of refinement followed with user retesting, using 14 think-aloud interviews. Key themes identified during think-aloud interviews which led to modifications included: 'navigational difficulties' and 'enhancement of content and visibility'. Four positive themes were also reported to include: 'appropriate use of children's drawings', 'superior look and feel', 'value of the 'Talking, Telling and Sharing framework'' and 'pedagogical methods to improve impact'.

Conclusions: This study provides a detailed description of how the person-based approach was used to plan, develop and test an e-learning intervention, aimed at improving its acceptability, feasibility and effectiveness during implementation. Providing a detailed description of the foundations that underpinned the development of this e-learning intervention, promotes transparency in the planning and design process, therefore aids methodological rigour.

Legal entity responsible for the study: Ulster University.

Funding: HSC R&D Office, Northern Ireland.

Disclosure: All authors have declared no conflicts of interest.

CN23 Supporting melanoma patients and their carers: A qualitative exploration of social interaction between patients, carers and healthcare professionals

J. Bird[1], M. Nolan[2], S.J. Danson[1]

[1]Academic Unit of Clinical Oncology, University of Sheffield, Sheffield, UK, [2]School of Nursing & Midwifery, University of Sheffield, Sheffield, UK

Background: Melanoma incidence continues to rise in Europe, the USA and Australia with mortality rates remaining relatively stable, meaning more patients undergoing surveillance. Treatments may include multiple surgeries, BRAF/MEK inhibitors and immune therapies. Clinical Nurse Specialists (CNS) provide support for melanoma patients and their carers in the UK. The aim of the overall study was to explore the changing experiences and support needs of melanoma patients and their carers throughout the disease pathway. Here we report the specific interactions between healthcare professionals and patients.

Methods: The study employed a qualitative methodology using a constructivist grounded theory approach. Theoretical sampling was used to recruit 17 melanoma patients from outpatient clinics within a UK teaching hospital. 11 carers and 11 Healthcare professionals (HCPs) participated with patient agreement. Patients and carers were interviewed in-depth, up to 6 times over 2 years and HCPs were interviewed on 2 occasions. Initial topics were modified as interviews took on an emergent design. Focus groups were conducted at the end of data collection: one with patients and one with CNSs.

Results: Owing to differing job titles used by nurses in the UK, not all patients recognised that there was a nurse available to support them. Patients and carers needed to build a trusting relationship with nurses in order to use them for support with nurse-led clinics providing continuity. Patients, carers and CNSs agreed on important points in the pathway resulting in four key phases: diagnosis and initial treatment, surveillance, metastatic disease and bereavement. Patients and carers did not appear to use the service more for knowing it was there, but it provided reassurance. Stage IV disease had the greatest input, with access to community services.

Conclusions: Developing a trusting relationship with a nurse enabled patients to feel supported. This was facilitated by the continuity provided in nurse-led clinics but differing job titles could create a barrier to patients understanding that there was someone they could contact with concerns or worries. CNSs recognised the key time points where support was most needed.

Legal entity responsible for the study: Sheffield Teaching Hospitals NHS Foundation Trust.

Funding: National Institute for Health Research.

Disclosure: S.J. Danson: Employee: NIHR National Speciality Lead for Cancer, Early Phase Trials. All other authors have declared no conflicts of interest.

CN24 Assessing the effect of telephone support on patients with myeloma multiple (MM) in the Catalan oncology institut in Girona

C.L. Puigmarti, M. Sole, G. Osca, Y. Gonzalez, N. Kelleher

Haematology, Catalan Institute of Oncology (ICO)-Hospital Universitari Josep Trueta, Girona, Spain

Background: MM is an incurable plasma cell malignancy characterized by excess paraprotein secretion with secondary organ effects including bone destruction and anaemia, renal damage and immune system impairment. MM presents as a relapsing-remitting illness throughout the patient's life, resulting not only in individualized management but also in complicated treatment with continuous revision and management of the cumulative secondary effects. MM is diagnosed at a median age of 69 years and due to the increase of the population age, it is expected that its incidence be doubled in coming years. Our Myeloma Functional Unit (MFU) has been working since 2017. The MFU is a multidisciplinary team set up in order to provide better care to these patients. In this unit, the MM specialist nurse is in charge of supporting all aspects of patient care as well as contacting with them to ensure adherence to treatment and to control secondary effects. Telephone contact also serves as a clinical support for patients. This study aimed to assess the effect of telephone support on patients with MM and whether the results can be used to identify weak points in education and patient care.

Methods: We prospectively collected phone calls made between January and April 2018 for evaluation. Calls were evaluated using a questionnaire which took into account patient's sex; maker of the call; the enquire motive; date of the call and overall results.

Results: The data is gathered from a sample of 169 calls registered. 62% of patients were male and 38 % female. Call makers were: 49% from MM specialist nurse, 31% patients, 17% caregivers and 3% others. Some of the calls were to clarify more than one issue. The enquiry motives of calls were: 49 % related to secondary effects, 39% related to appointments, 29, 5 % related to treatment information, 17% general issues. Finally regarding out comes: 80% were resolved by MM specialist nurse and 20 % of the calls required a physician help.

Conclusions: Most of the calls were resolved by MM specialist nurse. A greater nurse – led communication between the MM specialist nurse and patient and the option of resolving doubts or problems by telephone can reduce the medical visits of patient with MM between treatments and improve their quality of life.

Legal entity responsible for the study: Cesca Llopis Puigmarti.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii689–viii693, 2018
doi:10.1093/annonc/mdy341

CANCER NURSING: NEW CANCER NURSE RESEARCH

CN25 Professional grief in nurses exposed to patient deaths: The reality of a Portuguese institute of oncology

S.M.R. Gomes

Palliative Care Unit, Portuguese Oncology Institute of Coimbra, Coimbra, Portugal

CN26 The cost of survival: A mixed-method exploration of healthcare-related factors predicting colorectal cancer survivors' quality of life

A. Drury[1], S. Payne[2], A-M. Brady[1]

[1]School of Nursing and Midwifery, Trinity College Dublin, Dublin, Ireland, [2]International Observatory on End of Life Care, Lancaster University, Lancaster, UK

CN27 The influence of social networks on cancer survivors' self-management support: A survey analysis

G.H. Howard-Jones[1], A. Richardson[1], I. Vassilev[2], D. Fenlon[3], S. Ewings[2]

[1]Oncology, University Hospital Southampton Foundation Trust, Southampton, UK, [2]Health Sciences, University of Southampton, Southampton, UK, [3]Health Sciences, Swansea University, Swansea, UK

CN28 Transmural collaborative care in oncology: Experiences of general practitioners

M. Daem[1], E. van Roekeghem[2], M. Grypdonck[2], P. Pype[3]

[1]Cancer Center, Ghent University Hospital, Ghent, Belgium, [2]University Centre for Nursing and Midwifery, Ghent University, Ghent, Belgium, [3]Department of Family Medicine and Primary Health Care, Ghent University, Ghent, Belgium

Background: Cancer care is mostly situated in hospitals. Advanced practice nurses (APN) play an increasing role in this care. The role of Belgian general practitioners (GPs) in oncology is unclear. Clarification of the roles taken up by GPs is necessary to understand how communication between those involved in the patients' care can be improved. The aim of this study is to explore what Flemish GPs see as their role in oncology and what relations and information is needed to provide care for oncology patients.

Methods: A qualitative study based on individual interviews with a convenience sample of 14 Flemish GPs. Techniques of Grounded Theory are used to analyze the data.

Results: The participating GPs describe their role in the first and last phases of the illness trajectory as mostly clear. During the treatment and follow-up phase, their role is more variable because it depends on their perception of responsibility towards the

patient. Their perception of medical responsibility, whether they work proactively and expectations of the specialist define care. As follow-up is less systematic, proactively working GPs feel like they are left out of care. They would like to receive more and timely information (on psychosocial aspects). There is no true transmural teamwork and GPs are rarely well informed about the role of APNs.

Conclusions: Because of the variety of roles GPs describe, differentiation in communication is recommended, where an APN could be involved. To improve this collaboration, across the borders of primary and secondary/tertiary care, further efforts are needed.

Legal entity responsible for the study: Ghent University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN29 The use of patient reported outcome (PRO) instruments in immune checkpoint inhibitor (ICI) therapy for cancer: A systematic review

S. Colomer-Lahiguera[1], D. Bryant-Lukosius[2], S. Rietkoetter[2], L. Martelli[2], K. Ribi[3], A. Orcurto[4], R. Juergens[5], M. Eicher[1]

[1]Department of Oncology - Institute of Higher Education and Research in Healthcare (IUFRS), Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, [2]School of Nursing/Department of Oncology, McMaster University, Hamilton, ON, Canada, [3]Institute of Higher Education and Research in Healthcare (IUFRS), University of Lausanne, Lausanne, Switzerland, [4]Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, [5]Division of Medical Oncology, Juravinski Cancer Centre, Hamilton Health Sciences, Hamilton, ON, Canada

Background: ICI have shown significant clinical benefit for patients diagnosed with varied types of cancer. With an increasing use of these therapies, it is of urgent interest to achieve a comprehensive understanding of the overall patient experience – thus PROs should be systematically included in clinical ICI trials. We conducted a systematic review of published literature to identify and categorize PRO instruments and examine related utility and measurement issues in studies reporting on ICI.

Methods: Literature was searched using PubMed, Embase, PsycINFO, Medline and CINAHL databases (June 2017). Search terms included controlled vocabulary and specific keywords related to: (1) Food and Drug Administration (FDA) approved ICI, (2) PRO, and (3) Oncology. Eight reviewers independently screened titles/abstracts followed by a full text selection based on predefined criteria. We included clinical trials, intervention studies, systematic reviews, study protocols, observational studies, and case reports. Information regarding the clinical trial protocol and PRO tools was collected. (PROSPERO CRD42018090912).

Results: Of the 24 articles included in the review, 13 reported PRO data from primary clinical studies, nine were quality-adjusted life year analyses, and two were study protocols. These articles referred to a total of 14 clinical trials reporting PRO results. Of these, 12 used cancer-specific (11 EORTC-QLQ-C30 and 1 FACT-G) and 11 a generic quality of life (QoL) questionnaire (10 EQ-5D and 1 SF-36). Whereas in seven cases, only cancer-specific and generic questionnaires were used, five studies combined them with disease-specific modules, and two included a symptom-specific questionnaire. Furthermore, six studies used PROs to conduct analyses of health economics and work productivity.

Conclusions: Cancer-specific or generic QoL questionnaires are the most widely used PRO measures in clinical ICI trials. As ICI therapies exhibit unique characteristics different from conventional cancer therapies, such broad instruments may not capture the specific ICI-related symptoms, toxicities, and impact on the patient's QoL. Hence, the adaptation or development of ICI specific PRO tools should be further investigated.

Legal entity responsible for the study: Centre Hospitalier Universitaire Vaudois (CHUV) - University of Lausanne (UNIL) and McMaster University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN30 Laryngectomized patients caregivers' life experience: A phenomenological study

V. Bressan[1], E. Dri[1], S. Stevanin[2], L. Cadorin[3], A. Rizzuto[4], G. Bulfone[1], L. Ghirotto[5]

[1]Department of Medical Sciences, University of Udine, Udine, Italy, [2]Agency for Health and Social Care, Veneto Region, Venice, Italy, [3]Continuing Education Center, National Cancer Institute CRO Aviano, Aviano, Italy, [4]Department of Otolaryngology/Head & Neck Surgery, Udine University Hospital, Udine, Italy, [5]Research, Azienda Santa Maria Nuova-IRCCS, Reggio Emilia, Italy

Background: Laryngectomized patients often depend on their caregivers who have a central and difficult role in supporting them dealing with financial, social, and relational issues. In fact, they feel very responsible and committed, especially considering the time devoted to take care of their beloved. Besides, providing care induces caregivers high stress levels, emotional distress, anxiety and the fear of cancer recurrence or progress. Few studies investigated laryngectomized patients caregivers' life experience during both the whole course of illness and at the end of the treatment. Therefore, the purpose of our study was to explore, through a phenomenological approach, the lived-experience of primary family caregivers of laryngectomized patients undergoing radical surgery.

Methods: Qualitative semi-structured and audiotaped interviews were held with 12 laryngectomized patients' primary family caregivers. Data were analysed using the descriptive phenomenological approach outlined by Colaizzi.

Results: Three key themes emerged: the caregivers lived experience of illness; the change of caregivers' daily life and how they support their sick beloved. The experience of caregivers' lived relations changes from being a family member to a supportive carer, and the illness of their beloved negatively affects their psychological lived experience. Their perception of time and Quality of Life change as their perception of the future becomes uncertain. Finally, they feel guilty mainly because of the limited amount of time they can devote to their beloved.

Conclusions: The study findings allowed to understand in depth how the presence of a laryngectomized person in the family may affect the life of the caregiver, even after the treatment phase. This suggests the need for healthcare professionals to support caregivers throughout the whole care journey and especially in dealing with the perception of time during the diagnosis and care phases. Further research should be conducted on factors contributing to time perception alteration and possible interventions to support caregivers to cope with it.

Legal entity responsible for the study: Valentina Bressan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN31 Comparing nurses' and patients' research priorities in cancer care: A mixed methods systematic review

L. Cadorin[1], I. Truccolo[2], V. Bressan[3], N. Suter[1]

[1]Continuing Education Centre, CRO Aviano National Cancer Institute, Pordenone, Italy, [2]Scientific and Patient Library, CRO Aviano National Cancer Institute, Aviano, Italy, [3]ENT Department, University of Udine, Udine, Italy

Background: Cancer nurses struggle to meet the challenges in providing quality nursing care in changing environments characterized by advances in drugs and technologies, aging populations, increasing rates of cancer and survival, rising costs, long-term survival patients and increasing economic constraints. Research priorities need to be established within this context because they can encourage the new generation of nurses to respond competently to patients' advanced care needs.

Methods: A systematic review was performed to compare and discuss nurses' and cancer patients' main cancer research priorities according to the PRISMA guidelines (PROSPERO registration: CRD42017059721). Studies retrieved were evaluated with a Mixed Methods Appraisal (MMAT). All medical databases were searched from January 2000 to July 2017. Study inclusion, data extraction, and assessment were performed by two researchers independently (inter-rater agreement, kappa =0.70; SE = 0.87; $p < 0.01$).

Results: Among 16 studies identified, 13 included nurses' research priorities, 2 patients', and 1 both. They included descriptive cross-sectional (50%), Delphi (44%), and exploratory qualitative studies (6%). Qualitative studies varied from 75% to 100% of the total MMAT score. Nurses' priorities were as follows: cancer behavioral psychological/social issues and professional dimensions. Patients' priorities were patient life dimensions and health promotion. Cancer care dimensions and continuum of care emerged as research priorities of both.

Conclusions: The results underline nurses' and patients' research priorities to investigate the patients' advanced care needs and provide a useful template to guide cancer-nursing research. Identifying priorities helps focus on particular issues rather than promoting isolated and unrelated studies of patients' needs. Most of the nurses who participated were affiliated with professional associations and do not reflect the entire nursing population. Moreover, very similar survey questionnaires have been used (the items did not cover all areas) with the possible priorities not considered by participants. More studies are needed for the creation of a cancer research priority agenda.

Legal entity responsible for the study: CRO Aviano National Cancer Institute.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN32 Most prevalent unmet supportive care needs in Greek ambulatory advanced breast cancer female patients receiving chemotherapy

A. Psychogyiou, S. Katsaragakis, C. Lemonidou, D. Protogiros, E. Patiraki

Nursing, National and Kapodistrian University of Athens, Athens, Greece

Background: This cross-sectional study, supported by the National and Kapodistrian University of Athens, aimed to describe the unmet supportive care needs of ambulatory advanced breast cancer female patients receiving chemotherapy and the association between patients' characteristics and their unmet needs.

Methods: A convenient sample of 117 ambulatory (response rate 96%) advanced breast cancer (stage III or IV) female patients receiving chemotherapy, from two outpatient units of cancer hospitals in Attica consented to participate between July 2017 to February 2018. Patients were assessed by the translated in Hellenic language Short-Form Supportive Care Needs Survey Questionnaire: a 34 items 5-point (1-5) Likert type scale that covers five domains of need: health system and information (HIS),

psychological (PS), physical (PH), care and support (CS), and sexuality needs (S). Their unmet needs were determined overall and by domain (rated 3 to 5 points). A form consisting of demographic and clinical characteristics were also collected. The level of statistical significance was set at 0.05.

Results: The mean age was 62.2 (±11.3) years. Most patients were married/ partnered (47.9%) with children (84.6%), retired (56.4%), with a low income (56.4%) who had undergone antineoplasmatic treatment previously (96.6%). The mean number of unmet needs of each patient was 16.7 (±7.5) (0-34) and the median number was 18. The mean/ median number of unmet needs in each domain was PS 7.0 (±3.4) (0-10)/ 9, HIS 5.1(±3.3) (0-11)/5, PH 3.5(±1.6) (0-11)/ 4, CS 0.9 (±1.4) (0-5)/0 and S 0.4 (±0.9) (0-3)/ 0. The prevalence of the ten most frequent unmet needs was over 70% and belonged to PS (6 items) PH (3 items), and HIS (1 item) domain. None of the sample's demographic and clinical characteristics was statistically significant associated with the total need score of SCNS-SF34 or PS, PH, HIS domains ($p>.050$). Higher income was associated with less PS ($x(3)^2=9.1$, $p=.028$) and HIS needs ($F(3)=3.1$, $p=.029$). Having children was associated with less HIS needs ($t(115)=2.1$, $p=.042$).

Conclusions: The most prevalent unmet supportive care needs in our Greek sample were psychological informational and physical, but further research is needed to clarify them.

Legal entity responsible for the study: Department of Nursing, School of Health Sciences, National and Kapodistrian University of Athens.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN33 A new beginning of collaboration: The Danish Cancer Nursing Research Network

K.B. Dieperink[1], M. Kjerholt[2], P.R. Riis Olsen[3]

[1]Department of Oncology, Odense University Hospital, Odense, Denmark, [2]Haematology, Sjællands Universitets Hospital, Roskilde, Denmark, [3]Oncology, Aarhus University Hospital, Aarhus, Denmark

Background: Research in cancer nursing is pivotal for patients, their families and for the nursing profession. Cancer nurses have to deliver good quality care during the whole trajectory from pre-diagnosis to treatment, rehabilitation and palliation. However, the numbers of Danish nursing researchers within the cancer discipline are small and they work somewhat isolated all over Denmark. The researchers would benefit from forming a stronger network and to collaborate across the country.

Methods: The network was established during a snowball effect and from mouth to mouth. Members invited are nurses with a PhD from all over Denmark, researching within different areas of the cancer discipline. The network is organized with a steering committee consisting of three members representing three of the five Danish regions.

Results: In October 2016 the Danish Cancer Nursing Research Network was born. At the moment 31 Danish nursing researchers are affiliated to the network, and is growing. The aim of the network is to: ○ Draw national and international attention to nursing research to the benefit of cancer patients and their families ○ To facilitate collaboration in cancer research among members ○ To exert influence on a political level to promote developments in healthcare and to raise attention to the importance of nursing research The network has during 1.5 years arranged four successful meetings and a master class for PhD student, and is beginning to include PhD students. The network also aims to connect and collaborate with international nurse researchers. We have flashed our existence and call for collaboration through EONS' newsletter February 2018.

Conclusions: The Danish Cancer Nursing Research Network is a new but already strong and expanding organization which will influence Danish cancer nursing on different levels.

Legal entity responsible for the study: The Danish Cancer Nursing Research Network.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN34 Individual network meetings in cancer care: From young people with cancer to adults with brain tumours

P.R. Riis Olsen

Oncology, Aarhus University Hospital, Aarhus, Denmark

Background: A malignant brain tumour often includes cognitive impairment. This affects both patients and families. Compared to other cancer patients, studies show that they are significantly in more need of social support and help for everyday activities. A network focused approach offering individual network meetings with and for young people with cancer has shown to facilitate the involvement of a supportive social network around the patient and the family, which can assist them in keeping their world together.

Methods: A participatory action research design was employed to develop and implement a researched based service that would promote and encourage a supportive social network for patients with primary brain tumours and their families. Patients and close relatives preferences and attitudes towards an offer of a network meeting were explored. The study involved parallel processes of individual interviews with patients and usually their spouses, focus group interview and group sessions of co-operative inquiry, education and interaction between the researcher and a group of ten clinical nurses.

Results: Based on the findings the individual network meeting for patients with brain tumours has been shaped to fit their needs and wishes and are now fully implemented in the clinic. A group of nurses has been trained in planning and leading network meetings and acts as implementation agents. Early presentation of individualised network meetings is welcomed as an opportunity and accepted by about 40% of the patients and relatives. Data from the study are currently being analysed for publication.

Conclusions: Network meetings are highly valued by patients and their social network who have experienced a meeting. The interactive approach in action research has supported the implementation of the complex service - a service which has potential in other nursing areas. The presentation will focus on preparing and conducting network meetings and findings will be highlighted.

Legal entity responsible for the study: Professor Charlotte Delmar, Section for Nursing. HEALTH. Aarhus University. Denmark. Matron Morten Keller, Department of Oncology, Aarhus University Hospital, Denmark.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

CN35 Does being cancer patient or family caregiver of cancer patient effect bone marrow donation awareness?

G. Bagcivan[1], N. Ozen[2], D. Bayrak[3], F.I. Cınar[4]

[1]Education Department, Gulhane Training and Reseach Hospital, Ankara, Turkey, [2]Faculty of Health Sciences, Istinye University, Istanbul, Turkey, [3]Health Science Faculty, Cankiri Karatekin University, Cankiri, Turkey, [4]Gulhane Nursing Faculty, University of Health Sciences, Ankara, Turkey

Background: Extensive literature from Turkey and around the world have described factors associated with donating bone marrow and knowledge about bone marrow donation. However to the best of our knowledge, this is the first study that focused on awareness of cancer and non-cancer patients and their family caregivers as well bone marrow donation and transplantation. The aim of this study was to determine if there are any differences between cancer and non-cancer patients and their family caregivers' awareness of bone marrow donation and transplantation.

Methods: This is a descriptive study conducted in Turkey. We recruited the patients and family members who were admitted to Medical Oncology, Hematology and General Medicine. This study was approved by the hospital Institutional Review Board. Data was collected by researchers after written inform consent was obtained from each patient and family member via face to face interviews using the data collection form developed by researchers based on literature.The SPSS 21.00 was used to analyze the data. The Chi-square test was performed to evaluate differences among groups.

Results: Although most of the patients and family caregivers were aware of what bone marrow transplantation and bone marrow donation are they did not know how to donate bone marrow. Most of the patient and family caregivers who know what the bone marrow transplantation and donation are stated that they learned about bone marrow transplantation and donation through television, internet, and health professionals. Compared to the non-cancer patients, believing in bone marrow transplantation is lifesaving, knowing exactly what the bone marrow transplantation is, and how to donate bone marrow were more in the cancer patients. Likewise cancer patients' family caregivers were more aware of what exactly bone marrow transplantation is, and how to donate bone marrow.

Conclusions: Several studies showed that those who have been informed about BMT, and National marrow donation program were significantly more willing to donate bone marrow. This is important since in many cases lack of encouragement and insufficient information discourage a person from bone marrow donation.

Legal entity responsible for the study: Gulcan Bagcivan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN36 A review of the challenges faced by carers of patients diagnosed with head and neck cancer before, during and after treatment

C.E. Johnston[1], M.A. Tanay[2]

[1]Haematology/Oncology, Guy's and St. Thomas' Hospital NHS Trust, London, UK, [2]Faculty of Nursing, Midwifery and Palliative Care, King's College London, London, UK

Background: Caring for individuals with cancer has been identified as a rewarding task for carers to undertake. However, it has also been identified as a stressful burden, often negatively impacting the carers physical and psychosocial health and wellbeing. Head and neck cancer (HNC) patients experience a range of complex care needs such as the inability to swallow safely, communication difficulties and poor psychological health following treatment. These side effects consequently impact those looking after the patient at home.

Methods: In January 2017 four electronic databases, CINAHL, Medline, PsycINFO and ASSIA, were systematically searched to identify relevant literature addressing the proposed research question. A manual hand search was then conducted so that further

relevant papers could be retrieved. A total of eight qualitative research papers and one mixed methods paper were selected that met the eligibility criteria. These papers were then critically appraised using CASP's critical appraisal tool and analysed using thematic analysis.

Results: Nine studies involving 105 carers were included in this review. All studies utilised semi-structured interviews to gather data. The studies were conducted in the United Kingdom (n = 3), Canada (n = 1), Sweden (n = 1), Australia (n = 2), Ireland (n = 1) and America (n = 1). From the thematic analysis four themes emerged from the data set identifying the specific challenges HNC carers faced; challenges due to new roles and responsibilities, information challenges, support challenges and relationship challenges.

Conclusions: This review identified the specific challenges experienced by carers of individuals diagnosed with HNC. The multiple caregiving responsibilities they undertake, impacted both their physical and emotional wellbeing. Furthermore, these challenges were found to be exacerbated by the inadequate provision of information and support facilitated by healthcare professionals. Awareness of these extensive challenges will help to identify ways of supporting carers in adapting to their new roles and responsibilities. Results may also guide development of future interventions and strategies aimed at providing information and psychosocial support for carers.

Legal entity responsible for the study: Charlotte Johnston.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN37 Evaluation of support and information needs for patients with cancer in a phase I trials unit

S. Stapleton[1], L. O'Leary[1], M. van Zyl[1], J. Hanwell[1], T. Wiseman[2]

[1]Drug Development Unit, Royal Marsden Hospital NHS Foundation Trust, London, UK, [2]Applied Health Services Research, The Royal Marsden NHS Foundation Trust, London, UK

Background: Advances in the understanding of the biological basis of cancer have resulted in a paradigm shift in drug development. Phase I trials with translational elements are conducted in clinical trials units for patients with cancer. The objective of this study was to evaluate any unmet needs of support and information for patients on Phase I trials. The aim was to utilise patient exerience to assess the need to change or develop delivery of information and support.

Methods: A qualitative approach was used. Patients and relatives of patients with cancer on Phase I trials formed two focus group. Group 1 consisted of 8 participants and group 2 10 participants, both lasted one hour. A semi structured schedule was used to prompt discussion, the focus groups were audio-recorded and transcribed verbatim. The data were organised using the Nvivo software package and analysed using Braun and Clarke's thematic analysis framework.

Results: Four themes emerged from the data 1) face to face support; there was a general consensus that the best way to recieve information about treatment and disease was face to face. The relationships with the clinical staff were strong and important to maintain. At times when the trials unit was not accessible patients felt vulnerable 2) remote support; email was felt to be a good way to communicate information regarding appointments, the telephone clinic was useful for contact regarding sympton issues. Digital methods of information and support were potentially useful but needed to be thought through properly 3) getting the right information, at the right time , in the right way; patients felt that they needed extra information particularly in terms of feedback regarding the trials and signposting to support services 4) Relationships with other patients; this theme was about the benefit and value patients had in supporting each other within the treatment areas, however this was conflicted and may require extra support at times as there was a negative impact when fellow patients became unwell or died.

Conclusions: Based on the results from the analysis written patient information was redesigned. A quarterly forum is in development where patients can meet recieve well being advice and also feedback regarding the trials they are participating in.

Legal entity responsible for the study: Royal Marsden NHS Foundation Trust.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN38 Dignity of Greek patients with advanced cancer: A cross-sectional study

S. Katsaragakis[1], F. Deskou[2], S. Sgourou[1], M. Christou[1], M. Dimoula[1], K. Maniati[2], D. Protogiros[1], E. Patiraki[1]

[1]Nursing, National and Kapodistrian University of Athens, Athens, Greece, [2]Palliative Care Unit Galilee, Palliative Care Unit Galilee, Spata, Greece

Background: A core concept in caring patients with advanced cancer is to treat them and preserve dignity independently the service of care. This cross-sectional study's purpose was to explore the dignity of patients with advanced cancer.

Methods: A convenience sample of 99 (response rate 85%) patients with advanced cancer was recruited between April to December 2017 by a palliative care unit (PCU) (day (PDC) and home care (PHC)) and oncology units (chemotherapy outpatient (OU) and inpatient (IU)) of Athens. Patients with advanced cancer (stage III or IV) who consented, completed the Patient Dignity Inventory (PDI), a 25 items scale, 5 point Likert scale (1 (no problem) -5 (overwhelming problem) divided into: Symptom (SD) and Existential distress (ED), Peace of Mind (PM), Dependency (D), and Social Support (SS). Also Hospital Anxiety and Depression Scale (HADS), Edmonton Symptom Assessment Scale - short version and a demographic/ clinical form were collected.

Results: Most patients were female (54.5%), the mean age was 64.9 years. Breast (22.2%), colorectal (16.2%) and lung cancer (15.2%) were the most frequent diagnoses. Almost half patients (56.6%) were hospitalized (36.4% OU, 20.2% IU) and the others were cared for at the PCU (28.2% PHC, 15.2% PDC). The PDI mean scores were: Total Dignity (TD) 50.2 (25-125), SD 15.3 (6-30), ED 12.7 (6-30), PM 4.7 (3-15), D 5.8 (3-15), SS 4.5 (3-15). Most of the demographic and clinical characteristics were not associated with total or subscales scores of PDI. On the other hand, women ($p=.035$) and breast cancer patients reported less SS ($p=.022$). The OU patients reported better TD ($p=.029$), SD ($p=.001$), ED ($p=.002$) and D ($p=.003$) than OU and PHC but not PDC. Higher scores of TD were significantly correlated with experience of pain, tiredness, lack of appetite, shorten of breath, anxiety and depression ($p<.006$). Reports of anxiety and depression measured by HADS were correlated with higher total and subscales dignity scores ($.001 < p < .006$).

Conclusions: The findings of this study support a quite good level of perceived dignity in Greek patients with advanced cancer. More research is needed to clarify the differences of dignity among various care settings. We thank Special Account for Research Grants and National and Kapodistrian University of Athens.

Legal entity responsible for the study: Nursing Department, National and Kapodistrian University of Athens.

Funding: Special Account for Research Grants, National and Kapodistrian University of Athens.

Disclosure: All authors have declared no conflicts of interest.

CN39 Development and implementation of national guidelines on lifestyle issues and cancer: Report from an ongoing quality improvement project

K. Vuollet Karlsson[1], C. Landegren[2], B. Westman[3]

[1]Regional Cancer Centre North, Norrlands Universitetssjukhus, Umea, Sweden, [2]Regional Cancer Center Syd, Region Skåne, Lund, Sweden, [3]Stockholms Läns Landsting, Regional Cancer Center Stockholm Gotland, Stockholm, Sweden

Background: Lifestyle habits such as tobacco use, alcohol consumption, insufficient physical activity, sun exposure and unhealthy eating habits are risk factors for cancer but also increase the risk of side-effects and poor outcome from cancer treatments. The Swedish Cancer Nursing Society initiated and developed a multi-professional project where they adapted the current national guidelines for lifestyle habits of preventing disease (by National Board of Health and Welfare), to the cancer context.

Methods: The project includes developing written guidelines for staff and an evidence-based educational program for cancer contact nurses (CNs). The CNs has a unique position to inform and support patients and their families on lifestyles changes. The education program (one full day training and one half day follow-up) started in May 2018 and includes lectures and case discussions that cover all cancer related lifestyle issues. It also includes systematic assessment and models for change. All Swedish CNs (approx. 1000) will be invited to participate.

Results: A first evaluation of the program will be presented during EONS11 at ESMO 2018. Data will be collected via surveys and interviews with CNs and also from cancer care provider data sources (on what lifestyle interventions that have been delivered to patients).

Conclusions: The project will be on the way to implement evidence-based knowledge about lifestyle habits to CN.

Legal entity responsible for the study: Swedish Nurses Oncological Associations.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN40 Developing a patient reported experience measure (PREM) in secondary breast cancer (SBC)

C. Farrell, S. Foy, A. May, R. Lee, C. Gaskell, J. Yorke

School of Oncology, The Christie NHS Foundation Trust, Manchester, UK

Background: Metastatic breast cancer (SBC) is now seen as a chronic disease, however the number of patients currently living with SBC is unknown. Despite widespread recognition of the importance of understanding and evaluating patients' experiences, little research has been undertaken within SBC. Generally, there has been significant expansion in the development and application of patient reported questionnaires that measure care experiences (PREM), which is a major indicator of healthcare quality, however there is no specific PREM for people with SBC.

Methods: This study aims to develop and pilot test a unidimensional PREM in SBC for clinical application using a mixed methods sequential exploratory design. Semi-structured interviews were conducted with 25 people with SBC to explore their experiences,

priorities and needs diagnosis of metastatic disease and during palliative treatment. Potential items for PREM-SBC were extracted from interview data focusing on patients' experiences and priorities for care. Cognitive interviews were undertaken with patients to ensure all items listed were clear and easily understood.

Results: Following cognitive interviews a draft PREM questionnaire was created for patients with SBC. The structured questionnaire contains 48 items (statements) based on patients' experiences, treatment / care, priorities and needs. A five point scale is used to rate each item from strongly agree to strongly disagree. Patients report the PREM is easy to complete, taking less than 5 minutes. Further pilot testing is currently being undertaken (n = 130) to assess the validity, reliability and repeatability of PREM-SBC, drawing comparisons with other quality of life measures.

Conclusions: There is currently a lack of research focusing on patients with SBC. A draft PREM-SBC questionnaire was developed and pilot tested for clinical use. This will increase understanding of patients' experiences, needs and priorities to enhance patient care.

Legal entity responsible for the study: The Christie NHS Trust.

Funding: Roche.

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology 29 (Supplement 8): viii694, 2018
doi:10.1093/annonc/mdy274

CANCER NURSING: LEADERSHIP

CN41 Cancer situation in Sub-Saharan countries: Development of educational, diagnosis and treatment plans

J.C. de la Torre-Montero[1], N. Gil-Gómez[2], J.L. Ribes bernal[3], N. Domenech Climent[4], A. Ojer Perea[5], P. Beorlegui Murillo[5], J.M. Gavala Arjona[6], R. Cumplido Corbacho[7], I. Magallon Pedrera[8], M.A. Peñuelas Saiz[8]

[1]Spanish Society of Oncology Nursing, Comillas Pontifical University, Madrid, Spain, [2]Spanish Society of Oncology Nursing, Hospital Quirón Madrid, Madrid, Spain, [3]Spanish Society of Oncology Nursing, Hospital Clinic, Barcelona, Spain, [4]Spanish Society of Oncology Nursing, Hospital Virgen de los Lirios, Alcoy, Spain, [5]Spanish Society of Oncology Nursing, Clinica Universitaria de Navarra, Pamplona, Spain, [6]Spanish Society of Oncology Nursing, Hospital son Espases, Palma de Mallorca, Spain, [7]Spanish Society of Oncology Nursing, Hospital Universitario Virgen del Rocio, Seville, Spain, [8]Spanish Society of Oncology Nursing, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Background: The situation of patients with cancer around the world means, in terms of access to diagnostic tools, adequate surgical interventions, medical treatments and optimal radiotherapy, as well as the educational tools for professionals, presents a great disparity in terms of access throughout the globe, but especially in sub-Saharan countries. Once again, putting into evidence this situation is necessary in order to raise awareness among the participants involved in this situation: patient, professionals, Scientific Societies, but especially governments and international organizations. Health services, sanitary equipment and medical access in developing countries are unequable: from rural areas to cities, the ratios of population, patients and professionals are far from the recommendations of the WHO. The aim of this project is to determinate the dimension of educational and non-educational needs, such as: diagnostic methods and treatments, based on the difficulties presented while having access to the different resources.

Methods: A qualitative approach was performed as first step. Objectives are to determinate needs about diagnosis equipment, treatments, and level of expertise within the personnel: including physicians, nurses, physiotherapist, technicians, and community health workers (this is a common figure in these countries). Quantitative analyses will start taking place during summer campaigns by African and European health professionals.

Results: Access to medicines is expensive, even for the most basic treatments; when a patient begins a chemotherapy treatment, usually completes the first or second cycles of treatment. Only people who have access (economically) to a regular health system can afford a complete line of chemotherapy. About cancer diagnosis, in many countries there are basic X-ray services, including CT scan, but no PET or RMI.

Conclusions: If we think in oncology services, there is a big gap from developed societies in terms of education resources. If we think in patients with cancer in some countries in Africa, we can sadly affirm that most of them are patients in palliative care, and instead of receiving the most qualified and supportive care, their options about pain control or other treatments are very few.

Legal entity responsible for the study: Julio Cesar de la Torre Montero.

Funding: Comillas Pontifical University; San Juan de Dios School of Nursing and Physical Therapy. SEEO Sociedad Española de Enfermería Oncológica. ONGD Asociación AMAP.

Disclosure: All authors have declared no conflicts of interest.

CN42 The Gastrointestinal and Lymphoma Unit lead nurse research role in Royal Marsden Hospital

J. Duncan[1], V. Michalarea[1], T. Coyne[2], J. Thomas[1], D. Cunningham[2]

[1]GI and Lymphoma, Royal Marsden Hospital NHS Foundation Trust, London, UK, [2]GI Research, Royal Marsden Hospital NHS Foundation Trust, London, UK

Background: Clinical research has expanded in many fields with oncology growing vastly in the last 5 years. Specialised nursing and healthcare support is imperative for the smooth operation of the research aspect of a unit, aiming to deliver better care to patients (pts) participating in clinical trials.

Methods: Retrospective review of the structure of the Research Clinics between November 2016 and April 2018 in Royal Marsden Hospital in the Gastrointestinal and Lymphoma Unit.

Results: The Lead Research Nurse (LRN) structured the team by identifying the complexities involved in running a dedicated Research clinic, developing new roles and assigning the appropriate research team members to support the Clinical Research Fellows. The LRN introduced the role of Assistant Practitioners (APs)who support the running of the clinic by taking vital signs, performing ECG's and other trial related procedures, such as entering source data into the Electronic Case Report Forms for the sponsor of each clinical study. This has enabled the Clinical Research Nurses (CRN) to spend more time with pts, assessing them for new or existing adverse events, recording concomitant medications, checking blood results, and completing Holistic Needs Assessments at required points throughout treatment. The LRN expanded the role of the Biological Specimen Coordinator (BSC) enabling them to perform phlebotomy on Research pts and take consent for a Translational Research protocol, making their role more hands on and improving retention in this job group.

Conclusions: The LRN has a crucial role leading, supervising and developing a split site team consisting of ten CRNs: 5 senior CRNs, 5 junior CRNs, a Translational Research Manager, 5 BSCs and 2 APs. We have achieved a holistic approach for the trial pts whose needs might differ from the usual treatment setting due to the experimental nature of these trials. Our well-structured process has helped pts build better rapport with the team, understanding the importance of all members and various aspects in clinical research. Further training is warranted with Research nurses undertaking advanced practice education, with the view for this model to be adopted in other specialties and institutions.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 8): viii695–697, 2018
doi:10.1093/annonc/mdy277

CANCER NURSING: PATIENT SAFETY

CN43 Patients' learning and participation in their breast cancer care

L.E. Boman[1], K. Sandelin[2], Y. Wengström[3], C. Silén[1]

[1]Department of Learning, Informatics, Management and Ethics, Karolinska Institute, Stockholm, Sweden, [2]Molecular Medicine and Surgery, Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, [3]Department of Neurobiology, Care Sciences and Society, Division of Nursing, Karolinska Institutet, Huddinge, Sweden

Background: Patients' participation in treatment and care is considered to increase their safety and well-being. There is a lack of knowledge about what participation means for the patients and how it can be supported in breast cancer care. A prerequisite for patients' participation is their knowledge. Changing perspective, from patients' information needs to their learning, can increase our understanding about how participation can be facilitated. The purpose of this study was to explore patients' experiences of learning, understanding and participation in their breast cancer care.

Methods: Sixteen patients with breast cancer were interviewed. The interviews were analyzed according to abductive content analysis taking the perspective from learning theories.

Results: The first part of the study explored patients' learning. The patients are forced to interact with a vast amount of information. Bodily sensations and experiences from being part of events are important sources. The information is interpreted to an understanding which is concealed or expressed which affect patient participation. The struggle to understand and manage the new life situation is an ongoing process for a long time. The preunderstanding and driving forces of the patients, time for contemplation and dialogue with staff, were essential features in this struggle(1). The second part explores patient participation. The concept of patient participation was defined differently by different patients and there was uncertainty about its meaning. The patients' understanding of their disease, treatment and care affected their participation. A prerequisite for participation was the respectful treatment from health care staff contributing to a feeling of being "seen" as a human being. The patients' wishes varied as did their needs to participate in treatment decisions. Participation also meant a continuous struggle to manage self-care during a long period of time and access to health care is needed to support patients. (1)Engqvist Boman et al. Patients' learning and understanding during their breast cancer trajectory. Patient Education and Counseling 100 (2017) 795–804.

Conclusions: New kinds of training programs for staff and patients are suggested, focusing on patients' learning and the new roles of partnership.

Legal entity responsible for the study: Karolinska Institutet, Department of Learning, Informatics, Management and Ethics.

Funding: Karolinska Institutet in collaboration with the Regional Cancer Centre Stockholm-Gotland, Stockholm County Council.

Disclosure: All authors have declared no conflicts of interest.

CN44 Incidence and risk factors of phlebitis in patients with peripheral parenteral nutrition administration

S.Y. Oh[1], J.M. Lee[1], J.W. Kim[1], S.H. Kim[1], J.M. Park[1], G.Y. Yeo[1], J.E. Hyun[1], J-H. Park[2]

[1]Nursing, Asan Medical Center, Seoul, Republic of Korea, [2]College of Nursing, Ajou University, Suwon, Republic of Korea

Background: Peripheral parenteral nutrition is one of the easiest ways to provide nutrition for patients who have difficulty with enteral nutrition. But, on the other hand it is attended with danger such as, phlebitis. The purpose of this study was to investigate incidence of phlebitis and its risk factors in patients with peripheral parenteral nutrition administration.

Methods: Prospective observational study was performed with 289 hospitalized adult patients with gastrointestinal diseases. The researchers evaluated peripheral venous catheter that administered peripheral parenteral nutrition until their removal and investigated the incidence of phlebitis using phlebitis scale of Infusion Nurses Society (2016). Logistic regression model was used to identify risk factors involved with occurrence of phlebitis. The statistical significance limits were set at $p < 0.05$.

Results: The incidence of phlebitis was 37.0% (107 cases). Among them, Grade I was 24.6% (71 cases), Grade II was 12.4% (36 cases) and Grade III and IV did not occur. Platelet count (OR 2.13, CI 1.07-4.26, p=.032), nutrition infusion rate (OR 0.36, CI 0.16-0.79, p=.012) and infusion period (OR 1.02, CI 1.00-1.03, p=.033) had statistically significance with phlebitis occurrence.

Conclusions: Using peripheral parenteral nutrition must be carefully reconsidered for patients with risk factors of phlebitis. In using peripheral parenteral nutrition, adjusting infusion rate deserves to be considered with care. Moreover, in case of extension of peripheral parenteral nutrition therapy, medical team must regards using another way such as middle line or central line for nutrition therapy in a serious light.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN45 Specialized nursing interventions in optimizing patient communication undergoing total laryngectomy

A.A. Frade, S.S.A. Miguel

Service of Head and Neck Surgery, Otorhinolaryngology and Endocrinology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E., Lisbon, Portugal

Background: Permanent and immediate laryngeal voice loss, resulting from total laryngectomy can be psychologically devastating to the patient and family, generating feelings of stress, fear, and frustration (Brunner et al, 2016). In the immediate postoperative period, writing and lip read are the most commonly methods of communication used by patients. However, this surgery is often accompanied by neck dissection, resulting in neck swelling, which difficult the movement of the lips and limits limb mobility required for readable writing (Matos et al, 2009). In conclusion, these approaches may not be effective, leaving patients frustrated and unable to express their care needs (Brunner et al, 2017). Thus, communication between patients and health professionals becomes difficult, generates anxiety and anguish in the person and family and has implication in the process care. Specialized care is therefore required for this type of patients, especially those provided by nursing, highlighting the use of augmentative and/or alternative communication strategies (AAC).

Methods: A critical reflection based on the results of a previous review, were performed to identify which AAC strategies promoting effective communication in the laryngectomized patient.

Results: Strategies identified as promoting effective communication include the use of low-technology and high-technology devices.

Conclusions: The use of AAC strategies improves the quality of care provided and allows a better understanding of the needs of the laryngectomized patient, which consequently will give them greater autonomy, control over their life and facilitating their adaptation. Beyond these implications for nursing, effective communication is a right of the individual and an essential component of the quality of care and patient safety.

Legal entity responsible for the study: Ana Frade, Susana Miguel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN46 Safe navigation of CARs in a changing landscape

M. Davies[1], E. Dolan[2], S. Neeson[2], E. Blowers[3], K. Linton[4], F. Thistlethwaite[5]

[1]The National Institute for Health Research (NIHR) Manchester Clinical Research Facility, The Christie NHS Foundation Trust, Manchester, UK, [2]Clinical Research Facility, The Christie NHS Foundation Trust, Manchester, UK, [3]Patient Recruitment, The Christie NHS Foundation Trust, Manchester, UK, [4]Medical Oncology, Manchester Cancer Research Centre, Manchester, UK, [5]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK

Background: Advanced Therapy Medicinal Products (ATMPs) such as CD 19 chimeric antigen receptor (CAR) therapies offer unprecedented promise for long term remission and even cure in pre-treated and refractory B cell malignancies. Extensive interest in new T cell engineered treatments for other malignancies has developed as a result. These complex treatments are associated with acute and potentially fatal toxicities, making patient safety paramount. CARs are often delivered on haematopoietic stem cell transplant (HSCT) units with JACIE accreditation, an internationally recognised quality system. To enhance capacity for growing numbers of ATMP trials The Christie has utilised the NIHR clinical research facility (CRF).

Methods: Process mapping of the patient pathway alongside a gap analysis using JACIE standards has provided a framework to underpin the development of the CRF including: Advanced therapies team Increase in establishment Practice educator Education programme & HSCT placements JACIE quality manager to align SOPs and policies Changes to medical cover.

Results: Engagement across the organisation is a priority, with a focus on safety and mitigating risk. Recruitment to key posts is underway, along with specialised staff training. Relationships are being forged and strengthened with essential specialties such as critical care and neurology. The first clinical trials are open but recruitment and use of

the CRF will be carefully managed to ensure the infrastructure and processes are fit for purpose. The Christie is the lead organisation in a new consortium, iMATCH (Innovate Manchester Advanced Therapy Centre Hub) which has been awarded substantial funding from Innovate UK to scale up delivery of ATMPs and form a national network of Advanced Therapy Centres.

Conclusions: CD19 specific CAR therapy is poised to become a new standard care for selected B cell malignancies. Trials of ATMPs for a range of malignancies are growing exponentially, therefore safe delivery outside of an experienced area such as HSCT is important but challenging. Creative approaches to patient care, wide collaboration and executive level support are key. While iMATCH sets the challenge to increase the number of ATMPs available it has also facilitated city wide links and a national network to find solutions to complex problems.

Legal entity responsible for the study: The Christie NHS Trust.

Funding: Has not received any funding.

Disclosure: F. Thistlethwaite: Research grant: Novartis; Consulting: Pfizer, BMS, Octimet, Achilles Therapeutics, Evelo Biosciences; Honorarium: Novartis; Speakers' bureau: BMS. All other authors have declared no conflicts of interest.

CN47 Patients' interpretations and experiences of participation in cancer care

J. Jackson, J. Rundgren

Coordinating Contact Nurse, Regional Cancer Center Stockholm Gotland, Stockholm, Sweden

Background: The definition of patient participation is multifaceted but often reduced to solely implicate the involvement in treatment decisions. In many countries, including Sweden, there is a current shift from patient-centered care to person-centered care. This emphasizes the importance to view the patient as an equal partner and always include his or her description of their unique situation. To facilitate the participation of patients and to put their needs first, we need a wider understanding of how participation is interpreted and experienced by the patients themselves. Hence our aim was to examine this among patients with gynecological, hematological, head-neck or upper gastrointestinal cancer.

Methods: A qualitative cross-sectional study was carried out. This included all patients in the Stockholm-Gotland region, diagnosed in 2016 with one of the above-mentioned cancer types. A free-text question was formulated which asked the participants to describe their experiences of participation. The question was included in a larger questionnaire study from the Regional Cancer Center and sent out to 1658 patients. Framework Analysis was used as the method to analyse and interpret the data.

Results: A total of 434 participants chose to answer the study specific free-text question and 222 of those answers were deemed to meet the aim of the study. The analytical process resulted in three themes; communication, staff attitudes and relation. Above all, the participants described how individualized information and a perceptive attitude among staff were key prerequisites for participation. Furthermore, they pointed out that absence of continuity became an obstacle for creating meaningful relations with their care provider and thus hindering their participation.

Conclusions: To meet the current and future demands of individualized cancer care we need to redefine our understanding of patient participation. The emphasis, according to patients, should be on facilitating conditions to aid participation. Our understanding is that these conditions resonate the key aspects of person-centered care. The challenge lies in implementing person-centered care in the whole team and across each patient's cancer trajectory.

Legal entity responsible for the study: The Regional Cancer Center Stockholm-Gotland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN48 Peripherally inserted central venous catheters did not increase the risk of deep venous thrombosis in advanced colorectal cancer and lung cancer patients with bevacizumab

M. Qiu, Y. Chen, B-L. Zhang, X-Y. Wang

Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: Deep Venous thrombosis (DVT) is one of the serious adverse events associated of bevacizumab, which is also one of the most notable complications associated with peripherally inserted central catheters (PICCs). However, there was no report about their correlation directly. The purpose of this study was to explore whether the use of PICCs increases the risk of DVT in advanced colorectal cancer and lung cancer patients with bevacizumab.

Methods: From June 2011 to April 2017, patients with documented advanced colorectal cancer and lung cancer who received bevacizumab were selected from West China hospital log-out registries. The patients inserted with central venous catheters (CVCs) or ever had thrombosis were excluded. According to whether use PICCs or not, patients were divided into two groups. The incidence of DVT during the use of bevacizumab between two groups was compared. Many risk factors were also analyzed.

Results: A total of 217 patients received bevacizumab were included in this analysis. 186 patients were colorectal cancer, 31 were lung cancer. Among them, 137 patients were inserted with PICCs and 80 patients were not. 5.1% (11/217) patients had DVT during the use of bevacizumab. 4 cases had upper extremity vein thrombosis, 1 had subclavian vein hrombosis and others were lower extremity vein thrombosis. Single factor analysis revealed that patients inserted with PICCs were more likely to have DVT than others (6.6% vs. 2.5%, $P = 0.318$), but it had no statistical difference. The incidence of DVT was higher in patients with diabetes mellitus (DM) than non-(DM) (21.1% vs. 3.5%, $P < 0.05$). Logistic analysis revealed that the use of PICCs had no statistical significance for the occurrence of the DVT. However, diabetes was a risk factor for DVT in advanced colorectal cancer and lung cancer patients with bevacizumab.

Conclusions: Peripherally inserted central venous catheters did not increase the risk of DVT in advanced colorectal cancer and lung cancer patients with bevacizumab. The patients with diabetes mellitus may be prone to develop DVT, whom we should manage more carefully during the use of bevacizumab.

Legal entity responsible for the study: Meng Qiu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN49 Cancer nurse perspective on the emerging field of biosimilars in cancer care

J. De Munter[1], P. Crombez[2]

[1]*Cancer Centre, Ghent University Hospital, Ghent, Belgium,* [2]*Hematology, Jules Bordet, Brussel, Belgium*

Background: Biological medicines has transformed cancer care drastically. As Biologics are incorporated into cancer treatment, cancer nurses play a key role in education, administration, pharmacovigilance and managing side effects of biological medicines. Expiring patents of innovator biologics creating opportunities to develop biosimilars and the number in oncology will continue to increase. The use of biosimilars will bring new challenges for cancer nurses related to education, treatment and follow-up of cancer patients.

Methods: A search of PubMed, Sciencedirect and regulatory agency websites was conducted for references related to the use of biosimilars and cancer nursing.

Results: To ensure optimal and safe use of biosimilars, all stakeholders incl. physicians, cancer nurses, pharmacists and patients need to understand the complexities of biosimilars and take decisions that will improve patients treatment, safety and Quality of life outcomes. As biosimilars are introduced into clinical practice, education of cancer nurses is paramount to ensure the best outcomes for patients safety. Training of nurses on new products, incl. biosimilars is often ad hoc and incomplete. As a result, cancer nurses may be unaware of the complexities and consequences of using biologics, incl. biosimilars. The knowledge gap in biosimilar medicines and switching or substitution of these medications could result in incorrect patient information, non-optimal use and adverse events which can lead to a delay in access and a decreased therapeutic gain for the patient.

Conclusions: Cancer nurses have an important role in the multidisciplinary approach and treatment of patients on biologics, incl. biosimilars. They have a lead role in education and counselling during introducing and follow-up of the transition between innovator and biosimilar medicines and vice versa, to improve patient outcomes and drug safety. Additional studies on biosimilars are needed to identify current knowledge gaps and educational needs of cancer nurses across Europe. Education about biosimilars is critical for successful incorporation in to oncology practice. A deeper understanding is needed across all cancer related professions with a strong emphasis on collaboration with all stakeholders including patients.

Legal entity responsible for the study: Johan De Munter.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN50 Overview of an acute oncology service in a UK cancer centre

M.R. Foulkes

Berkshire Cancer Centre, Royal Berkshire Hospital - NHS Foundation Trust, Reading, UK

Background: In the UK there has been increasing emphasis on the ability to review oncology patients who are admitted as an emergency. Two reports, NCEPOD report into systemic Anti-Cancer Therapy: For better, for worse? (2008) and the NPSA Report 'Patient safety risks of incorrect dosing of oral anti-cancer medicines' (2008) identified shortcomings in the manner in which patients presenting to emergency departments following systemic anti-cancer treatmentrs (SACT) were cared for. This had led to increased mortality, morbidity and extended lengths of stay. In addition to the above patients presenting as an emergency with Metastatic Spinal cord compression were found to have delays in urgent treatment and patients who had a cancer diagnosis following an emergency admission had poortrer outcomes than those identified in a more controlled fashion. At the Royal Berkshire NHS Foundation trust we responded to NHS England guidance by establishing an oncologist-led acute oncology service with nursing support. We have been succesful in reducing length of stay for oncology

patients, forming sucesaful partnerships with acute physicians, succeasfully auditing and treating neutropaenic sepsis and bringing in a 7 day Acute Oncology service. This poster p[resentation will provide an overview of this service as part of the Oncology Nursing Track.

Methods: The presentation will cover a narrative overview of our experience of establishing, auditing and developing an Acute Oncology Service at a busy District General Hospital with a Cancer Centre. We will present audit information to support this narrative review.

Results: We will present data covering Acute Oncology activity, effectiveness, presentation and referral by tumour group, referral type and source. This will be presented in graphical format in order to support the narrative review.

Conclusions: The overall conclusions will outline our generally positive exprience of establishing and developing Acute Oncology services. We hope that this will be relevant to others wishing to do the same across Europe.

Legal entity responsible for the study: Mark Foulkes (Macmillan Lead Cancer Nurse and Nurse Consultant in Acute Oncology).

Funding: Has not received any funding

Disclosure: The author has declared no conflicts of interest.

CN51 The development and evaluation of an online oncology portal

J. De Munter[1], E. Decoene[1], A. Van Hecke[2]

[1]Cancer Center, Ghent University Hospital, Ghent, Belgium, [2]Public Health, UCVV Nursing Science, University Ghent, Ghent, Belgium

Background: Care for patients with cancer is complex and the number of cancer survivors is increasing. This involves frequent monitoring and adequate medical and psychosocial support. The need for health related information among cancer patients is large. In Flanders, patients with a chronic disorder show a high degree of interest in online consultation of their medical records.

Methods: An online oncology portal was developed on the basis of literature, best practices and in co-design with patients, health care providers and IT developers. Co-design guarantees that the portal is tailored to the needs of the cancer patients. In this innovative project, a qualitative and quantitative evaluation of the portal was performed with patients (n = 45) and care providers (n = 10).

Results: On the platform the cancer patient can consult his individual treatment plan. In each phase of the care pathway online information, questionnaires and symptom diaries are attached. The platform provides a secure chat with the care providers (sending messages, video call), an overview of appointments and finally the patient can access his test results. Patients were positive about the possibility of consulting test results and reporting their side effects. Patients felt safely 'monitored' at home and experienced a strict follow-up from the oncology team. Generally, they found the platform user-friendly and complete.

Conclusions: This eHealth project is dynamic and is continuously optimized. This includes the implementation of the portal in patients with other types of cancer and in other hospitals. Finally, a mobile app is developed, signals for care providers are implemented in the system when patients report alarm symptoms and patients are empowered actively offering self-management advice. Up to today, more than 70 healthcare institutions are connected to the eHealth hub and all hospitals have the possibility to use all the functionalities of the oncology platform.

Legal entity responsible for the study: Cancer Center, Ghent University Hospital.

Funding: Belgian Foundation against Cancer.

Disclosure: All authors have declared no conflicts of interest.

CN52 Pilot study: Nurses' role in management of cutaneous toxicity in patients with targeted therapies anti EGFR-Is' treatment

O. Diamanti[1], T.M. Zacheo[2], C. Lando[1], C. Magro[1], G. Pauletti[1], E. Zemella[1], C. Fano[1], F. Bonadies[1], E. Sarno[1], A. Venturi[1], P. De Vecchi[1], S. Menuzzo[1], S. Gallimberti[1], D. Grosso[1]

[1]Centro Coordinamento "Infermieri di Ricerca", Istituto Oncologico Veneto IRCCS, Padua, Italy, [2]Direzione Professioni Sanitarie, Istituto Oncologico Veneto IRCCS, Padua, Italy

Background: EGFR-Is (Epidermal Growth Factor Inhibitors) such as cetuximab, panitimumab and RTK (Receptor Tyrosine Kinase) such as erlotinib, regorafenib are "Targeted Therapies" with a selective capacity. However their use causes new side effects, such as the skin toxicity, the most prevalent of which is the maculo-papular rash. Several studies emphasize that education and prevention can reduce this toxicity which, if not treated promptly, may compromise the ongoing chemotherapy treatment and have a negative impact on the patient's QoL.

Methods: This is a randomized mono center, two-treatment arms and interventional study. 178 patients, enrolled in approximately 2 years, will be randomized 1:1 to receive intravenous treatment (Cetuximab or Panitumumab) or oral treatment (Erlotinib or Regorafenib). All patients, in Arm A (experimental group) and in Arm B (control group), will complete a HOC Questionnaire Created composed by 14 items and Dermatology Life Quality Index (DLQI). Furthermore, it will be created a HOC brochure by nurses containing advice and information about the skin toxicities and their management. Questionnaires, brochure and interviews will be administered as shown in the table. Note: a and b only Arm A

Table: CN52

Study period	Screening phase (-14 to -1)	Every 4 weeks (until at first tumor assessment)
Informed Consent Form	X	
Inclusion/Exclusion Criteria	X	
HOC Questionnaire Created	X	
DLQI Questionnaire	X	X
Brochure[a]	X	
Interview with nurse[b]	X	X

Results: The sample size will be hypothetical that the incidence of cutaneous toxicity in the Arm A group, will be lower than that of the Arm B group as per CTCAE 5.0. It will be considered clinically relevant to observe a better QoL and a 20% reduction in the incidence of cutaneous toxicity in the Arm A and a redistribution of toxicity levels such as to produce an effect size of 0.068.

Conclusions: Allowing patients to be more involved in their treatment and toxicity management of toxicities related, oncology nurses can help them to maintain their QoL and to promote adherence to treatment. The project hopes to confirm the hypothesis of cutaneous toxicity reduction 20% in Arm A and a better QoL compared to Arm B (control group).

Legal entity responsible for the study: Istituto Oncologico Veneto.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology 29 (Supplement 8): viii698–viii701, 2018
doi:10.1093/annonc/mdy278

CANCER NURSING: SYMPTOM MANAGEMENT

CN53 Rectal cancer survivorship: The struggle of the low anterior resection syndrome (LARS)

E. Pape[1], P. Pattyn[1], A. van Hecke[2], N. Somers[3], D. Van De Putte[1], W. Ceelen[1], E. van Daele[1], W. Willaert[1], Y. van Nieuwenhove[1]

[1]Gastrointestinal Surgery, Ghent University Hospital, Ghent, Belgium, [2]University Centre for Nursing and Midwifery, Ghent University, Ghent, Belgium, [3]Faculty of Medicine, Ghent University, Ghent, Belgium

CN54 Nurse-led approaches to self-management of symptoms in routine Swiss outpatient care: A qualitative exploration

K. Ribi[1], M. Bana[2], S. Peters[3], S. Kropf-Straub[4], E. Näf[5], S. Zürcher[4], M. Eicher[6]

[1]Institut Universitaire de Formation et de Recherche en Soins – IUFRS, University of Lausanne, Lausanne, Switzerland, [2]School of Health Sciences (HEdS-FR), HES-SO University of Applied Sciences and Arts Western Switzerland, Fribourg, Switzerland, [3]Multidisciplinary Oncology Center, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, [4]Departement of Practice Development in Nursing, Hospital Group Lindenhof, Bern, Switzerland, [5]Departement of Practice Development in Nursing, Solothurner Spitäler AG, Kantonsspital Olten, Olten, Switzerland, [6]Departement of Oncology - Institut Universitaire de Formation et de Recherche en Soins – IUFRS, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland

CN55 Evaluation of a nursing aftercare intervention for patients with head and neck cancer treated with chemoradiation

C. Braat[1], G. Verduijn[1], H. van der Stege[2], M. Offerman[3], M. Peeters[2], A. van Staa[2], W. Oldenmenger[4]

[1]Radiotherapy, Erasmus MC Cancer Insitute, Rotterdam, Netherlands, [2]Kenniscentrum Zorginnovatie, Hogeschool Rotterdam, Rotterdam, Netherlands, [3]Head and Neck Oncology, Erasmus MC, Rotterdam, Netherlands, [4]Oncology, Erasmus MC Cancer Insitute, Rotterdam, Netherlands

CN56 When symptom complexity is the norm: A mediation analysis between pain, anxiety, depression and fatigue

A. Charalambous

Nursing Science, Cyprus University of Technology - Nursing Science, Limassol, Cyprus

CN57 Does individual genetic background predict acute radiation skin reactions in women undergoing adjuvant breast cancer radiotherapy?

D. Oliva[1], F. Lewin[1], N. Lewin[2], M.P. Nilsson[3], M. Strandéus[1], B-Å. Andersson[2], L. Sharp[4]

[1]Oncology, County Hospital Ryhov, Jönköping, Sweden, [2]Department of Laboratory Medicine, Region Jönköping, Laboratory Medicine, Jönköping, Sweden, [3]Futurum - The Academy for Healthcare and Department of Medical and Health Sciences, Linköping University, Linköping, Futurum -, Jönköping, Sweden, [4]Cancer Care Improvments, Regional Cancer Center Stockholm Gotland, Stockholm, Sweden

Background: Skin reactions during radiotherapy (RT) are common in women with breast cancer (BC). Different methods have been tested to reduce or prevent this toxicity. The aim of this study was to explore if genetic variation can be linked to acute radiation skin reactions (ARSR).

Methods: One hundred and nineteen women undergoing RT for BC during the period of 2011 to 2013 were included. Symptoms such as itching, burning and irritation were self-reported twice (during the first and last week of RT) using the VAS-scale. Assessments of the irradiated skin were measured using the Radiation Therapy Oncology Group scoring system for acute RT (RTOG-scale). Blood-based SNP analysis were performed using peripheral blood sample (obtained before start of RT). In total, 29 SNPs of well-defined functional genes were investigated.

Results: All women were assessed with ARSR in various degree according to the RTOG-scale. During the last week of RT, the women self-reported itching (n = 97, 82 %), burning (n = 64, 54 %) and irritation (n = 96, 81 %.). Three SNPs in the following genes were found to be associated with ARSR: XRCC2, IFNg and CCL5/Rantes.

Conclusions: We found an association between three SNPs and ARSR. The possibility of using these SNPs as prognostic biomarkers for radiation-induced toxicity needs further investigation.

Legal entity responsible for the study: County Hospital Ryhov, Jönköping Sweden.

Funding: This investigation was partly supported by Foundation for Clinical Cancer Research in Jönköping and Futurum Academy for Health and Care, Region Jönköping County, Sweden and FORSS - Medical Research Council of Southeast Sweden.

Disclosure: All authors have declared no conflicts of interest.

CN58 Effect of aromatherapy massage on chemotherapy-induced peripheral neuropathic pain and fatigue in patients receiving oxaliplatin

N. Izgu[1], L. Ozdemir[1], F. Bugdayci Basal[2]

[1]Nursing Faculty, Hacettepe University, Ankara, Turkey, [2]Medical Oncology, Ataturk Chest Diseases and Surgery Training and Research Hospital, Ankara, Turkey

Background: Patients receiving oxaliplatin may experience peripheral neuropathic pain and fatigue. Aromatherapy massage, a nonpharmacological method, may help to control these symptoms.

Methods: The aim of this open-label, parallel-group, quasi-randomized controlled pilot study was to investigate the effect of aromatherapy massage on chemotherapy-induced peripheral neuropathic pain and fatigue in patients receiving oxaliplatin. Stratified randomization was used to allocate 46 patients to 2 groups: intervention (n = 22) and control (n = 24). Between week 1 and week 6, participants in the intervention group (IG) received aromatherapy massage 3 times a week. There was no intervention in weeks 7 and 8. The control group (CG) received routine care. Neuropathic pain was identified using the Douleur Neuropathique 4 Questions; severity of painful paresthesia was assessed with the numerical rating scale; fatigue severity was identified with the Piper Fatigue Scale.

Results: At week 6, the rate of neuropathic pain was significantly lower in the IG, when compared with the CG. The severity of painful paresthesia based on numerical rating scale in the IG was significantly lower than that in the CG at weeks 2, 4, and 6. At week 8, fatigue severity in the IG was significantly lower when compared with CG ($P < .05$).

Conclusions: Aromatherapy massage may be useful in the management of chemotherapy-induced peripheral neuropathic pain and fatigue. This pilot study suggests that aromatherapy massage may be useful to relieve neuropathic pain and fatigue. However, there is a need for further clinical trials to validate the results of this study.

Legal entity responsible for the study: Hacettepe University.

Funding: Hacettepe University Scientific Research Projects Coordination Unit.

Disclosure: All authors have declared no conflicts of interest.

CN59 Cancer pain knowledge and attitudes of nursing and medical professionals in a Greek general hospital

C. Palassari, S. Katsaragakis, J. Kaklamanos, D. Protogiros, E. Patiraki

Nursing, National and Kapodistrian University of Athens, Athens, Greece

Background: Health care professional's knowledge and attitudes are strongly related with sufficient cancer pain management. The study explored nursing and medical professionals' cancer pain management knowledge and attitudes.

Methods: A cross-sectional survey was conducted. The convenience sample consisted of nursing and medical professionals (internal medicine sector) of a public general hospital, Athens. Sample's inclusion criteria: informed consent and > 5 months' work experience. Between September - December 2016, 98 physicians (P), 70 registered nurses (RN) and 36 nurse assistants (NA) with response rates 81.8%, 77.8%, 90% respectively, completed the Greek version of the Nurses' Knowledge and Attitudes Survey Regarding Pain: a 39 items tool divided into 22 true/ false, 13 multiply choices and 4 pain case studies items, as well as a demographic form.

Results: Most of the participants were women (76.5%), reporting caring for more than 100 patients in cancer pain per year (40.7%). The sample's mean age was 39.5 years and work experience 12.8 years. The prevalence of the five most frequent wrong responses (over 88.2%) was related with assessment and pain management interventions, addiction, patient pain self-report, and route of medication's administration. Opioids titration, patients' religious and cultural related pain behaviors, older patients and pain tolerance were the five most frequent correct answers (over 80.4%). P responded more correct answers (mean 20.8) than RN (17.5) and NA (15.8) ($p < 0.0001$). Age, education and clinical experience in cancer care explained 28% variance of correct answers. Younger participants, working at oncology wards, holders of a doctoral and attending continouing cancer pain education (strongest indepented factor (R^2Change=.007)), were related with more correct answers.

Conclusions: Greek participants knowledge deficits in pain management support the universal concern of inadequate knowledge and attitudes of health care professionals, however, encouraging theoretical and clinical training may enhance their ability to improve practice. We thank Special Account for Research Grants and National and Kapodistrian University of Athens for funding to attend the meeting.

Legal entity responsible for the study: Nursing Department, National and Kapodistrian University of Athens.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN60 The experience of dysgeusia in allogenic hematopoietic cell transplantation survivors: A qualitative study

D. Bomben[1], A. Bin[2], M. Venturini[1], T. Bulfone[1], L. Ghirotto[3], V. Bressan[1]

[1]Department of Medical Sciences, University of Udine, Udine, Italy, [2]Oncology Department, Udine University Hospital, Udine, Italy, [3]Research, Azienda Santa Maria Nuova-IRCCS, Reggio Emilia, Italy

Background: Taste disorders are one of the most common side effects of treatment in oncology patients and often occur after allogeneic hematopoietic cell transplantation (allo-HCT). Dysgeusia is rarely a life-threatening complication, therefore, in many cases it does not receive close medical attention. Furthermore, information about this disorder is largely based on the clinician's own experience. However, taste disorders, can impact on the quality of life in survivors of allo-HCT, and compromise their enjoyment of eating, food intake, weight and nutritional status. The number of performed annual transplantations continues to grow annually and the number of older long-term survivors increases. There is little literature that is focused on studies of survivors of allo-HCT with taste disorders. We conducted a qualitative descriptive study to explore experiences of dysgeusia in patients that have undergone of allo-HCT and examined what strategies they used to mitigate it.

Methods: Using purposive sampling, survivors of allo-HCT were recruited. Audiotape interviews were conducted until data saturation was achieved. Each interview was transcribed verbatim, and content analyses were performed to extract significant themes and subthemes.

Results: Three major themes embracing various aspects of allo-HCT survivors' experiences were identified: 1) the shape of taste; 2) everything is irritating and it is arduous to eat; 3) finding new strategies to overcome the problems. Together, they highlight the experiences of survivors showing how taste disorders can affect the physical, psychological and social dimensions of a person for the rest of their life.

Conclusions: A cumulative burden is the result of dysgeusia and its clinical course reinforced also by related symptoms. Healthcare professionals must focus their attention on the management of these symptoms and offer interventions to safeguard the patient's social, physical and psychological well-being. Finally, further research is needed to explore the experiences of allo-HTC patients who have taste disorders throughout their cancer journey that introduces a more holistic approach which involves health professionals, caregivers and family members.

Legal entity responsible for the study: Valentina Bressan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN61 "It may not affect you": Lived experiences and support needs of women who developed peripheral neuropathy following chemotherapy treatment for cancer

M.A. Tanay[1], J. Armes[2]

[1]Faculty of Nursing, Midwifery and Palliative Care, King's College London, London, UK, [2]Faculty of Health and Medical Sciences, University of Surrey, Surrey, UK

Background: Some cancer drugs cause chemotherapy-induced peripheral neuropathy (CIPN) or damage to the nerves. CIPN affects the hands and feet, with patients reporting symptoms such as numbness, tingling, pain and muscle weakness. The nature of symptoms depends on the chemotherapy agents and drug dose that patients receive. Options to minimise the severity of symptoms may involve dose reduction, delay or discontinuation of chemotherapy. This study explored lived experiences of women who developed peripheral neuropathy following cancer chemotherapy treatment.

Methods: The study was conducted in the United Kingdom and was advertised through cancer charity websites and social media accounts. Using set eligibility criteria, purposeful convenience sampling was carried out. Women diagnosed with breast or ovarian cancer who experienced or are still experiencing neuropathy following chemotherapy treatment were recruited. Semi-structured recorded telephone interviews were conducted (n = 15). Interpretative phenomenological analysis (IPA) was used to analyse data.

Results: The analysis resulted to four main themes: struggle to process CIPN information, information and trust when making treatment decisions, experience of symptom reporting and challenges of mitigating CIPN symptoms. Similar to previous studies, participants used analogies to describe CIPN symptoms such as 'like walking on pebbles, sand, needles or gravel'.

Conclusions: Findings suggest that interventions to improve understanding of CIPN symptoms by patients and clinicians are needed in practice. A broader insight of patients' experiences of CIPN helps progress development of interventions to enhance communication, assessment and management of CIPN symptoms.

Legal entity responsible for the study: King's College London.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN62 App about chemotherapy: Helping the patient with cancer

B.T. Espersen

Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Background: Patients with cancer are bombarded with information – both in connection with examinations, diagnosis and treatment. Patients cannot always cope with the huge quantity of oral and written information from the hospital. Even highly educated patients voice their inability to take in the amount of given information. Reading skills and the ability to understand are often not taken into account. Furthermore 15-20 % of the normal population is known to be weak readers. The use of mobile technology in health care has shown a fortified self care and improved quality of life. Therefore, we aimed at developing an app which could serve several purposes: Opportunity to use different sources of information, information at the right time and the right place, information "on the go", the text read out loud (or earphones) and information to relatives and friends – no matter where they live.

Methods: The text from our written information was adjusted to the electronic media. The new text has been commented by patients, relatives and health care personnel. Finally, the text can be read out loud with a tap on the loudspeaker icon. There are 2 apps, which can be downloaded for free (Google play and App Store) App 1 is a general guide with focus on the most asked questions in relation to cancer, chemotherapy and targeted treatment - e.g: Does the treatment influence other people? How can my disease affect my relatives? What will I tell my children? Can I go on holiday? What about work? Can I drink alcohol? Can I be physically active? What about alternative treatment? App 2 describes 16 possible side effects separately and guides the patients and relatives in relation to preventing and minimizing the discomfort.

Results: See conclusion.

Conclusions: Some patients prefer the apps to the traditional written information. They download to both mobile phone and tablet. They find it very manageable and easy to navigate, and the text short and straight forward. The apps are an extra source of information for some patients, and they recommend the apps to family, friends and other patients. If patients find the oral and written information satisfying, they do not use the apps. The technology can be a barrier especially with older patients.

Legal entity responsible for the study: Department of Oncology, Aarhus University Hospital, Denmark.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

CN63 Usability test for a CINV diary application for smartphones at oncology nursing

P. Fernández- Ortega[1], Y. Escobar[2], E. Trigoso[3], R. Blat[4], M. Cantero[2], A. Alvarez[5]

[1]Nursing Resarch, Institut Català d'Oncologia Hospital Duran i Reynals, Barcelona, Spain, [2]Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [3]Nursing OncoPediatric, Hospital La Fé, Valencia, Spain, [4]Nursing, Hospital Mar Parc Salut, Barcelona, Spain, [5]Nursing, Hospital de Leon, Leon, Spain

Background: Chemotherapy-induced nausea and vomiting (CINV) continue to be a clinical problem, particularly in the delayed phase. Great variability between perception of healthcare professionals and patients, regarding incidence & severity of CINV[1-9]. CINV lack of control worsens the quality of life of patients and it is associated with complications[12-13] increasing costs for healthcare services[14].CINV app is a free service addressed to patients treated with emetogenic chemotherapy (CT), empowering patients to report CINV impact in life and relevant information. This study aims to evaluate the usability and acceptability of a smartphone app to improve CINV management in patients receiving CT, by cancer nursing.

Methods: We used 4-dimensions test (content, graphic design, navigation and clinical utility) to evaluate APP's usability and acceptability. Clinical and technical researchers worked together to develop the app's test. 8 National Hospitals with specialized oncology nursing services were included. 45 cancer nurses invited to participate (from 9 to 23 April 2018) and 33 filled in the test, after making a clinical case simulation through the app.

Results: Described Table

Table: CN63

Variables	N = 33	Nurses level agreement
Contents		84%
Navigation		84%
Graphic design		94%
Utility		89%

App was easy to use and had relevant content, although improvement is possible. 91% nurses agree that more than 50% of their patients will be able to use the APP and 88% believe that report generated will be useful in practice.

Conclusions: The CINV app addresses main concerns for patients receiving chemotherapy, clinical situation and individual emetic risk of patient or complexity of the prescribed antiemetic regimen and impact of CINV in their daily life. Soliciting feedback from oncology nurses, we ensured that the app was acceptable and beneficial for patients and clinicians. Some points to improve the app in future. Reporting of symptoms after CT enhances CINV management, self-care, and participation without being a burden to patients, indicating that app can be used in clinical practice by patients.

Legal entity responsible for the study: Yolanda Escobar.

Funding: Vifor Pharma.

Disclosure: All authors have declared no conflicts of interest.

CN64 Perceived symptoms of Greek cancer patients during chemotherapy using the memorial symptom assessment scale

D. Palitzika[1], E.C. Fradelos[1], V. Alikari[1], P. Charitopoulos[1], E. Zioga[1], S. Zyga[2], M. Lavdaniti[1]

[1]Nursing, Alexander Technological Educational Institute, Thessaloniki, Greece, [2]Nursing, University of Peloponnesus, Thessaloniki, Greece

Background: Cancer patients experience a variety of concurrent symptoms during their chemotherapy. These symptoms can be physical or psychological and may vary in terms of occurrence, severity and distress. The aim of the present study was to assess the existence of symptoms during chemotherapy.

Methods: This was a non-experimental and descriptive study. It was conducted in a large hospital in a major Northern Greek city. The subjects were 200 cancer patients undergoing chemotherapy in cycle 2 and cycle 3. Data was collected using the Memorial Symptom Assessment Scale (MSAS) and questionnaire with demographic and clinical characteristics.

Results: The majority of patients was male (61%) with mean age 58.9 (S.D. 9). 79.5% was married 47.5% had completed compulsory education. Moreover, 48% suffered from lung cancer, 42% colorectal cancer, 7.5% pancreatic cancer and 2.5% stomach cancer. In the 2nd cycle of chemotherapy the mean of Global Distress Index (GDI) was 2.20, Physical Symptom Subscale (MSAS PHYS) was 2.38, Psychological Symptom Subscale (MSAS-PSYCH) was 2.26 and Total MSAS score (TMSAS) was 2.26. Also, in the 3rd cycle of chemotherapy the mean of GDI was 2.20, MSAS PHYS was 2.43, MSAS-PSYCH was 2.17 and TMSAS was 2.27. The following symptoms presented increase between 2nd and 3rd cycle of chemotherapy: feeling nervous, nausea, feeling drowsy, and problems with urination, vomiting, diarrhea, problems with sexual interest or activity, mouth sores, weight loss. The symptoms with the highest mean in 2nd and 3rd cycle of chemotherapy were numbness/tingling in hands/feet and feeling drowsy.

Conclusions: The results of this study demonstrate that cancer patients undergoing chemotherapy experience various symptoms. Therefore, nurses should take into account these findings and plan appropriate, suitable care plans and interventions in order to alleviate them and improve patients' quality of life.

Legal entity responsible for the study: Alexander Technological Educational Institute - Research Laboratory " Care in Adult Cancer Patients"

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN65 How to monitor outpatients undergoing active anticancer treatment? A feasibility study of the web-based tool "Onco'nect®"

M. Belhadj, E. Kempf, A. Lebel, A. Guillemin, H. Boussion, C. Joly, I. Baumgaertner, E. Assaf, C. Saldana, B.J-C. Rousseau, C. Tournigand

Oncologie Médicale, Hôpital Henri Mondor, AP-HP, Créteil, France

Background: Monitoring adverse effects (AEs) induced by antitumor therapies remain a clinical challenge for outpatients with cancer. Their delayed management might impair patient quality of life and lead to dose-lowering or discontinuation of treatment. The use of e-health may improve the communication between caregivers and patients, as well as the continuity of care. We assessed if Onco'nect®, a new digital follow-up tool, could be used easily by cancer outpatients undergoing active antitumor treatment in a routine clinical practice setting.

Methods: Outpatients diagnosed with any type of cancer and undergoing intravenous or oral anticancer in the department of Medical Oncology of Creteil Teaching Hospital were eligible. No informatics knowledge was required for patients to be included in the study. At different times of each chemotherapy cycle, patients were sent a standardized 12-question survey assessing AEs. A chat was available for patients and caregivers to improve their communication. Grade $\geq$2 AEs, and deliberate requests of patients raised an alert system. Caregivers were notified of such events by emails and "red alerts" on the web-based interface.

Results: Our study enrolled 51 patients, with distinct types of anticancer treatment (chemotherapy, oral therapy, immunotherapy and clinical trial therapy): 5 (9.8%) patients were over 75-year-old. Four patients could not use a computer or a smartphone but had a relative able to help. We called 21 (41.2%) patients at least once because they reported $\geq$ grade 2 AEs. We modified symptomatic treatments, or diet and lifestyle in 11 (21.6%) cases. Four patients deliberately raised the alert system, resulting in one hospitalization. The chat was used to: manage daily AEs, answer patients' questions, send prescriptions, receive medical imaging and blood test results. After a 2-month use, all the patients asked reported that Onco'nect® was easy to use and clinically-efficient.

Conclusions: Onco'nect® is a user-friendly web-based tool to monitor outpatients undergoing anticancer treatment. It can be integrated in a current practice in oncology, even with elderly patients. Onco'nect® might help to anticipate chemotherapy prescriptions and reduce the admission in emergency rooms.

Legal entity responsible for the study: Service d'Oncologie Médicale, Hôpital Henri Mondor, AP-HP, Créteil.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CN66 Medical makeup in cancer patients and its impact in their quality of life

R. Lechou, M. Lavdaniti

Nursing, Alexander Technological Educational Institute, Thessaloniki, Greece

Background: Cancer treatment cause many toxicities included skin toxicities. Although skin toxicity often resolve upon therapy discontinuation these side effect can negatively affect self esteem, treatment compliance and quality of life.

Methods: A literature review was conducted using the electronic databases PubMed and Google scholar, with respect to the period from 2008 to 2018. The following key words were entered: "medical makeup", "cancer", "anticancer treatment" and a combination thereof. The exclusion criteria for the articles were languages other than English.

Results: Medical makeup was tested under dermatological control on damaged skin. It was water- and sweat-resistant, perfume-free, preservative-free, superior coverage (40-50% pigments) and has natural results. In a multicenter study (9 centers) were studied 90 patients presenting with visible cutaneous side effects from chemotherapy: altered complexion, total or partial eyebrow alopecia, irregularity of lip contour, dry lips. The corrective medical makeup improved the quality of life in 81.2% of patients and helped 76.8% of patients to brave the stares of others. Also, health professionals should inform women cancer patients about medical make-up, its benefits and give some instructions for applying make-up.

Conclusions: Medical makeup has many benefits in enhancing patients' self-esteem. Health professionals must find ways to implement it in cancer patients who have skin toxicity. Also, in Greece there is a great need for further research for this issue, on a large population with precise characteristics in order to arrive at safe results about medical makeup.

Legal entity responsible for the study: Alexander Technological Educational Institute - Research Laboratory "Care in Adults Patients with Cancer".

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.